Clinical Cases in Dermatology
Series Editor: Robert A. Norman

Shannon C. Trotter
Austin Cusick *Editors*

Clinical Cases in Pruritus

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Clinical Cases in Dermatology

Series Editor

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Clinical Cases in Pruritus

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Contents

Chapter 1
72-Year-Old Male with Itchy, Erythematous Papules on His Trunk

Amy Mehlman, Austin Cusick, and Shannon C. Trotter

A 72-year-old male presented with itchy, erythematous papules on his trunk, most concentrated in the middle of his chest and back. The eruption had been present for 6 months and treated unsuccessfully with topical clotrimazole and over the counter emollients. He reported using a hot tub on a daily basis and stated that the lesions often look like a blister and they pop very easily.

On physical examination, there were multiple erythematous and pink papules, some with hemorrhagic crust mostly concentrated on the chest and back. Several were excoriated. A biopsy of one of the lesions was obtained and showed spongiotic dermatitis with acantholysis.

Based on the clinical case description, what is the most likely diagnosis?

1. Psoriasis
2. Seborrheic dermatitis
3. Grover's disease
4. Confluent and reticulated papillomatosis

Diagnosis

Grover's disease.

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Discussion

Grover's disease (GD), also known as transient and persistent acantholytic dermatosis, is a benign, pruritic skin condition first described by Ralph Grover in 1970, for whom it is named [1]. GD presents as an intensely pruritic, erythematous rash described as papular to papulovesicular in nature, with lesions commonly crusted over or eroded [1, 2]. These lesions may also be described as papulosquamous [1]. The lesions most commonly appear on the trunk but are also located on proximal extremities. The neck, face/scalp, palms, soles, axilla, and mucosal membranes are affected but to a lesser degree. Duration of the rash caused by GD is typically self-limited and clears within a few weeks; however, GD may also be chronic with a waxing and waning presentation or a recalcitrant pattern for several years [1, 2]. While classically associated with severe pruritus, the pruritic association with GD may vary from mild to severe. Treatment of GD not only targets the initial manifestations and inflammation, but the treatment also is used to manage the itch co-existing with the disease [2].

The incidence and prevalence of GD have yet to be firmly established, but some sources report the incidence to be between 0.1–0.8% [1, 2]. GD has a predominance towards males more commonly than females with a 2:1 ratio, and the mean age of onset between the ages of 62–64 years [2]. However, there have been reported cases of GD in young adolescents and older populations. GD is more commonly seen in white patients but has also been reported in black, Hispanic, and Middle Eastern patients to a lesser degree [2].

There are many suspected triggers and inciting medications that may lead to GD. Proposed triggers include heat, diaphoresis, sunlight, ionizing radiation, and prolonged bed rest. Other heat-related triggers include exercise, fever, hot tub bathing, and unspecified excessive heat [3]. Several medical conditions can be implicated in GD development such as end-stage renal disease, hemodialysis, solid organ transplantation [4], atopic dermatitis, contact dermatitis, xerosis cutis, pyoderma gangrenosum, bacterial infections, viral infections, tinea versicolor, scabies, and malignancies [1, 2]. While heat and diaphoresis are suggested triggers, many cases are paradoxically associated with cold, dry air [1, 2]. Some investigation has supported that GD was diagnosed at a rate four times higher during winter months than in the summer, suggesting that xerotic skin and cold, dry air conditions may promote the disease [5]. Medications that are associated with GD include sulfadoxine-pyrimethamine, ribavirin, anastrozole, interleukin-4, cetuximab, BRAF inhibitors (vemurafenib, dabrafenib), and immune checkpoint inhibitors such as ipilimumab [1]. If medication-induced, the inciting medication is typically continued, with the addition of symptomatic management for pruritus [2]. Ultimately, all of the risk factors discussed culminate to the point of disrupting epidermal integrity. Over time, the disruption of epidermal integrity predisposes the patient to develop GD [3]. Moreover, hypothesized occlusion of pores and epidermal ducts lead to direct epidermal damage from molecular seepage into the epidermis. Rarely, autoantibodies to desmoglein protein have been implicated [3]. Other associations are only linked to GD by pure speculation.

GD is diagnosed clinically and by histological analysis of skin biopsies. Histologically, GD is described as exhibiting a pattern of acantholysis, loss of keratinocyte cohesion, within the epidermis [1]. A GD lesion visualized using dermoscopy is described as a brown, star-like pattern with vessels surrounded by halos [2]. Four histological variants of GD exist, but several other subtypes have been described as well. The four main variants are Darier-like, pemphigus vulgaris-like, Hailey-Hailey-like, and spongiotic. The Darier-like subtype is notable for upper epidermal acantholysis and dyskeratosis. The pemphigus-like subtype shares similarities with pemphigus vulgaris in that disruption is above the basal layer of the epidermis with basal layer retention. The Hailey-Hailey-like subtype is similar to the Darier-like presentation without scattered dyskeratosis. Lastly, the spongiotic subtype shows significant fluid retention in the epidermis with visible keratinocyte connections [2]. The Darier-like and pemphigus vulgaris-like are the most reported subtypes [2]. Subsequent investigation of GD subtypes has demonstrated significant variability on physical exam and dermoscopy with respect to the histological characterization. For example, the spongiotic subtype may be unique in dermoscopy through a scale presentation on a yellow-to-red background [6].

Treatment

GD has an overall rather unpredictable course, which complicates the ability to undergo a high-quality investigation for treatment. Supporting evidence is typically reliant on case-based presentations, small sample studies, or anecdotal evidence [2].

Ultimately, the foremost intervention against GD is dependent on the isolation of exacerbating factors and avoiding triggers if possible. The classic triggers including excessive heat, sunlight, and dry air can easily be determined and removed. Other triggers, including organ transplant and medication-induced GD, may not be so easily attenuated [2]. Isolation and removal of exacerbating factors coupled with the natural self-limiting course of the disease is often sufficient in mild cases [3].

When the disease is slightly more complex, therapeutic intervention is often required. The initial treatment may need to be tailored to the exacerbating factor. For example, in xerotic skin precipitating GD, topical emollients prove beneficial with possible conjunction of a topical corticosteroid. Furthermore, topical corticosteroids tend to be most effective in mild disease with significant pruritus, targeting both components. Suggested topical corticosteroids include triamcinolone acetonide or fluticasone propionate [2]. If refractory to lower potency topical steroids, some evidence supports topical vitamin D analog monotherapy. Vitamin D exerts action through increasing calcium availability within the keratinocyte, amplifying keratin accumulation with secondary anti-inflammatory effects on immune system cells [2]. If pruritus continues, antihistamine therapy can be added to the above-mentioned therapies to target the inflammation itself [2].

In more severe or refractory disease with unrelenting pruritus, other medications can be used at a systemic level. Oral retinoid analogs can be used alone or in

combination with phototherapy or a vitamin D analog [2, 7]. Results with oral retinoids typically range from weeks to months in treatment duration. Additionally, tapered oral corticosteroids demonstrate relatively rapid resolution of disease with possible lasting remission. Of note, relapse of the disease has been reported on the initiation of steroid taper as well. Both oral therapies mentioned above have presented relative success within their reports; however, it is important to remember the paucity of high-quality research secondary to the disease's natural course [2].

If the disease is refractory to both topical and oral therapies, phototherapy may prove beneficial. Psoralen ultraviolet A therapy (PUVA) has demonstrated resolution up to 2 years post therapy. It is noted that a brief exacerbation during PUVA therapy may present [2]. More therapies have recently been investigated and show some promise for disease treatment. Specifically, etanercept has demonstrated disease resolution in a refractive case [2]. Etanercept efficacy suggests the possibility of a different underlying pathologic mechanism in GD that could be investigated. Other therapies that have been investigated with some support in the literature include triple antibiotic ointment, trichloroacetic acid, skin electron beam radiotherapy, and methotrexate [8]. The future in treating GD is reliant on the ability to establish the complete mechanism of pathology and to perform high-quality research on therapies that target this mechanism more specifically.

Key Points

- GD presents as an intensely pruritic, erythematous rash described as papular to papulovesicular in nature that is commonly crusted over or eroded.
- Often, GD is associated with specific triggers such as excessive heat, diaphoresis, sunlight, ionizing radiation, and prolonged bed rest. However, others may include xerosis, organ transplantation, drug initiation, and underlying malignancy.
- Classic GD is described as a brown star-like lesion with a surrounding halo on dermoscopy. On histological examination, acantholysis is the predominant finding with other findings being subtype-specific.
- Treatment of GD is reliant on possible avoidance of triggers as the disease is self-resolving in most cases. Therapies for mild disease include emollients, topical corticosteroids, and topical vitamin D. Severe, refractory disease with unrelenting pruritus is often treated with oral retinoids or oral corticosteroids.

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Chapter 2
80-Year-Old Female with Itchy Hives and Bullae on the Trunk and Extremities

Kassandra Riggs, Austin Cusick, and Shannon C. Trotter

An 80-year-old female presented with hives and pruritic, tense bullae on her trunk and extremities, sparing her face and scalp. She recalled having hives for 2–3 months before developing the large bullae. She was treated with antihistamines for the hives with little improvement. Once the bullae started to form, she was also treated with a first-generation cephalosporin antibiotic for 2 weeks with no improvement.

On physical examination, there were multiple tense bullae on an urticarial base covering her trunk and extremities. There were also scattered excoriation marks across her body. A biopsy was performed and showed a subepidermal blister with eosinophils and superficial dermal edema. A direct immunofluorescence test was also done and showed linear IgG and complement deposits at the basement membrane zone (Fig. 2.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Allergic contact dermatitis
2. Bullous impetigo
3. Poison ivy
4. Bullous pemphigoid

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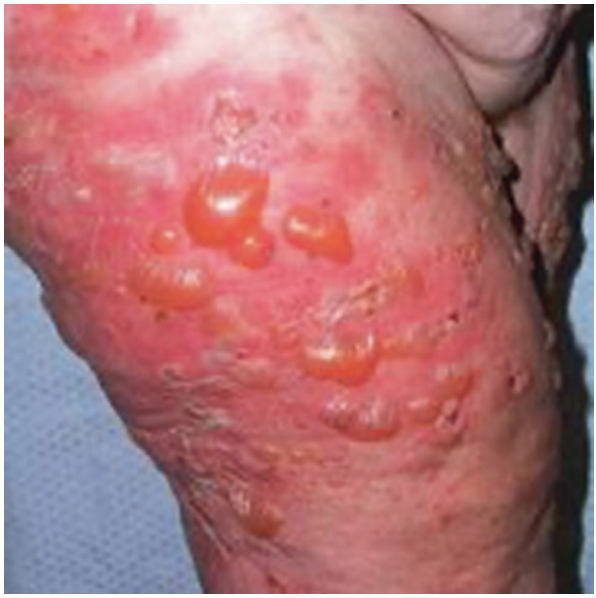

Fig. 2.1 Tense bullae on the trunk and the extremities. Courtesy of Dr. Matthew Zirwas

Diagnosis

Bullous pemphigoid.

Discussion

Bullous pemphigoid (BP) is an autoimmune subepidermal blistering disorder that is associated with significant morbidity [1]. This disease most commonly affects elderly patients, primarily those 70 years and older. Due to the increased likelihood of comorbid conditions and increased susceptibility to infection, the disease has a higher rate of complications and mortality [1]. The mean age of patients varies worldwide, and this disease is more prominent in females as compared to males [2]. While the clinical presentation of BP is variable, the most characteristic symptomatology is tense bullae and generalized pruritus with spontaneous exacerbations and remissions.

A prodromal stage of the disease may present with non-bullous eczematous or urticarial-like lesions before the onset of blisters [3]. However, non-bullous pemphigoid is often regarded as an underdiagnosed variant of the disease rather than a prodromal stage. The bullous stage of the disease is typically characterized by up to hundreds of vesicles and bullae on an erythematous base. BP blisters are tense with

a clear exudate differentiating them from the flaccid bullae of pemphigus vulgaris. These lesions are intensely pruritic and largely located on the abdomen, trunk, and proximal extremities [4]. The lesions are rarely in mucosal sites, but mucosal involvement is present in up to 30% of patients [5].

The pathogenesis of BP involves autoantibodies against two different hemidesmosome proteins. Bullous pemphigoid antigen 180 (BP180), also known as bullous pemphigoid antigen 2, is a transmembrane protein that extends from the hemidesmosome dense plaque into the basal keratinocytes of the basement membrane lamina densa [6]. Bullous pemphigoid antigen 230 (BP230) or BPAG1e is a coiled-coil protein that connects the transmembrane hemidesmosome proteins to the keratin intermediate filament network [6]. Most patients affected by BP have autoantibodies against the immunodominant region of BP180. Moreover, the level of IgE and IgG autoantibodies against this region can indicate the severity of disease [4]. Both autoreactive Th1 and Th2 cells are involved in the immune response [4]. Once the antibodies bind the antigens, the complement system is activated resulting in the release of proteolytic enzymes that destroy the hemidesmosomes [7]. Complement mediated destruction of the hemidesmosome is the causative factor in tense bullae formation. Mast cell and eosinophil activation also play a role in the development of these lesions [8, 9]. Once the mast cells are activated degranulation occurs, similar to that of an allergic response or graft rejection [8]. Numerous eosinophils have been found throughout the dermis of the lesions, with most of the cells being degranulated [8]. These cell changes subsequently lead to the development of pruritus.

Rheumatoid arthritis, Hashimoto thyroiditis, autoimmune thrombocytopenia, dermatomyositis, and systemic lupus erythematosus have all been linked to BP [10]. Multiple case reports have shown an association between bullous pemphigoid and malignancy. This association may be due to the age of the patient population that is primarily affected by the disease [5], or due to a paraneoplastic syndrome [11]. Epidemiological studies have shown a significant association with neurologic diseases such as multiple sclerosis, Parkinson's disease, and dementia [12].

Several pharmacologic medications are potential causative agents in BP development. These medications include DPP-4 inhibitors, furosemide, spironolactone, phenothiazine, and certain checkpoint inhibitors [1]. Patients who developed BP in association with these medications have a better prognosis and a better therapeutic response once the offending agent has been removed.

The diagnosis can be made with direct immunofluorescence performed on a biopsy of the BP skin lesion or with enzyme-linked immunosorbent assay (ELISA) detection of the anti-BP180 or BP230 antibodies. The most sensitive test for BP is direct immunofluorescence [13]. As a result of the immunofluorescence staining, the diagnosis of BP can be made when there is positive linear IgG or C3 staining along the basement membrane [1]. Common histologic findings on biopsy are eosinophilic spongiosis, subepidermal blister formation, and dermal inflammatory cell infiltrates [14].

Treatment

The main approach to the treatment of bullous pemphigoid is to promote healing of the current lesions, decrease pruritus, and prevent future blister formation. The standard treatment of BP is topical or systemic steroids [5]. High potency topical corticosteroids are preferred over systemic therapy, as they are associated with fewer side effects. Systemic glucocorticoids are used in younger patients with widespread disease, rather than localized disease.

Application of clobetasol cream 0.05% 2 times/day (10–30 g/day) is the most recommended dosage of topical steroids [1, 15]. Clobetasol use is then gradually reduced over the next 12 months. Oral prednisone 0.5–1.0 mg/kg/day can be used if systemic glucocorticoids are selected for treatment [1]. Patients are generally treated for a duration of 6–10 months unless the symptoms are refractory to corticosteroids. A maintenance phase of 10 mg/day of oral prednisone or 10 g/week of topical clobetasol is continued for 1–6 months after the patient stops experiencing disease symptoms [5].

A variety of glucocorticoid sparing agents are effective treatments for some patients with mild to severe disease. Azathioprine with a dose of 0.5–2.0 mg/kg/day is a common adjuvant therapy [1, 5]. Azathioprine's mechanism of action involves the reduction of B cell proliferation and antibody formation. Patients taking azathioprine should be monitored for myelosuppression. Mycophenolate mofetil is similarly effective to azathioprine, with a dosage of 35–45 mg/kg/day at a maximum daily dose of 2 g [1, 5]. Methotrexate 15 mg/week can be used with folic acid supplementation and side effect monitoring [1, 5]. Doxycycline's anti-inflammatory properties make it a possible adjuvant therapy at a dose of 100 mg BID [1, 5]. Tetracycline is often combined with nicotinamide to provide an alternative to systemic steroid therapy [16]. Dapsone at a dose of 100 mg/day may be used as it decreases the release of IL-8 and subsequent neutrophil chemotaxis after autoantibody activation [1, 5].

Key Points Bullous pemphigoid (BP) is an autoimmune, subepidermal, blistering disorder that is associated with pruritus and tense bullae formation in elderly individuals.

- The bullous stage of disease is typically characterized by up to hundreds of vesicles and tense bullae on an erythematous base localized to the abdomen, trunk, and proximal extremities.
- The diagnosis can be made with direct immunofluorescence performed on a biopsy of the BP skin lesion or with ELISA detection of the anti-BP180 or BP230 antibodies.
- The standard treatment of BP is topical high potency or systemic steroids with the possible addition of adjuvant therapy.

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Chapter 3
20-Year-Old Female with Diffuse Itchy, Scaly Skin

Erica Haught, Austin Cusick, and Shannon C. Trotter

A 20-year-old female presented with itchy, scaly patches, and plaques of 3 years duration. She reported having sensitive and dry skin since she was an infant. She tried over the counter emollients and topical steroids for treatment but with little control over her symptoms or the frequency of flares. The patient also reported seasonal allergies and a family history of asthma. She saw an allergist and tested positive for an allergy to tree nuts, pollen, and grass.

On physical examination, there were several scaly, lichenified patches and plaques, most notably in the popliteal and antecubital fossa. Her skin was dry overall, and she had hyperlinear palms (Fig. 3.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Atopic dermatitis
2. Psoriasis
3. Viral exanthem
4. Irritant contact dermatitis

Diagnosis

Atopic dermatitis.

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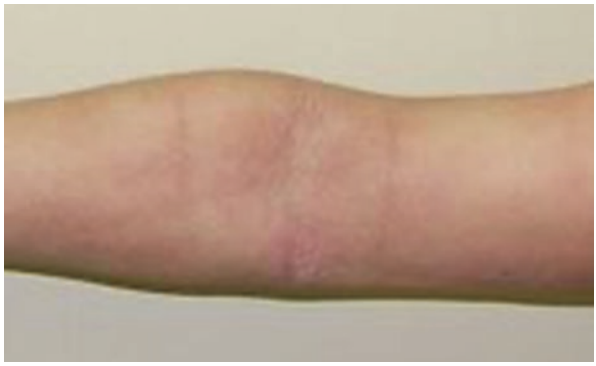

Fig. 3.1 Scaly lichenified plaques in the antecubital fossa. Courtesy of Dr. Matthew Zirwas

Discussion

Atopic dermatitis, or eczema, is a chronic relapsing inflammatory cutaneous disease associated with pruritic, dry skin. It affects 11–15% of children [1, 2]. Atopic dermatitis usually has an onset before 5 years with approximately half affected still having the disease in adulthood [3, 4].

Clinical presentation can vary depending on the type and age of the patient. In acute atopic dermatitis, there are pruritic, erythematous vesicles, and papules [5]. Subacute and chronic lesions are dry, scaly, erythematous papules. Lichenification often follows with long-standing scratching of the lesions. Infants up to 2 years old have pruritic scales on the cheeks, scalp, and extensor surfaces [5]. Children, adolescents, and adults often present with plaques in flexure regions with adults having more localized lesions. Different clinical variants of atopic dermatitis include nummular, follicular type, prurigo nodularis-type, atopic cheilitis, atopic hand, and eyelid eczema [6, 7].

Atopic dermatitis is often associated with a personal or family history of atopy, history of asthma [8], a history of allergic rhinitis [9], a genetic predisposition to sensitive IgE production following allergen exposure, or a loss of function mutations in the filaggrin protein or related pathway [10]. Patients have increased epidermal water loss [11] from abnormalities in the tight junctions of the stratum granulosum [12] and decreased proteins such as filaggrin, desmoglein, and others that play an important role in epidermal barrier function [13]. The innate immune response, which partly consists of antigen-presenting cells, uses toll-like receptors (TLRs) that recognize molecules of microbes which leads to the release of inflammatory mediators and dendritic cell maturation. Patients with atopic dermatitis have been found to have reduced TLR2 and TLR9 [14, 15], leading to defects in the innate immune response and increased inflammation. Another theory of pathogenesis is patients with atopic dermatitis have an enhanced Th2 type adaptive immune response which leads to suppression of terminal keratinocyte differentiation genes, increasing epidermal hyperplasia [16]. Atopic dermatitis skin lesion pathophysiology is associated with Th2, Th22, and Th17 cell activation. Th2 cells activate IL-4,

IL-13, and IL-21. Th22 and Th17 cells activate IL-22 and IL-17, respectively. Th2 and Th22 cytokines suppress the expression of genes relating to proteins such as loricrin, involucrin, and filaggrin [17]. Suppression of these genes results in disruption of the epidermal barrier, allowing allergen or microbial invasion. Th2 cytokines also inhibit the production of antimicrobial peptides (AMPs) which are necessary to activate the innate immune response. Th17 and Th22 cytokines both have a role in upregulating S100A genes that encode epidermal differentiation complex clusters that promote increased expression of pro-inflammatory response [18]. Th22 cytokines are also involved in induction of epidermal hyperplasia [19]. Pruritus in atopic dermatitis is specifically associated with IL-31 as well as the previous cytokines mentioned [9]. While the exact mechanism of IL-31 is unknown, this cytokine in the Th2 cascade demonstrated pruritus, alopecia, and dermatitis representative of atopic dermatitis in murine models. Furthermore, IL-31 has been linked to airway hypersensitivity in mouse models. This infantile research helps further describe atopic dermatitis and its associated diseases [9]. An overview of the T-helper cells, cytokines, and downstream effects can be found in Fig. 3.2.

With respect to atopic dermatitis, the mechanism of pruritus is complex with various factors. In the periphery, unmyelinated C-fibers located in the epidermis and dermis are considered the predominant culprits [20]. Pruritic pathways can be

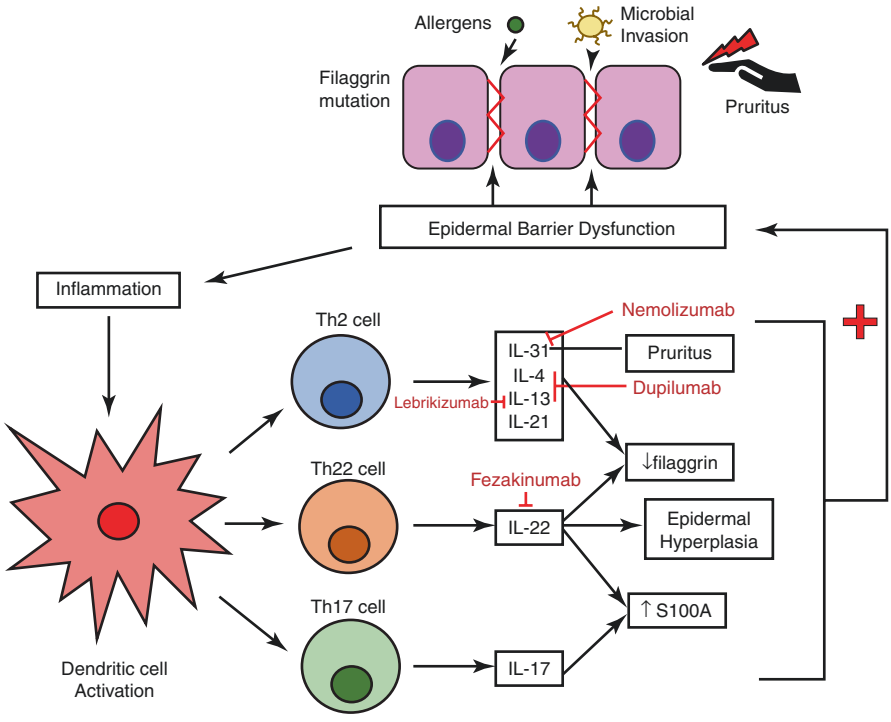

Fig. 3.2 AD pathological mechanism and treatment targets [9, 14–19]

separated based on histamine dependence; however, significant overlaps between pathways are evident. For example, several pathways use transient receptor potential channels (TRP) V1 and A1 [20]. Furthermore, increased skin innervation is present in atopic dermatitis models which can be related to increased pruritic sensation. Pruritogens linked to the disease include proteases, histamine, endothelin-1, thymic stromal lymphopoietin, and, previously mentioned, IL-31 [20].

Several scoring methods are available to help determine the severity of disease and determine the effectiveness of treatment. One scoring system that does both is the Patient Oriented-Scoring of Atopic dermatitis (PO-SCORAD). This new scoring system was designed from the SCORAD system created prior. Both methods assess the severity of disease by determining the area of disease, intensity (based on secondary characteristics), and subjective symptoms. PO-SCORAD allows for the evaluation of the disease across its waxing and waning pattern [21]. The PO-SCORAD was able to assess the severity of atopic dermatitis to the same degree as SCORAD. With this patient self-reporting of disease, the physician can also isolate the entire waxing and waning nature of the disease. Furthermore, the daily investigation of symptoms can help correlate the success of treatment [21].

Treatment

Management of atopic dermatitis depends on whether the disease is mild, moderate, or severe. In any form of the disease, one should eliminate exacerbating factors such as overheating the skin, excessive bathing without moisturizer, low-humidity environments, stress, aggravating detergents, etc. [22]. Patients should maintain skin hydration by applying emollients twice a day and after bathing. Thick creams and ointments may better relieve xerosis compared to lotions. Anti-itch ingredients in moisturizers typically include menthol camphor and pramoxine. In severe disease, wet dressings may aid in the relief of pruritus.

There are many topical medications approved for atopic dermatitis and the pruritus associated with the disease. Topical corticosteroids can be used to treat atopic dermatitis, with low potency in mild disease and medium to high potency in moderate disease. High potency corticosteroids can be used for flare-ups but should be limited due to potential side effects [23]. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are Food and Drug Administration (FDA) approved for use in 2 years and older and do not have the adverse effects of steroids such as skin thinning [23]. They are used as second-line and similar in strength to medium-potency steroids. Of note, topical calcineurin inhibitors classically carry a black box warning for increased risk of lymphoproliferative malignancy in animal investigation [24]. However, recent investigation has found no clinical evidence suggesting malignancy development in children using tacrolimus in atopic dermatitis [25]. Crisaborole, a phosphodiesterase four inhibitor, is FDA-approved for mild to moderate disease in 3 months of age and older [26]. Topical doxepin, a tricyclic antidepressant with antihistamine properties is another second-line option [27]. Older children, adolescents, and adults can be treated with phototherapy utilizing

ultraviolet B or ultraviolet A1; however, this is often reserved for moderate to severe disease refractory to oral therapy. Phototherapy can reduce histamine release from basophils and mast cells limiting disease and pruritus [28].

The use of systemic agents may play a role in further management of atopic dermatitis and the following sequelae. In moderate to severe disease, systemic immunomodulators such as oral cyclosporine can be used short term for atopic dermatitis. Although there is limited, high-quality evidence for methotrexate used to treat atopic dermatitis, it is an option for long-term treatment in moderate to severe disease [29]. Azathioprine and mycophenolate are second-line agents for long-term use in moderate to severe atopic dermatitis. Dupilumab is a humanized monoclonal antibody IgG4 that binds to the IL-4 receptor and therefore blocks signals from IL-4 and IL-13. It is approved for use in moderate to severe atopic dermatitis for patients 6 years of age and older who failed treatment with the other systemic immunomodulators [30]. By blocking the actions of IL-4 and IL-13, the Th2 response is decreased. The results of blocking IL-4 and IL-13 include increased expression of filaggrin, loricrin, and involucrin which are proteins involved in the integrity of the epidermal barrier [17]. With cytokine blockade, AMP production will be increased, resulting in a more robust innate immune response. The expression of terminal differentiation products in keratinocytes will be increased. With inhibition of IL-13, epidermal changes include a decrease in spongiosis and an increase in lipid synthesis which is important for stratum corneum structure [15]. Oral H1 antihistamines are effective at reducing pruritus. Due to the sedative effects of H1 antihistamines, they may also help with disruption of sleep due to itching. [31]. Investigation of non-sedating antihistamines, like fexofenadine, has also shown efficacy in atopic dermatitis pruritus [20].

Experimental treatments for atopic dermatitis include oral and topical Janus kinase (JAK) inhibitors such as tofacitinib and baricitinib [32]. Their cytokine signaling blocking abilities treat inflammation associated with plaque psoriasis. Nemolizumab, an anti-IL-31 monoclonal antibody has been studied because of IL-31's role in chronic inflammation [33]. Lebrikizumab, an anti-IL-13 monoclonal antibody, has been studied with suggestions that combination therapy with topical steroids may be efficacious [34]. Further, a clinical trial studying fezakinumab, an IL-22 antibody, showed a decrease in SCORAD from baseline when compared to placebo [35].

Key Points

- Atopic dermatitis is an inflammatory skin disease associated with pruritus, dry skin, asthma, and allergic rhinitis.
- The pathogenesis of atopic dermatitis includes abnormalities in the epidermal barrier function and immune system. Most notably, dysfunction in the filaggrin-protein and increased Th2 response is implicated.
- Management of atopic dermatitis should be titrated to the disease clinical presentation and impact on patient quality of life.
- Topical treatments for atopic dermatitis include corticosteroids, calcineurin inhibitors, crisaborole, and doxepin.
- Systemic treatments include antihistamines and immunomodulators such as cyclosporine, methotrexate, and dupilumab for severe refractory disease.

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Chapter 4
33-Year-Old Male with Itchy, Erythematous Papules on His Trunk

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A 33-year-old male presented with itchy, crusted erythematous papules and plaques on his trunk, extremities, and groin of 4 months duration. He reported intense itching, especially at night. He was treated with oral and topical steroids with little improvement.

On physical examination, there were multiple pink, crusted papules on the trunk and extremities. The lesions concentrated around the umbilicus and waistband. Evaluation of the genitalia showed several erythematous nodules on the scrotum. There were linear scaly plaques in between the fingers (Fig. 4.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Scabies
2. Seborrheic dermatitis
3. Grover's disease
4. Atopic dermatitis

Diagnosis

Scabies.

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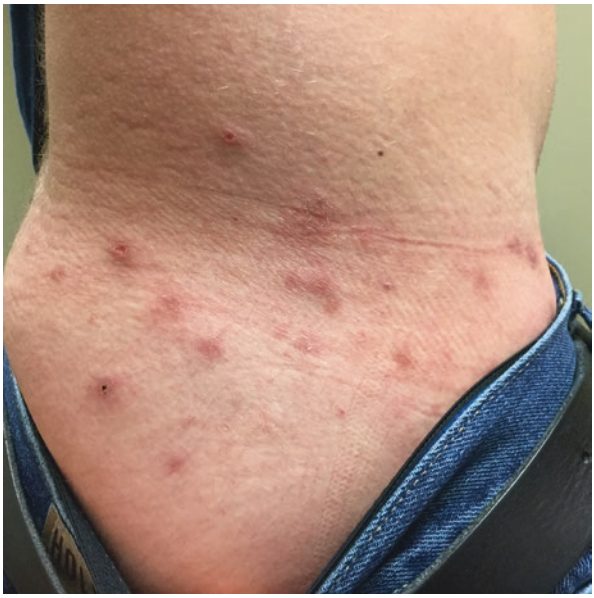

Fig. 4.1 Crusted erythematous papules on the patient's right flank

Discussion

Scabies is a skin infestation of the obligate parasitic mite *Sarcoptes scabiei*, which is described as an eight-legged brown-white mite [1, 2].The female mite embeds herself within the epidermis, specifically the stratum corneum, where she lives out her life cycle and lays eggs, propagating the infestation [2, 3]. These mites can only survive off their host for approximately 24–36 hours or potentially longer if in a humid environment [1]. The transmission of scabies occurs from direct, prolonged skin-to-skin contact with an infected person. While fomite transmission is very uncommon, it is more likely to occur in cases of crusted scabies where the parasitic load is much higher [1]. In those with crusted scabies, living mites have been found in dust particles on flooring and furniture [4].

From an epidemiological standpoint, scabies occurs worldwide affecting around 100 million people in both high and low-income countries; however, it is more common in regions such as Latin America as well as tropical areas such as East Asia, Southeast Asia, South Asia, and Oceania [1, 2]. Outbreaks of scabies can easily occur in circumstances such as overcrowded living areas including institutional settings, long-term care facilities, and prisons. In resource-poor areas, infestation occurs in homeless populations or amongst natural disaster victims [1, 2].

Classic scabies presents with severe pruritus, often worse in the evenings, and begins 3–6 weeks after initial infestation or 1–3 days if previously infested. This pruritus is a delayed-type of hypersensitivity reaction resulting from the mites themselves, their eggs, or their feces [1]. As the females dig into the skin, they create burrows that are described as slightly raised, ranging from silver-grey to

white-brown lesions presented as thin thread-like lines. The entrance of the mites into the skin can become V-shaped, described as the wake sign [3]. Due to the pruritic nature of scabies, the burrows may not be visible due to excoriation or superimposed secondary infection [1]. Scabeitic lesions often present as numerous small, erythematous papules that are typically excoriated [1]. Areas of the integument that are commonly infected include webbing and sides of fingers, flexor wrist surface, extensor surface of elbow, axillary folds, periumbilical, waist, male genitalia, female areolas, buttocks, posterior thighs, and the lateral, posterior feet surfaces [1, 5]. It should be noted that scabies infestations spare the head, except in cases of children. Children are also more likely to have lesions on their palms, soles, and all aspects of their fingers. Children may have a more inflammatory reaction than adults and present with lesions more vesicular, pustular or bullous in appearance [1].

Nodular scabies is a less common manifestation of classic scabies, presenting with firm, persistent dome-shaped papules that are erythematous and incredibly pruritic. These papules are typically 5–6 mm in size and can be found in the groin, buttocks, genitalia, and axillary folds [1].

Crusted scabies-also referred to as Norwegian scabies, scabies crustosa, Boeck scabies, keratotic scabies, or surrepticus scabies is considered to be non-classic scabies resulting in hyperkeratotic plaques or scales very high in parasitic number [1, 5]. It is a very highly contagious form of scabies due to its high parasitic load, and it often requires a combination of topical and systemic scabicidal treatment [5]. Crusted scabies are more commonly seen in those who are immunocompromised, specifically those with an impaired cellular immunity such as in AIDS, leprosy, lymphoma, older adults, Down's syndrome, or even long term topical corticosteroid use [1]. This non-classic type of scabies can present with minimal to no pruritus. If left untreated, however, the infestation can quickly spread to the entire integument. Crusted scabies can also present with thickened, discolored nails. Laboratory analysis will demonstrate eosinophilia and increased levels of immunoglobulin E (IgE) [1].

Diagnosis of scabies is categorized into three levels by the International Alliance for the Control of Scabies (IACS): confirmed (A), clinical (B), and suspected (C) [3]. The IACS criteria for diagnosing scabies gives several suggestions for visualizing the mites, eggs, or feces to confirm the diagnosis. This can be done by using dermoscopy, high powered devices that directly visualize the skin such as optical coherence tomography, reflectance confocal microscopy/video dermoscopy, or light microscopy of skin scrapings. Skin scrapings are typically acquired using viscous liquids such as mineral oil to ensure sample effectiveness [3, 5]. Scabies is misdiagnosed in as many as 45% of the cases, which demonstrates the need for improved clinical education, diagnostic methods, and availability [6].

Complications from scabies are typically due to secondary bacterial infections that occur, such as from streptococcal or staphylococcal species. These infections can result in impetigo, abscesses, cellulitis, sepsis, rheumatic fever, post-streptococcal glomerulonephritis, ecthyma, furunculosis, and paronychia [1, 2]. There have been cases in scabies related to *Staphylococcus aureus* bacteremia causing high mortality in indigenous Australian populations [7].

Treatment

Traditional treatment of classic scabies relies heavily on topical scabicides, although the compliance is typically low. Treatment of scabies using topical agents can be especially difficult in children, who often require application over their scalp, face, ears, and neck [4]. There are several topical options for the treatment of scabies outlined below:

- Permethrin 5% Cream—This is a scabicidal and ovicidal agent that disrupts the voltage-gated sodium channels of arthropods which results in disrupted neurotransmission in the mites. It is also a synthetic pyrethroid agent. This medicated cream should only be used in those older than 2 months of age, as there are potential neurological complications [4]. It is safe for use in pregnancy [5].
- Crotamiton 10% cream or lotion—this medication is safe for infants but requires multiple applications. It is also safe to use in pregnancy [5].
- Lindane (gamma benzene hexachloride) 1%—This medication is the second line for topical treatment in many developed countries. It has a more systemic absorption than permethrin and crotamiton, but it has more adverse reactions reported such as aplastic anemia and seizures. It is not recommended for children younger than 3 years old [4].
- Ivermectin 1%—This medication is scabicidal but is not ovicidal. It is not recommended for use in those younger than 6 months old [4]. Some research suggests that topical ivermectin may result in lower rates of post-scabies itch compared to the use of oral ivermectin; however, there is no difference in their clinical effectiveness if used as directed [8].
- Benzyl benzoate 25% Lotion—This medication also has the possibility of neurologic complications and should be diluted to 12.5% in children and 6.25% in infants. However, dilution of the lotion also decreases its efficacy. It is not recommended to use this medicated lotion in those younger than 2 years old [4]. This medication preparation is not available in North America [5].
- Malathion 0.5%—This acts as a cholinesterase inhibitor. It should not be used in infants younger than 6 months old [4].

Novel topical treatments have been proposed for use, including tea tree oil, which is a known antimicrobial that has shown scabicidal properties, eugenol compounds, TOTO soap, and Lippie oil [2, 4].

Systemic treatments can be used as well. There is one commonly prescribed oral medication for scabies, but there are several others that have the potential for use based on case studies. The most commonly used medication is ivermectin. As previously mentioned, ivermectin is scabicidal but not ovicidal. It is also a substrate for the cytochrome CP450 3A4 pathway and use should be cautioned in those taking other medications that interact with CP450 [4]. Ivermectin works by disrupting the ligand-gated chloride channels, leaving them permanently open. Ivermectin should

be used with caution in children less than 15 kg [4]. Other oral medications to consider are albendazole which acts by inhibiting the polymerization of tubulin and inhibiting microtubule glucose uptake, resulting in parasitic death. There are currently no studies on albendazole's effectiveness or safety in scabies for children [4]. Other novel systemic treatments include moxidectin which is very similar to ivermectin but has a longer half-life. Isooxazolines (afoxolaner, fluralaner) may also be beneficial for treating scabies, but the FDA cautions use for risk of neurotoxicity [2].

Treatment failure has been seen in up to one-third of cases. Some proposed risk factors for treatment failure include a lengthy duration of symptoms longer than 1 month before treatment, additional cases of scabies in the family or household, and the use of childcare [9].

Pruritus and rash may persist for up to 2–4 weeks even after successful treatment. Treatment of postscabietic itch can be accomplished with non-sedating antihistamines in the morning followed by sedating antihistamines in the evening or before bed. Systemic or topical corticosteroids may also be used for pruritus [5]. If the symptoms of pruritus and rash persist for longer than 4–6 weeks after treatment completion, consider allergic or irritant dermatitis from topical treatment, inadequate treatment, incorrect initial diagnosis, reinfestation, or delusion of parasitosis [5].

Successful treatment will not be obtained without thorough cleaning measures and the simultaneous treatment of the family or household members. It is recommended to wash all linens and clothing in hot water of at least 60 °C and drying them in a hot dryer [4, 6]. Things that are unable to be washed such as throw pillows or toys should be tightly sealed in a plastic bag for 1 week [6]. Clinicians should be on the lookout for any secondary bacterial infections that may arise and treat them accordingly [4].

Key Points

- Scabies occurs worldwide but in developed countries is seen in resource-poor areas or institutionalized living situations such as long term care facilities and prisons.
- Scabies presents with severe pruritus in the evening, accompanied by skin lesions such as burrows or papules likely in the presence of excoriation.
- Areas of the integument that are commonly infected include: webbing and sides of fingers, flexor wrist surface, extensor surface of elbow, axillary folds, periumbilical, waist, male genitalia, female areolas, buttocks, posterior thighs, and the lateral, posterior feet surfaces Scabies spares the head except in children.
- Scabies can be treated with topical or systemic agents, or even the combination of both to treat the high mite burden in crusted scabies. Ivermectin and permethrin are the most prescribed medications.
- Postscabietic itch can persist for 2–4 weeks after successful treatment. Treatment options include antihistamine agents and possibly topical steroids.

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Chapter 5
55-Year-Old Female with Itchy, Erythematous, Scaly Plaques on the Trunk

Mara Leyendecker, Pankaj Bansal, Austin Cusick, and Shannon C. Trotter

A 55-year-old female presented with itchy, erythematous scaly plaques on her trunk for 10 years duration. She had been treated previously with topical steroids and phototherapy with some improvement of her skin, but little impact on her itching. She also reported morning stiffness in her wrists and ankles. The patient also reported occasional episodes where her fingers became red and swollen.

On physical examination, there were multiple erythematous scaly plaques on the trunk and extremities. Fingernails demonstrated pitting and oil spots. Evaluation of her fingers revealed no edema or erythema (Fig. 5.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Psoriasis
2. Atopic dermatitis
3. Discoid lupus
4. Seborrheic dermatitis

Diagnosis

Psoriasis.

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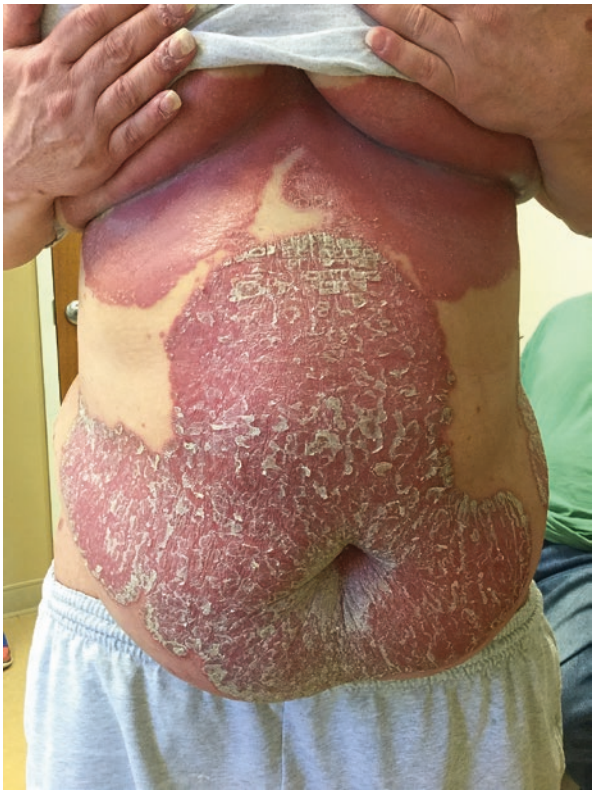

Fig. 5.1 Erythematous scaly plaques on the patient's trunk

Discussion

Psoriasis is an autoimmune disease that can have both skin and joint manifestations. There is approximately a 2% prevalence of this disease worldwide with the biggest percentage of individuals affected being Caucasian [1]. Several different subtypes of psoriasis have been identified each with differing presentations and severity. Psoriasis vulgaris is the classical form of psoriasis and occurs in most cases. It presents as a plaque-type, pruritic rash with silvery scales that can commonly appear on the trunk, extensor surfaces, and scalp [1]. Other subtypes of psoriasis include guttate psoriasis which is common after certain infections, including streptococcal infections, and pustular psoriasis, which presents with either localized or generalized pustules [1]. There is a strong genetic predisposition in individuals who are diagnosed with psoriasis especially in those with first degree relatives who also have the disease [2]. Specifically, an association between psoriasis and the human leukocyte antigen (HLA)-B27 gene has been demonstrated indicating further the role of genetic predisposition in disease development. Besides genetic predisposition, other risk factors include stress/anxiety, environmental factors, and certain drugs. Drugs commonly described as exacerbating include

beta-blockers, lithium, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors [3]. Furthermore, infections, smoking, alcohol consumption, and comorbid conditions like hypertension, diabetes, and metabolic syndrome are aggravating factors [3]. Patients with psoriasis are also at an increased risk of developing other medical conditions including non-alcoholic steatohepatitis and irritable bowel disease [1].

Initially, activation of antigen presenting cells (APCs) begin the cascade. Once a specific trigger occurs, T-cells, specifically Th17 cells, infiltrate the epidermis resulting in immune system activation. As a result, cytokines become activated including tumor necrosis factor-α (TNF-α), interleukins (IL), and interferon-gamma (IFN-γ), causing further skin damage [4]. IL-17 is a specific type of interleukin which has been shown to become expressed upon Th17 activation [5]. For this reason, treatments for psoriasis have been targeted at the immune system to decrease inflammation and skin lesions. Ultimately, dendritic cell activation can directly stimulate keratinocytes through TNF-α (Fig. 5.2). In addition, dendritic cells secrete IL-23 which, in turn, activates Th17 cells. These cells secrete IL-17, also stimulating keratinocytes. Keratinocyte activation causes significant pathology through epidermal hyperplasia and further immune cell recruitment [6].

Diagnosis of skin psoriasis can often be made through clinical exam alone. The psoriasis area and severity index (PASI) scoring can be used to create a baseline severity level and be used to monitor treatment success [7]. PASI scoring includes several factors of disease like intensity and area of involvement. Questions involving intensity will work to ascertain lesion erythema, induration, and desquamation [7]. Dermatology Life Quality Index (DLQI) may also be used in conjunction with PASI to holistically evaluate patient disease. Psoriasis often adversely affects a patient's quality of life yielding psychological distress over time. Sufficient treatment of disease evident by decreasing PASI will show resolving DLQI scoring and improvement in quality of life [8].

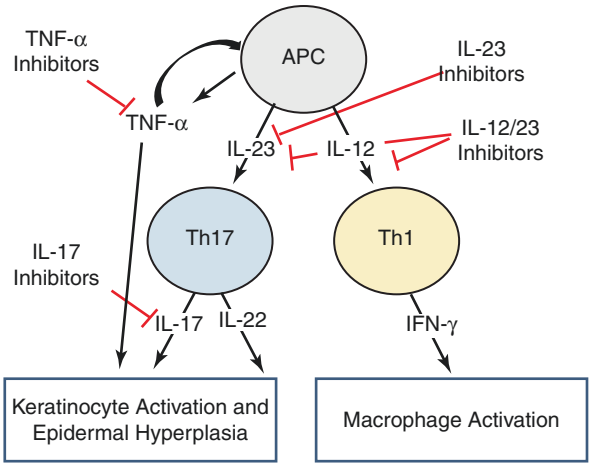

Fig. 5.2 Key cytokines and treatments in psoriasis pathogenesis [6]

If the diagnosis is difficult to ascertain clinically, a biopsy can be performed in search of classic, psoriatic, histopathological findings. Early microscopic findings are consistent with edema, blood vessel dilatation, and lymphocytic infiltrate. Then epidermal anomalies are evident with granular layer loss, epidermal thickening, and parakeratosis. More advanced disease will demonstrate acanthosis, rete ridge elongation, and mitotic activity. Additionally, neutrophils traverse the epidermis, congregating in the corneal layer as microabscesses. Further staining for components specific to certain immune cells can isolate the exact infiltrating units [9].

About 15–40% of patients with psoriasis can develop psoriatic arthritis (PsA), presenting with chronic polyarticular inflammatory arthritis. It can be associated with enthesitis, dactylitis, and sacroiliitis. Nail involvement in psoriasis is a risk factor for the development of psoriatic arthritis, especially DIP joint involvement. Joint disease activity is synchronous with skin disease activity in about 30–40% of the cases with both skin psoriasis and psoriatic arthritis. If untreated, psoriatic arthritis can lead to joint erosions, destruction/osteolysis (arthritis mutilans), and ankylosis [10].

Pruritus in psoriasis is specifically thought to be due to neurogenic mechanisms through the release of neuropeptides from the dermal nerve cells [11]. Recent studies have shown that pruritus is one of the most bothersome symptoms associated with psoriasis and that more than 90% of individuals diagnosed will experience this symptom [11]. Stress has also been shown to play a role in the pruritus pathway. Mental preoccupation with pruritus creates a chain reaction that results in itching and worsening of the lesions. Therefore, controlling pruritus and stress is important for psoriasis management.

Treatment

First-line treatments for individuals with limited cutaneous involvement typically include topical agents such as corticosteroids, retinoids, vitamin D analogs, and tacrolimus [12]. These treatments are considered first-line as the side effects are less severe and they do not involve systemic down regulation of the immune system. Topicals are limited by patient compliance and are not feasible options for the patient with moderate to severe cutaneous disease or psoriatic arthritis.

In more widespread cases, medications that target the immune mechanisms of psoriasis including disease-modifying anti-rheumatic drugs (DMARDS), phototherapy, TNF-α inhibitors, IL-17 inhibitors, and IL-23 inhibitors can be used. DMARDs such as methotrexate and cyclosporine have also been used in the treatment of cutaneous psoriasis. Cyclosporine is indicated for the treatment of adult, nonimmunocompromised patients with severe (i.e., extensive and/or disabling), recalcitrant, plaque psoriasis who have failed to respond to at least one systemic therapy [12]. Methotrexate is also approved to treat cutaneous psoriasis, but its use is limited due to its side effects, which include gastrointestinal (GI) upset, increased risk of infection, increased risk of lymphoproliferative disorders, and increased risk

of hepatotoxicity. It is also important to consider supplementing patients with folate when starting methotrexate to avoid the development of macrocytic anemia while also monitoring for further hematologic compromise, decrease in liver function, or myelosuppression [12].

Another treatment option that has been used for the skin manifestations of psoriasis includes phototherapy. The mechanism of phototherapy works through stimulating apoptosis of pathogenic T-cells and keratinocytes thus decreasing inflammation. Narrow-band UV has been used first-line for psoriasis and in combination with biologics for severe cases [13]. Secondly, psoralen ultraviolet A (PUVA) is a type of UV therapy that utilizes both psoralen, a photosensitizing agent, with UV therapy [13]. A psoralen is given systemically or topically and is used to allow UV therapy to penetrate the skin and exert cytotoxic effects [12]. Phototherapy is typically used for widespread skin lesions, for areas that may be hard to treat topically, or for patients where other medications may be contraindicated [12]. Although this is an effective treatment, the risk of skin cancer from UV radiation should be discussed with the patient before starting this treatment.

TNF-α inhibitors are effective for both skin and joint manifestations that can occur in psoriatic disease. They act through neutralizing TNF-α, further inhibiting cytokine formation, and skin inflammation [1]. There are several different drugs in this category that have been utilized for the treatment of psoriasis including etanercept, infliximab, adalimumab, and certolizumab [12]. Side effects of these medications occur rarely and can include injection site reactions and infections [14]. In rare cases, TNF-α inhibitors have been shown to cause a paradoxical psoriasis rash; this side effect should be monitored for in patients who may have worsening disease on this medication [15]. Certolizumab and golimumab are often used for psoriatic arthritis as well. Of note, patients must be screened for tuberculosis. Other baseline labs often include hepatitis screening and HIV testing [16]. There is no consensus on routine lab monitoring and testing may vary based on patient demographics and risk for co-morbidities.

Another class of biologics includes IL-17 inhibitors which are used to treat psoriasis and psoriatic arthritis. Secukinumab targets IL-17A and is approved to treat both psoriasis and psoriatic arthritis. In phase III clinical trials ERASURE and FIXTURE, significant improvements were demonstrated across the 52-week testing period in moderate to severe plaque psoriasis [5]. The FIXTURE study evaluated 300 and 150 mg of secukinumab against entanercept and placebo. Significant responses in therapy were found at 62.5% of patients with 300 mg therapy, 51.2% in 150 mg therapy, 27.2% with etanercept, and 2.8% with placebo. There is a wide range of side effects associated with this drug which commonly include nasopharyngitis, GI upset, headache, and fatigue [5]. Ixekizumab is an IL-17A inhibitor that has been used for the skin manifestations of psoriasis and was approved by the FDA in 2016 [12]. This approval comes following the results of the UNCOVER trials which investigated this drug's effectiveness in patients with moderate to severe plaque psoriasis [12]. The UNCOVER-2 and UNCOVER-3 trials specifically demonstrated this drug's effectiveness and superiority in psoriasis after 12 weeks when compared to both placebo and etanercept control groups [17]. Ixekizumab was

approved for psoriatic arthritis in 2017. A more recent investigation has demonstrated the superiority of ixekizumab in DMARD refractory skin and joint disease when compared to adalimumab [18]. Brodalumab is another monoclonal antibody specifically blocking the IL-17 receptor inhibiting downstream activity. Adverse events to be cognizant of include increased potential for infections, mild neutropenia, suicidal ideations, and injection site hypersensitivity [19]. AMAGINE 2 and AMAGINE 3 phase III clinical trials evaluated brodalumab in comparison to ustekinumab and placebo in plaque psoriasis. Ultimately, in both trials, high dose brodalumab demonstrated the best results in comparison. The difference in efficacy can be attributed to difference in mechansims. Secukinumab and ixekizumab both block IL-17A itself while brodalumab blocks the IL-17 receptor A [5].

Another cytokine in the Th2-cell cascade is IL-23. Recent investigation of this cytokine has strongly implicated it to both psoriasis and PsA disease. Monoclonal medications targeting this modulator include ustekinumab, guselkumab, tildrakizumab, and risankizumab [20]. Ustekinumab also has dual action with blockade of IL-12. Lastly, inhibition of phosphodiesterase four can successfully limit inflammatory cytokine production of IL-23 and TNF-α. Apremilast targets this enzyme becoming efficacious in treating psoriasis and PsA with less significant side effects like GI upset and depression [21]. Other agents used specifically for the treatment of psoriatic arthritis include tofacitinib, a Janus kinase inhibitor, and abatacept, an APC interaction inhibitor. It is important to note that treatment of psoriatic arthritis should take precedence over the treatment of skin manifestations of the disease due to its destructive nature (Fig. 5.3).

It is also important to consider lifestyle factors and comorbid conditions when treating individuals with psoriasis. Smoking, alcohol use, and obesity are factors that may contribute to worsening symptoms and should be discussed with patients [3]. Comorbid conditions should also be properly managed as treating the underlying condition may help with psoriasis symptoms. For example, psoriasis lesions can result in stress and anxiety for patients which may further perpetuate the disease manifestations. Treating and easing a patient's anxiety may help mediate symptoms and outbreaks. Also, weight loss in obese individuals has been independently associated with a significant reduction in psoriatic arthritis activity. Lastly, before starting medications that will alter the immune system, it is important to consider adverse effects, drug-drug interactions, and contraindications to these medications to avoid undesirable outcomes.

There is no specific therapy that is used to combat pruritus associated with psoriasis; however, data has demonstrated that medications used to treat the outbreaks associated with psoriasis are effective in decreasing pruritus [23]. A meta-analysis that was performed to determine the effectiveness of various psoriasis treatments on pruritus demonstrated decreased itch scores with several medications that are utilized to decrease psoriatic lesions [23]. Treatments that showed decreased itch scores when compared to placebo include phototherapy, etanercept, infliximab, ixekizumab, and several others [23]. This demonstrates the importance of patient compliance and choosing the proper treatment option to not only decrease lesion size and outbreaks but also to help eliminate the itch associated with them.

Treatments of Psoriasis	
Treatment	
TNF-α inhibitors	
	Etanercept
	Infliximab
	Adalimumab
	Certolizumab
IL-17 inhibitors	
	Secukinumab
	Ixekizumab
	Brodalumab
IL-23 inhibitors	
	Guselkumab
	Tildrakizumab
	Risankizumab
IL-23/IL-12 inhibitors	
	Ustekinumab
PDE4 inhibitors	
	Apremilast
JAK inhibitors	
	Tofacitinib
APC Interaction Inhibitor	
	Abatacept
DMARDS	
	Methotrexate
	Cyclosporine
	Sulfasalazine
Topicals	
	Corticosteroids
	Vitamin D analogs
	Retinoids
Phototherapy	
	PUVA
	Narrow-band UV

Fig. 5.3 List of medications classified by mechanism or mode of delivery [22]

Key Points

- Psoriasis is an autoimmune disease that is characterized by pruritic plaques with silvery scale occurring on the scalp, trunk, and extensor surfaces.
- Treatment of psoriasis varies depending on BSA, quality of life scores and co-existence of psoriatic arthritis.
- It is important to consider comorbid conditions when treating individuals with psoriasis, as well as discussing other risk factors they may have.
- Studies have demonstrated that in nearly all patients with a diagnosis of psoriasis there is associated pruritus caused by neurogenic mechanisms in the dermis.
- There is no specific treatment for pruritus associated with psoriasis; however, medications used to decrease lesions have shown effectiveness in decreasing itch.

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Chapter 6
40-Year-Old Female with Itchy, Erythematous Papules and Nodules on the Trunk and Extremities

Rosemary Oaks, Austin Cusick, and Shannon C. Trotter

A 40-year-old female presented with itchy, erythematous papules and nodules on the trunk and upper extremities. Several were excoriated and some were bleeding. She reported a history of atopic dermatitis as a child but stated she outgrew it over time. She was treated with antihistamines and topical steroids in the past with little improvement.

On physical examination, there were multiple, grouped erythematous and pink papules and nodules, with hemorrhagic crust. Some even appeared verrucous in nature. The lesions were more concentrated on the upper arms, back, and neck. Notably, there was sparing where the patient could not reach to scratch. A biopsy showed thick, compact orthohyperkeratosis with pseudoepitheliomatous hyperplasia and a superficial perivascular lymphocytic infiltrate (Fig. 6.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Perforating disorder
2. Persistent bug bites
3. Prurigo nodularis
4. Multiple cutaneous squamous cell carcinomas

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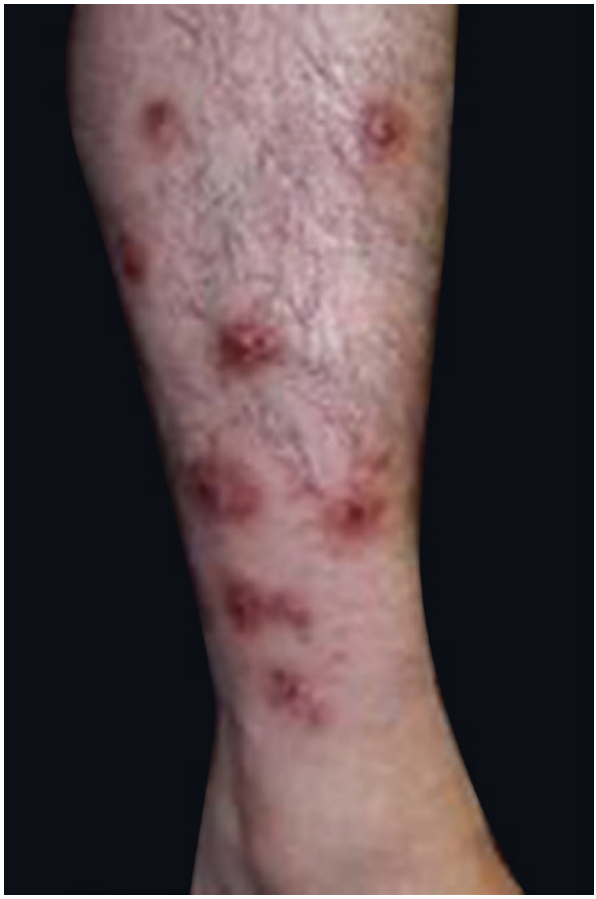

Fig. 6.1 Image of classic Prurigo Nodularis. Courtesy of Dr. Matthew Zirwas

Diagnosis

Prurigo Nodularis.

Discussion

Prurigo nodularis (PN) is a chronic, pruritic, papulonodular eruption the etiology of which is unknown. PN treatment is frustrating to both patients and medical providers. PN is rare, and thus robust information about its incidence and prevalence is lacking. Based on observational studies, PN primarily affects older individuals, African Americans, and those with atopic dermatitis [1]. It is unknown whether PN is a primary dermatologic condition or secondary to other conditions, but it frequently co-occurs with other diseases.

The characteristic skin lesion of PN is a firm, extremely pruritic, hyperkeratotic nodule which can range widely in size. Lesions from just a few millimeters up to 2 cm have been described. The lesions present symmetrically in a linear distribution on the extensor surfaces of the body. Lesions classically do not affect the face or hands but have been found on all body surfaces ranging in color and number [2].

The disease is associated with other medical conditions, but the mechanisms by which these diseases are connected is unknown. Associated conditions include focal causes of pruritus like insect bites as well as diffuse causes of pruritus such as psychological disorders, hyperthyroidism, hematologic disorders, renal failure, various gastrointestinal disorders, infectious diseases, etc. [2]. Intense itching generally precedes the development of PN lesions. For that reason, one of the dermatoses most frequently associated with PN is atopic dermatitis. Atopic PN is more commonly seen in children and presents earlier in life [3]. Another frequently described association is that of PN and chronic kidney disease (CKD). Large numbers of CKD patients receiving hemodialysis experience pruritus. In particular, one study found that 10% of participating CKD patients had dermatological manifestations consistent with PN [3]. Regardless of the associated conditions, PN patients develop a ferocious itch-scratch cycle which leads to a lower quality of life and severe disturbances to sleep and psychological state [1].

A proposed mechanism for the itch-scratch cycle is as follows: some dermatologic or systemic disease causes itch, which in turn results in neurogenic inflammation & influx of inflammatory cells to the region. The patient then mechanically scratches that region resulting in damage to the epidermal peripheral nerves. That damage leads to the activation of retrograde signaling pathways and more itch [1]. The continuous cycle leads to the formation of the pathologic nodules. Successful treatment relies in part on breaking the itch-scratch cycle with behavior modification and barrier protection of lesions.

On a cellular level, PN nodules have higher levels of protein products such as protein gene product (PGP) 9.5, low-affinity nerve growth factor (p75 NGFr), and calcitonin gene-related product (CGRP) nerve fibers in the dermis [3]. Nerve growth factor (NGF) is used by neurons for development and survival. It is produced by keratinocytes, mast cells, eosinophils, and T-lymphocytes. Researchers have found that NGF induces keratinocyte proliferation and has various biologic effects on the activity of inflammatory cells. One of those effects is the promotion of substance P (SP) production by neurons and histamine release by mast cells. SP is a tachykinin, which can produce inflammatory effects in cutaneous tissue. The observed inflammation and itch present in PN could be due in part to an increased density of SP-positive nerves [3].

Diagnosis of PN is clinical, and biopsy is not frequently performed. However, histologic findings have been described by researchers. Most frequently described include compact orthohyperkeratosis, irregular elongation of the rete ridges, and hypergranulosis. Inflammatory infiltrate is present in almost all patients and consists of both lymphocytes and histiocytes. Many specimens contain eosinophils and neutrophils as well [3].

If possible, evaluation and treatment for underlying causes of itch should be performed, as this may help eliminate the effects of the scratch-itch cycle. Even when scratching is avoided, lesions may take months to heal completely.

Treatment

Treatment of PN is a challenge, as solid evidence for effective therapy is scant. Many therapies have been utilized, and each patient will benefit from an individualized regimen. No standard approach has been selected. A multimodal regimen is often used, with the goal of reducing symptoms enough to allow lesions to fully heal [1]. Thus far, only topical steroids, pimecrolimus, and calcipotriol have been studied with randomized control trials in patients with PN; however, novel therapies are being investigated. Betamethasone 0.1% cream significantly reduced itch and resulted in nodule flattening in a comparison study against an antipruritic moisturizing cream [4]. In inflamed lesions, topical steroids can also be combined with an occlusive dressing to aid in stopping the scratch-itch cycle [5]. Treatment with potent topical steroids with the addition of intralesional steroids is considered first-line therapy at this time. In addition, sedating antihistamines such as diphenhydramine are often utilized at night to remedy the pruritic sensation.

Second-line therapy for those who do not respond to steroids is phototherapy with either narrow-band ultraviolet B light or with psoralen plus ultraviolet A [6, 7]. Many other immune-modulating therapies are being explored for the treatment of this chronic and stubborn disease. Unfortunately, recurrence is quite common, and complete resolution is rare.

There are additional topical medications to consider, most of which are not backed by randomized controlled trials and include topical calcineurin inhibitors, vitamin D derivatives, and topical capsaicin. Topical calcineurin inhibitors such as pimecrolimus and tacrolimus represent one treatment option. Treatment with pimecrolimus leads to a similar improvement in itch and quality of life when compared to treatment with hydrocortisone [8]. Regarding vitamin D derivatives, calcipotriol ointment significantly decreases the number of PN lesions when compared with betamethasone valerate [9]. Furthermore, topical capsaicin inhibits pruritus in localized, neuropathic forms of PN, and it results in skin flattening/softening of lesions with resolution of symptoms [10]. One study found that combination therapy with the antihistamine fexofenadine and the leukotriene inhibitor montelukast improved PN lesions and pruritus in a majority of patients [11]. Immunosuppressants like methotrexate and anti-inflammatories like thalidomide have been considered for patients with treatment-resistant PN. Regardless of the success of these therapies, they are not without severe side effects [3]. Other novel treatment concepts, such as inhibitors of neurokinin-1, opioid receptors, and interleukin-31 receptors, have been developed and are currently being clinically tested [1]. Currently in phase 3 clinical trials, dupilumab is demonstrating promise as a future treatment in refractory PN [12].

Key Points

- PN is a chronic, pruritic, papulonodular eruption the etiology of which is unknown.
- PN is characterized by firm, pruritic, hyperkeratotic nodules distributed symmetrically in a linear pattern on the extensor surfaces of the body.
- PN pathogenesis is linked to NGF increase in dermal analysis. This factor then leads to increased keratinocyte replication, inflammatory cell recruitment, and SP release.
- First-line treatment is based on corticosteroids, with phototherapy being utilized as second-line therapy. Many immune-modulating therapies are on the horizon for the treatment of this chronic, recurrent disease.

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Chapter 7
63-Year-Old Female with a Persistent Itchy Patch on the Shoulder Blade

Daniel A. Hyman, Austin Cusick, and Shannon C. Trotter

A 63-year-old female presented with a persistent itchy patch on the right shoulder blade for over 10 years duration. She DENIED ever having a rash in the area, including herpes zoster. She stated that the itch comes and goes and when she has her husband evaluates the site, there is never a rash. However, she has noticed a slight brown discoloration develop in the area gradually over time. Of note, she stated that this seems to have started after she was in a car accident and experienced significant whiplash. She tried over-the-counter emollients with no improvement.

On physical examination, there was a solitary tan patch on the right shoulder blade overlying the area where she reported itching. A few excoriation marks were also observed.

Based on the clinical case description, what is the most likely diagnosis?

1. Notalgia paresthetica
2. Café au lait macule
3. Melasma
4. Brachioradial Pruritus

Diagnosis

Notalgia paresthetica.

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Discussion

Notalgia paresthetica (NP) is a condition that involves pruritus and other symptoms in the mid-scapular region of the back [1]. NP has had many names over the years, since it was first described, and can be confused with macular amyloidosis. However, NP and macular amyloidosis are not synonymous terms. NP is under the categories of neuropathic itch and neurocutaneous dysesthesia. NP most commonly affects women in their 50s and 60s years of age, but cases of children have appeared in the literature. In these children, NP is most often associated with Multiple Endocrine Neoplasia, Type 2A [2]. NP may be underdiagnosed and therefore, an accurate incidence and prevalence of the disease is not known. Chronic itch has a high lifetime incidence of close to 1 in 5 with almost half being attributed to chronic neuropathic itch [3].

Notalgia paresthetica generally presents as a well-circumscribed, unilateral area of chronic pruritus in the upper back below the scapula (Fig. 7.1). Although pruritus is the hallmark symptom, other symptoms include burning, tingling, numbness, and pain. There may be a hyperpigmented patch corresponding to the location of the pruritus, most likely secondary to the chronic scratching, inflammation, or substance P release [4]. Histopathological evaluation of the patch will show post-inflammatory hyperpigmentation and possibly amyloid deposits. While there is some debate, most experts believe that NP and macular amyloidosis are separate

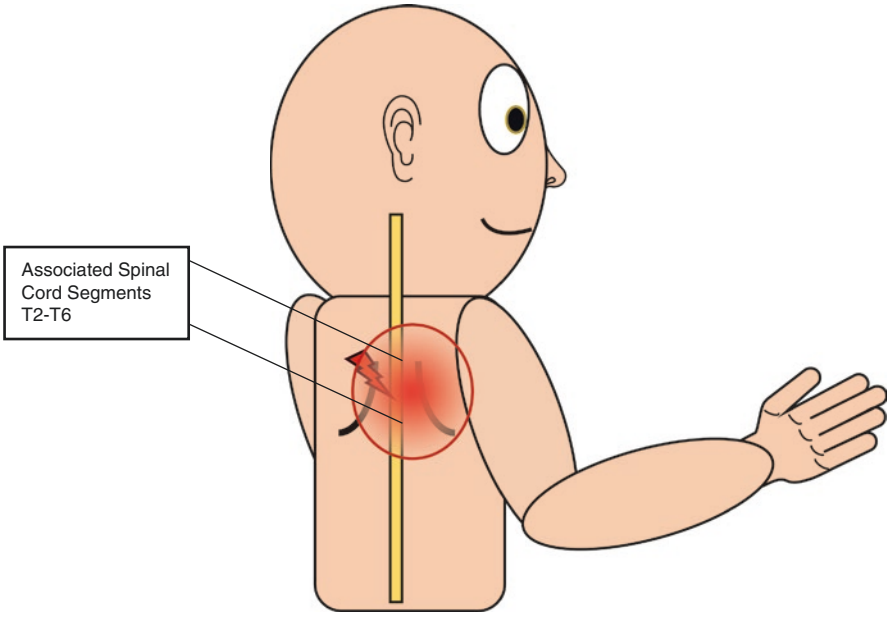

Fig. 7.1 Area most affected by NP presented as red haze and circle. The spinal cord is presented as yellow with the associated spinal lesions denoted by the text, boundaries, and lightning bolt

conditions because increased amounts of amyloid are only observed in some cases of hyperpigmentation associated with NP [2]. Definitive features on histopathology have not been established and are not necessary to diagnose NP.

It is thought that the mechanism of itching comes from the irritation and damage of the sensory nerves of the skin in the dermatomes T2 through T6 [2]. It is hypothesized that degenerative vertebral changes or other structural spine disease leads to the thoracic polyradiculopathy [3]. Other etiologies have been hypothesized including metabolic, genetic, and infectious causes [3]. There are no current findings on imaging of the spine to suggest the presence or severity of the disease, although cervical and thoracic degenerative disease is commonly seen [5]. More studies need to be conducted to fully understand the disease process and mechanism of itching.

A clinical diagnosis is sufficient after ruling out other conditions on the differential diagnosis. The differential diagnosis includes macular amyloidosis, post-inflammatory hyperpigmentation, pigmented contact dermatitis, xerosis, and tinea versicolor [4]. As mentioned above, histopathology and imaging findings cannot be relied on to make the diagnosis of NP. It is important to check for other neurological symptoms, which would make imaging appropriate. As will be discussed in the treatment section, if initial treatment fails, further workup may be needed.

Treatment

In addition to the mechanism of pruritus, standard treatment recommendations for NP have yet to be established. Treatment options include physical therapy/osteopathic manipulative treatment, topicals, injections, systemic agents, and light therapy [6]. No single treatment has been proven more effective than another. However, many patients achieve positive results with one modality or a combination thereof. The topical options include capsaicin and tacrolimus [6]. These are generally first offered to patients receiving a diagnosis of NP, along with a variation of physical therapy, osteopathic manipulative medicine, and home exercises.

Topical capsaicin is a popular treatment that tends to decrease pruritus and pain associated with notalgia paresthetica. The mechanism acts through depolarization of nociceptive and pruritic C-fibers that are positive for epidermal transient receptor potential vanilloid-1 (TRPV1) receptors [7]. Bee venom has been shown to have potential anti-inflammatory properties, making it a possible treatment for a variety of skin conditions in the future [8]. Capsaicin has been combined with bee venom with promising results [9]. Further studies are needed to better describe the efficacy of interplay between bee venom and capsaicin in providing neuropathic relief. Osteopathic manipulative therapy has been shown to significantly decrease pruritus [10]. Techniques that can be directly applied to NP include muscle energy to the upper thoracic and cervical regions, scapular fascial release, and autonomic balancing techniques [11]. A case study showed that cervical traction for a patient with

cervical spinal pathology on imaging can resolve symptoms of NP [12]. An example exercise protocol consists of back and shoulder stretches which have demonstrated a decrease in pruritus severity in a series of patients [13].

If these initial treatments fail, injections and systemic agents can be utilized. Injections include lidocaine, botulinum toxin A, and triamcinolone [6, 14]. Botulinum toxin A has been shown in case studies to decrease pruritus, but a randomized controlled trial failed to confirm these results [15, 16]. Systemic agents that are typically used for neuropathic pain have been tried for neuropathic itch under the presumption of peripheral sensory nerve involvement [17]. Of note, gabapentin has shown some success in decreasing pruritus in a case series [18]. Furthermore, amitriptyline, duloxetine, and oxcarbazepine are other medications that have been mentioned in the literature as possible agents for the treatment of NP [19–21].

Lastly, some procedures that have been described in the literature include surgical decompression, transcutaneous electrical nerve stimulation, and narrow-band ultraviolet B therapy [6, 22, 23]. An emerging procedural treatment option for pain in NP is cryolipolysis, a treatment that targets the subcutaneous fat without damaging the sensory nerves in the skin. It has been shown to diminish the sensation to pinprick and overall pain sensitivity, with no effect on itching [24]. This may become an appropriate therapy for patients with NP who have mild or no pruritus with pain as the predominant symptom. Keep in mind that imaging and neurology referral may be necessary to further investigate complex cases.

There is no clear etiology for NP and no proven superior treatment option or regimen. Physicians and patients should discuss the individuality of the disease and the many treatment options, with their benefits and risks. Frist line treatment may include topical therapy along with either osteopathic manipulative treatment, physical therapy, or prescribed exercises. Many patients achieve an acceptable and lasting decrease in symptoms from these treatments. If treatment fails, novel or more invasive treatments can be discussed further. The only clinical trial registered is a quadruple masked crossover study investigating the treatment of NP using incobotulinum toxin A [25]. Further comprehensive clinical trials will be needed to establish treatment recommendations going forward.

Key Points

- Notalgia paresthetica (NP) is a chronic neuropathic itch localized to the upper subscapular back, sometimes associated with a hyperpigmented patch. While causality is not proven, there is correlative evidence between thoracic spine pathology and NP development.
- Notalgia paresthetica is most likely caused by a disruption in the cutaneous sensory nerves leading to pruritus, burning, tingling, and pain. This manifestation is localized to the scapular T2–T6 dermatome region.
- Notalgia paresthetica has a wide variety of proposed treatments ranging from topical (capsaicin, lidocaine) and systemic treatments (gabapentin) to local and procedural modalities (Osteopathic Manipulative Medicine).
- Notalgia paresthetica is a chronic condition requiring education of the patient as well as the physician on expectations surrounding care.

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Chapter 8
56-Year-Old Male with Itchy Bilateral Forearms

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A 56-year-old male presented with itching on the forearms bilaterally. He reported that the itching has come and gone over the last 5 years. He stated that there is never a rash present unless the itching becomes severe and he scratches the area, leaving excoriation marks. He has tried topical steroids with no improvement. He reported serving in the military for several years and has a known history of cervical degenerative disc disease.

On physical examination, no rash was noted on the dorsolateral arms bilaterally. The skin was intact and healthy in appearance.

Based on the clinical case description, what is the most likely diagnosis?

1. Brachioradial pruritus
2. Notalgia paresthetica
3. Malingering
4. Meralgia paresthetica

Diagnosis

Brachioradial pruritus.

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Discussion

Brachioradial pruritus (BRP) is a condition that involves pruritus, burning, and tingling of the dorsolateral aspect of the forearm [1]. This condition generally presents with no rash and patients may have experienced symptoms for many years before presenting. The classic presentation includes a patient with pruritus over bilateral dorsal forearms with no pain or rash that waxes and wanes over the past few years, which gradually worsens. BRP was first described in 1968 as a solar pruritus over the proximal brachioradial muscle in the presence of actinic damage and xerosis [2]. Current thinking suggests that ultraviolet radiation, cervical nerve damage, or a combination of the two causes the skin manifestations of BRP. There is a strong correlation between an increase in symptoms and the summer months [3]. There have also been reported cases of underlying spinal cord tumors revealed due to further investigation of severe BRP [4].

BRP is generally bilateral and distributed over the C5 and C6 dermatomes (Fig. 8.1) [5]. Pain is not a reported symptom in the literature, which helps to differentiate this condition from other neuropathic itches or cutaneous dysesthesias such as notalgia paresthetica. The symptoms of itch, burning, and tingling, classically associated with BRP, wax and wane throughout the year [5]. Some patients have progressed to generalized pruritus, termed BRP-triggered generalized pruritus [6].

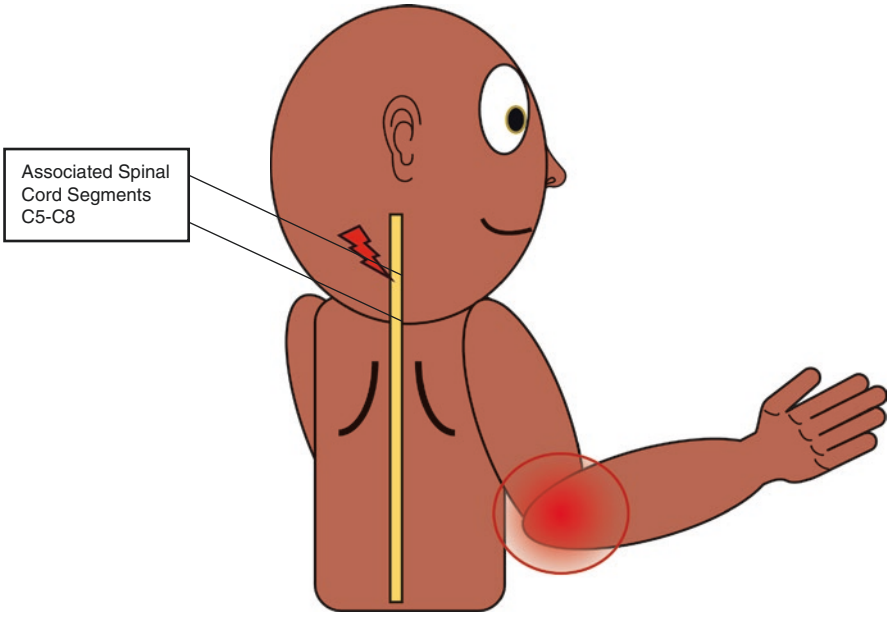

Fig. 8.1 BRP clinical distribution and associated spinal cord segments

There is a paucity of information in the literature on the epidemiology of BRP. A case series found a female to male ratio of greater than 3:1 with a mean age of 59 years [7]. However, one study has shown the condition to occur in younger individuals with a close to 1:1 ratio between females-and-males in a tropical location [8]. Caucasian and lighter Fitzpatrick skin types are more commonly associated with BRP [5]. There has been a report of a possible autosomal or X-linked dominant form of BRP in a single family with no subsequent reports in the literature [9]. This may have been due to similar lifestyles between the family members as most patients in this study worked long hours performing heavy lifting in the sun. Many of the family members had neck pain and associated cervical spine degenerative changes. No gene had been identified in the pathogenesis of BRP, but some individuals may have a genetic predisposition in the presence of environmental factors such as sun exposure.

Diagnosis of brachioradial pruritus can most often be done clinically. The ice-pack sign is pathognomonic for BRP. It is when a cold pack is applied to the area of pruritus relieving symptoms and then the return of symptoms when the cold pack is removed [10]. We postulate that the cold application decreases nerve conductance in the skin as these damaged sensory nerves are more susceptible to cold. Our conclusion is based on median nerve conduction study changes after cold application [11]. Skin biopsy is not helpful because it does not show any abnormal findings other than secondary changes. These secondary changes include actinic damage and excoriations. Lichenification and prurigo nodules can result from chronic scratching [1].

A cervical magnetic resonance imaging (MRI) is generally not indicated on presentation. Although cervical nerve root pathologies are commonly found on imaging, they do not correlate to severity, and the absence of findings does not rule out BRP. Most commonly, the C5–C8 nerve roots are affected [5].

A trial of treatment is recommended before further workup in the absence of other neurological signs or other primary skin conditions on differential diagnosis [1]. The differential diagnosis includes atopic dermatitis, notalgia paresthetica, neurotic excoriations, lichen simplex chronicus, photoallergic reactions, Sannino-Barduagni syndrome, and zoster sine herpete [5, 12, 13]. Lichenification may make it difficult to differentiate between BRP and lichen simplex chronicus [14].

The mechanism of pruritus is likely multifactorial given that a single etiology for BRP has not been proposed. The pruritus is likely due to an alteration, sensitization, or dysfunction of the C-fibers of peripheral cutaneous nerves. This has been shown through sensory testing of C-fibers before and after treatment [15]. Substance P and NMDA/glutamate are thought to be potential contributors downstream leading to pruritus [16]. Transient receptor potential ion channel family subtype V1, also referred to as transient receptor potential vanniloid-1, (TRPV1) has been implicated in the possible pathogenesis of BRP. TRPV1 is a heat-activated cation channel that is reactive to capsaicin. The nerves that express this protein mostly have afferents in the periphery, like the skin, with cell bodies in the dorsal root ganglion. Activation of TRPV1 allows cation influx, peripheral nerve depolarization, and potential

propagation to the central nervous system [17]. While heat directly activates the channel, local inflammatory mediators can increase sensitivity to heat and allow for increased activation. The close association between heat and BRP can advance TRPV1 activation as a likely step in the pathogenesis [17]. However, further studies are currently in progress to better understand the mechanism of itch in many types of chronic pruritus including BRP.

Treatment

Current treatment recommendations for BRP are similar to other forms of neuropathic and chronic itch. However, BRP may be caused or aggravated by ultraviolet radiation. Therefore, phototherapy is not a suggested treatment and sun protection can be key for patients [18]. First line treatment for BRP includes topical therapy and escalate treatment if initial therapeutics fail [1]. More aggressive treatment options include cervical spine manipulation, acupuncture, topical therapy, injections, systemic agents, and surgical decompression.

Given the ease of use, based on the location of the pruritus in BRP, topical agents are popular as a first-line agent. Topical capsaicin is the most commonly used topical medication because it targets pruritic C-fibers and TRPV1 as discussed in Chap. 7 of this series [19]. Another option of topical therapy is compounded amitriptyline and ketamine, which targets potential neurotransmitters that are involved in the mechanism of pruritus [20]. Other topical treatments include steroids, anesthetics, and antihistamines with minimal evidence to their effectiveness in reducing patient symptoms [5]. Cervical spine manipulation and acupuncture can also be used as first line therapies [21, 22].

If topical medications are ineffective or the symptoms are severe, oral agents can be quite helpful in the reduction of pruritus, burning, and tingling. Many of these include medications that are used for neuropathic itch and pain. They include amitriptyline, gabapentin, pregabalin, fluoxetine, risperidone, chlorpromazine, hydroxyzine, pimozide, and doxepin [23, 24]. Some of these medications have potentially serious adverse effects leading us to caution the use of these medications. Another oral medication with promising results is aprepitant, a neurokinin-1 (NK-1) antagonist, which acts by blocking substance P from binding to target receptors [25].

In patients with neck pain or neurological symptoms, cervical magnetic resonance imaging and neurology consult are recommended. If significant cervical stenosis is present, surgical decompression can immediately improve symptoms [26]. If BRP has revealed an underlying spinal cord tumor, removal of that tumor would be the first step in treatment before addressing any persistent symptoms of BRP [4]. Other neurologically-targeted treatments include cervical nerve root block, botulinum toxin A injection, and cutaneous field stimulation [27–29]. Cutaneous field stimulation (CFS) is a constant current applied to the skin with the goal of stimulating C fibers. In one study [29], CFS was performed for 20 minutes daily for 5 weeks on the forearms of BRP patients resulting in decreased pruritus. Skin biopsy, staining for calcitonin gene-related peptide and protein gene product 9.5 (PGP9.5) to

identify nerve axonal count, showed a reduction of nerve fibers post-treatment. However, symptoms gradually returned over time after discontinuation of treatment, most likely due to regeneration of nerve fibers [29].

Prognosis is very good for patients with BRP. There are numerous treatment options available to patients. It is also helpful that many patients find relief during the winter months. There will continue to be more insight into the mechanism and treatment of chronic pruritus, which will further help patients with BRP. Many studies are looking into the neurotransmitters and mediators of pruritus. Future treatments will better target these areas through either procedures or medications.

Key Points

- BRP is a chronic itch localized to the dorsolateral aspect of the forearms associated with heat, ultraviolet radiation, and, less commonly, cervical spine pathology.
- BRP is characterized by pruritus, burning, and tingling that may be more severe in the summer months. Pain is typically absent from this condition.
- BRP, in rare occurrences, is the only manifestation found in an underlying cervical spinal tumor.
- Treatment of BRP consists of topical medications like capsaicin or corticosteroids. However, systemic therapy with medications such as gabapentin, pregabalin, or amitriptyline can be employed if topical therapy fails. BRP secondary to cervical pathology can be relieved by treating the underlying disease.

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Chapter 9
68-Year-Old Male with Intense Itching Followed by Blisters on the Breast

Rosemary Oaks, Austin Cusick, and Shannon C. Trotter

A 68-year-old male presented with itching on his left breast for 3 days. He stated that the itch was intense and only moderately relieved by scratching. He then developed several tiny blisters in the area that continued to itch. He popped them when scratching the area. He denied lesions elsewhere on the body. His medical history was significant for varicella as a child. He has not treated the area and denies applying any topicals to the area prior to the rash developing.

On physical examination, there was an urticarial plaque on the left breast studded with vesicles following a dermatomal distribution. There was no rash noted elsewhere on exam (Fig. 9.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Bullous pemphigoid
2. Bullous impetigo
3. Herpes zoster
4. Allergic contact dermatitis

Diagnosis

Herpes zoster.

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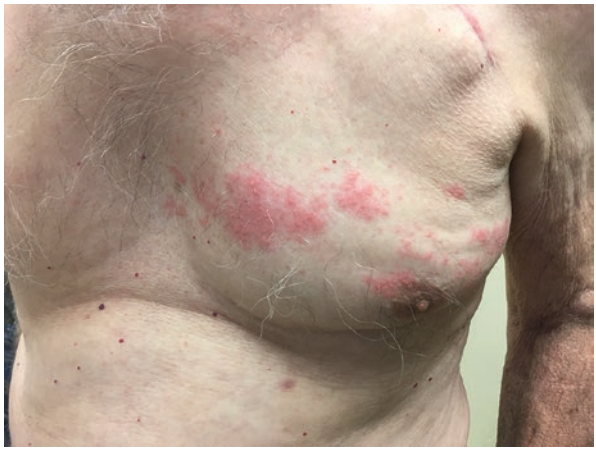

Fig. 9.1 Vesicular plaques in a dermatomal distriubtion on the left breast

Discussion

Herpes zoster is known more commonly as shingles and is caused by infection with the Varicella Zoster Virus (VZV). VZV is a herpesvirus and is responsible for causing two distinct diseases. Initial infection with VZV results in the childhood disease called chickenpox, which is characterized by a diffuse, pruritic rash. The chickenpox rash begins on the head and trunk with further spread to the extremities. During the initial infection with chickenpox, VZV gains access to sensory nerve ganglia and becomes latent [1]. VZV is able to hijack T-cells and establish latency [2]. An intact immune system ensures that the virus remains dormant and does not result in symptoms. Innate immune cells in the skin and nerves secrete type 1 interferons and other pro-inflammatory cytokines in order to control the virus during latency [2]. Herpes zoster is the secondary disease caused by VZV following reactivation [3].

Later in life, the latent VZV reactivates to replicate in the cell body of the sensory nerve and releases virions. Retrograde travel of viral progeny allows spread to the skin innervated by that sensory nerve causing localized irritation and inflammation. Herpes zoster is recognized by its distinctive clinical features. Initially, the rash is erythematous and papular, but it then progresses to a painful, unilateral, vesicular rash which generally occurs in the distribution of one dermatome. A simplified mechanism depicting this can be found in Fig. 9.2. The involvement of the V_1 branch of the trigeminal nerve may result in herpes zoster ophthalmicus, a type of ocular keratitis [3]. This manifestation can be vision threatening and requires rapid diagnosis and treatment. Involvement of the facial nerve with spread to the vestibulocochlear nerve can lead to herpes zoster oticus, clinically described as Ramsay Hunt syndrome type II. Involvement of the vestibulocochlear cranial nerve can present with hearing loss, tinnitus, or vertigo [4].

The incidence of herpes zoster increases with age, mostly affecting immunocompetent adults over the age of 50. Presumably, the rising incidence with

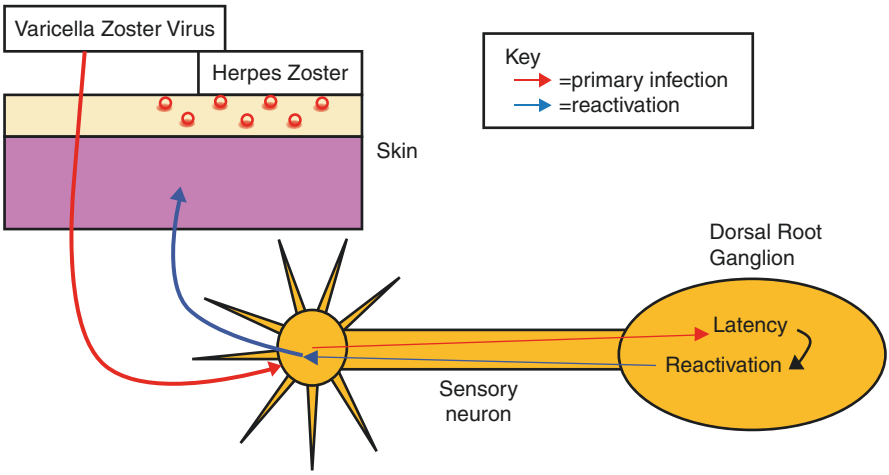

Fig. 9.2 Simplified mechanisms behind primary VZV infection and reactivation as Herpes Zoster [1–3]

increasing age is due to waning cell-mediated immunity against the virus. Inability of VZV-specific T-cells to maintain suppression is the leading theory for the pathogenic mechanism [2]. Emotional stress, immunosuppression, acute or chronic illness, new exposure to the virus, and the presence of malignancy are all known triggers for reactivation [4]. Immunosuppression and age are considered the biggest risk factors for reactivation. Additionally, white race and female gender are associated with an increased incidence of disease [3, 5, 6]. Two vaccines have been developed to boost cell-mediated immunity to the virus, decreasing the overall incidence of disease [7].

Once clinical manifestations are apparent, the lesions generally last for 7–10 days and are contagious until they have crusted [3]. Those who have not been diagnosed with or vaccinated against varicella previously are at risk of infection from exposure to open VZV lesions [3]. Along with the distinctive rash, acute pain is the most common symptom of herpes zoster [8]. This should not be confused with prodromal pain or postherpetic neuralgia (PHN), which is pain at the eruption site that persists after the rash of herpes zoster has resolved [8].

Pruritus, with or without accompanying pain, can be one consequence of infection [9]. The pathogenesis of postherpetic itch (PHI) remains unknown, but it is thought to be neuropathic and related to effects on itch-specific neurons [10]. It is hypothesized that damage from acute infection leads to immune dysregulation in that dermatomal distribution where pruritus then ensues [11]. Investigation into PHI suggests that there are distinct differences in etiology between PHN and PHI [12]. Murine models demonstrate specific neuronal groups related to itch [13]. As a result, treatment modalities commonly employed for the treatment of postherpetic neuralgia can paradoxically worsen the pruritus. Thus, more research will be necessary to learn more about this unique complication [9].

Treatment

Clinical management of uncomplicated herpes zoster infection can be accomplished by providing antiviral therapy in addition to adequate analgesia.

Antiviral therapy can decrease the severity of pain that patients experience and the time to pain resolution [14]. It is important to consider the time elapsed between presentation and symptom onset when deciding to administer antiviral medication. If the patient is presenting 72 or more hours after symptom onset and is not currently experiencing any new lesions, antiviral therapy can be avoided. However, if the patient is presenting less than 72 h from symptom onset or is currently experiencing new lesions, antiviral therapy is recommended [14].

Antiviral therapy can be provided using acyclovir, valacyclovir, or famciclovir. Acyclovir (800 mg 5 times a day), famciclovir (500 mg 3 times daily), and valacyclovir (1000 mg 3 times daily) are approved in the United States for acute VZV infection [14]. Most treatment regimens require 7 days duration or longer. All described antiviral agents are phosphorylated by viral thymidine kinase and host cellular kinases into a triphosphate form which then inhibits viral replication [14]. To date, no research has shown a difference in effectiveness between these three agents. However, acyclovir is dosed more frequently and considered more cumbersome in comparison to the other agents [15]. Acute neuritis can be extremely painful necessitating adequate analgesia. Pain control can be achieved with over-the-counter medications such as ibuprofen or acetaminophen, but severe pain may warrant treatment with opioids [14]. It is important to note that prophylactic treatment with glucocorticoids and/or neuropathic pain agents such as tricyclic antidepressants and gabapentin has not been shown to reduce the incidence of postherpetic neuralgia when used during the acute phase [14]. Therefore, these agents are not recommended for the treatment of acute infection. However, they remain a pillar of treatment after 90 days once PHN has developed [14].

A gold-standard approach for the treatment of PHI has not been established. PHI often does not respond to therapies classically used for PHN. Topical anesthetics such as 5% lidocaine patches are often used for treatment; however, the role of other agents used for neuropathic pain such as capsaicin, gabapentin/pregabalin, and tricyclic antidepressants are unknown. All described medications ultimately decrease ectopic neuronal firing [14]. Overall, antihistamines and topical corticosteroids have not been proven as effective [9].

Primary prevention of disease is achieved through vaccination for both chickenpox and herpes zoster. In the United States, children are recommended to receive two doses of the varicella zoster vaccine for the prevention of chickenpox infection. Additionally, regardless of previous infection or development of antibodies during primary infection, all adults are recommended to be vaccinated again later in life for the prevention of shingles. Two vaccines are licensed and recommended to prevent shingles in the United States. The live zoster vaccine has been used since 2006. The inactivated recombinant zoster vaccine has been in use since 2017 and is recommended as the preferred shingles vaccine at this time. The CDC currently

recommends one dose of the inactivated zoster vaccine for all adults age 50 and over. The live zoster vaccine can be used in adults over 60 when there are contraindications to the use of inactivated recombinant vaccine, such as allergy or shortage in supply [16]. Research has shown that the inactivated recombinant vaccine significantly reduces the incidence of herpes zoster reactivation, and PHN [16, 17]. Additional research reinforces the fact that the elderly population can still benefit from vaccination with live zoster vaccine as well [18].

Key Points

- Herpes zoster (shingles) is caused by the varicella zoster virus, the same agent that causes chickenpox.
- The rash consists of unilateral, painful, vesicular lesions in the distribution of one dermatome.
- The incidence of herpes zoster is determined by the host's immune system and thus is affected by age, disease state, and immunosuppression.
- Herpes zoster is treated with a combination of antiviral medication and pain control. This is often achieved with valacyclovir or famciclovir and over-the-counter pain medication.
- Postherpetic pruritus, although uncommon, can be debilitating and refractory to treatment.

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Chapter 10
40-Year-Old Male with Anal Itching

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A 40-year-old male presented with itching in the anal area of 3 years duration. He reported itching that comes and goes. He admitted to using baby wipes and facial exfoliation products to clean the area three to four times daily. He had a colonoscopy and sigmoidoscopy, both of which were normal. In addition, he was evaluated by infectious disease and a sexually transmitted infection (STI) workup was negative.

On physical examination, the skin around the anus was pink and lichenified. No hemorrhoids or skin tags were noted. There was no abscess or signs of infection on exam.

Based on the clinical case description, what is the most likely diagnosis?

1. Pruritus ani due to aggressive hygiene
2. Perianal streptococcus
3. Psoriasis
4. Herpes simplex

Diagnosis

Pruritus ani.

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Discussion

Pruritus ani is a transient or chronic itching of the anus or perianal skin. It is estimated to affect approximately 1–5% of the general population. Pruritus ani is most commonly seen in men between the fourth and sixth decades of life [1–3]. Approximately 75% of pruritus ani cases are secondary to inflammation, infection, neoplasms, or anorectal disorders [2]. Idiopathic pruritus ani is most commonly secondary to fecal contamination and trauma from wiping and scratching.

There are various dermatologic diseases also associated with pruritus ani, including but not limited to inverse psoriasis, contact dermatitis, atopic dermatitis, hidradenitis suppurativa, cutaneous squamous cell carcinoma in situ (Bowen's disease), scleroderma, erythema multiforme, dermatitis herpetiformis, lichen planus, and radiation dermatitis [4].

Infections are also a common cause of pruritus ani. Sexually transmitted diseases such as condyloma, herpes, syphilis, and gonorrhea often produce pruritus ani. Parasitic infections with *Enterobius vermicularis* (pinworms) are a common source of pruritus ani. Pinworm infection typically manifests as nocturnal pruritus that is more common in children than adults. Perianal Group B streptococcal dermatitis is another cause of pruritus ani that is common in children and adults [5]. This often accompanies a honey-crusted rash. Erythrasma caused by the bacteria *Corynebacterium minutissimum* is a cause of pruritus ani more commonly seen in older adults, the immunocompromised, or diabetics [6]. Erythrasma presents with a brown, scaly patch as the presenting dermatologic manifestation.

Another possible cause of pruritus ani stems from local irritation to the anus. Several factors increase this irritation like moisture buildup and fecal content leakage. Anal leakage may be influenced by diet content including increases in alcohol, caffeine, and spicy foods. Diarrhea often also accompanies the complaint [7]. Fecal soilage leads to perianal fecal contamination and resultant trauma from wiping and scratching. A proposed mechanism of fecal soilage is diarrhea and seepage due to abnormalities in the rectoanal inhibitory reflex and lower threshold of internal anal sphincter relaxation [8]. After an initial duration of insult, overcompensation by the patient develops in attempt to remedy symptoms and the coexisting uncleanliness. This consists of repetitive wiping and cleaning. Often, patients employ the use of sanitation products including wipes containing aggravating chemicals. Combination of chemical irritation and mechanical irritation amplifies the original pruritus, creating further exacerbation [7].

A lesser-known association of pruritus ani is food choice. Patients will rarely link their pruritus with commonly consumed foods and drinks. Commonly associated foods with pruritus ani are coffee, tea, chocolate, citrus fruits, fruit juices, tomatoes, cola, beer, wine, liquors, spicy foods, and dairy products [7].

Aside from an anorectal disease, infection, or fecal soilage, a common view suggests that although the original trigger of the pruritus has passed, the pruritus is prolonged by the itch-scratch cycle [9]. The itch-scratch cycle encourages the release of inflammatory cytokines, which worsen the pruritus, erythema, and increases the radius of the affected skin [10].

The diagnosis of pruritus ani mainly involves identifying the original insult. Ultimately, history and physical exam can help delineate the direction of investigation. Questions regarding duration, association with bowel movements, incontinence, history of gastrointestinal illnesses, and anal hygiene are useful in narrowing the diagnosis. On physical exam, direct visualization of the affected area is necessary for diagnosis. Digital examination of the anorectum should be performed to identify anorectal or dermatologic disease causing the pruritus ani. Furthermore, anoscopy may be indicated if lesions cannot be fully appreciated without more invasive measures. Chronic scratching may cause progression to premalignant pathologies and may need further investigation. Biopsies of such lesions may be indicated if any lesions appear suspicious for premalignancy [7].

Treatment

Unfortunately, evidence-based support for treatments of pruritus ani is limited; however, treatment of pruritus ani primarily consists of improving anal hygiene, avoiding moisture in the anal region, removing any offending agents, and skin protection. Reassurance and conservative measures are vastly successful in approximately 90% of cases [11]. First and foremost, the patient should cease scratching the affected area to reduce the inflammation and discontinue the itch-scratch-itch cycle. With patients that undergo excessive hygiene to the pruritic area, it is pertinent to educate on the positive feedback and amplification of continued scratching and the need to stop aggressive hygiene practices [7]. Scented soaps, prepared wipes, and vigorous scrubbing should be avoided [7]. In patients with anorectal disease, infection, and fecal soilage, treatment of the underlying condition is the route of management. Patients with fecal soilage should use fiber supplementation to increase stool bulk, and if diarrhea is the source of incontinence, antidiarrheal drugs may be indicated [12]. Tight fitted clothing should also be avoided, as it traps moisture in the perianal area. The anoderm should be kept clean and dry without excessive wiping, as this may cause dermal breakdown [13]. Topical therapies such as short-term, low potency steroids have also been shown to be effective in treatment [3]. Limiting the use of topical steroids to short term intervals will help avoid skin thinning and possible worsening secondary to topical administration.

If all treatments are unsuccessful, topical capsaicin has shown efficacy. It is believed that the capsaicin depletes substance P, a neurotransmitter involved with pain and itching [14]. It is also postulated that the capsaicin suppresses the histamine release to interrupt the itch-scratch-itch cycle [7]. The final novel treatment for pruritus ani is anal tattooing. Intradermal injection of methylene blue has been used to treat patients with pruritus ani that is refractory to other treatments [15]. A mixture of methylene blue, normal saline, bupivacaine with epinephrine, and lidocaine is introduced using a small gauge needle to cover the affected perianal skin up to the dentate line [7]. The mechanism of anal tattooing is reliant on the destruction of sensory nerve endings in the anal region. The destruction is from the dye contents of the injection. Side effects of this procedure include decreased

sensation in the area, possible anal leakage, and possible blue discoloration in the region of tattooing [7].

Key Points

- Pruritus ani is a localized, pruritic disease with a multitude of origins that include idiopathic, infection, mechanical, and dietary.
- A thorough investigation with history and physical exam will help diagnose the specific cause of pruritus ani. Visualization with anoscopy may be necessary with biopsy of anoderm that may be premalignant.
- Treatments typically begin with conservative management in limiting moisture, irritation, and the itch-scratch cycle. Further, isolating the primary cause will allow resolution.
- Treatment in refractory cases may include topical corticosteroids, capsaicin, and anal tattooing with methylene blue.

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Chapter 11
55-Year-Old Post-Menopausal Female with Genital Itching and Pain During Intercourse

Kassandra Riggs, Erica Haught, Austin Cusick, and Shannon C. Trotter

A 55-year-old post-menopausal female presented with itching and burning in the genital area for 1 year. She stated the itching was most concentrated in the vulva, but she also felt it in the anal area as well. She also reported increased pain with sexual intercourse and occasional constipation. She had not received a gynecological exam in 5 years. In addition to itching in her vaginal area, she also complained of an itchy white patch on the left abdomen.

On physical examination, there were white atrophic plaques encompassing both the vaginal area and extending around the perineum to the anus. On physical exam, she also had a white atrophic patch on the left abdomen. The remainder of her skin exam was normal (Fig. 11.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Vaginal yeast infection
2. Psoriasis
3. Lichen sclerosus et atrophicus
4. Allergic contact dermatitis

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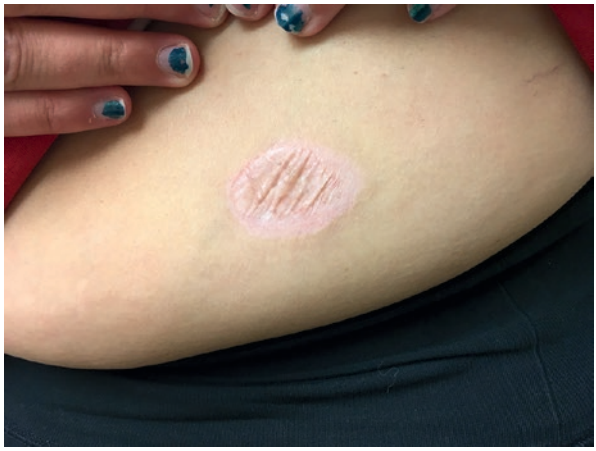

Fig. 11.1 A white atrophic patch on the left abdomen

Diagnosis

Lichen sclerosus et atrophicus.

Discussion

Lichen sclerosus (LS) is a chronic inflammatory dermatologic condition that has also been known as lichen sclerosus et atrophicus, balanitis xerotica obliterans (in males), kraurosis vulvae, and hypoplastic dystrophy. The disease is characterized by pruritus, pain, and scar formation. While LS most commonly affects postmenopausal women, it also affects prepubertal females and, less commonly, males [1]. The prevalence of LS for children and women over 80 years of age is about 0.1% and 3% respectively [1]. Of note, LS in children may be mistaken for child abuse.

LS can be vulvar, anogenital, or extragenital in location. Anogenital lesions are more common at 98% of cases with extragenital cases only consisting of 20% of cases [2]. These extragenital locations include the axilla, upper trunk, lateral thighs, and buttocks [3]. The clinical appearance of LS is generally characterized as thin, patchy, white skin lesions with a shiny appearance. Lesions may start as papules and eventually coalesce into large plaque formation. The most common symptoms include pruritus, soreness, dysuria, anal discomfort, dyspareunia, and possibly incontinence. The fragile, thin texture of the lesions can lead to erosions, fissures, ulcerations, and hemorrhagic bullae [1, 3]. Regarding vulvar lesions, chronic inflammation can lead to the distortion of vulvar architecture, including the loss of the labia minora. The classic description of the ‘figure of eight’ shaped lesion occurs when the vulvar lesion extends to involve the perianal skin. Severe complications of chronic lesions can include urinary obstruction, constipation, and malignant transformation.

Transformation to vulvar squamous cell carcinoma has been observed in up to 7% of patients with LS [3]. Due to the increased risk of malignant transformation, patients must be carefully followed so that premalignant lesions may be adequately managed. Biopsy of lichen sclerosus lesions is necessary to confirm the disease and determine the potential of malignancy.

While the etiology of lichen sclerosus is not fully known, there are multiple hypothesized theories as to the development of the lesions. There is a genetic predisposition for the disease, as there are higher rates of the disease among family members [4, 5] and twins [6]. The development of LS has also been considered as an immunologic response [2]. In a study of 350 females, 21% of individuals with LS had another autoimmune disease in addition to LS; furthermore, 42% of patients had a high autoantibody titer [7]. Some studies considered that there may be a correlation between the number of autoantibodies and disease activity, but a significant correlation has not been established. Common autoimmune conditions that have been associated with lichen sclerosus include autoimmune thyroiditis, vitiligo, type 1 diabetes mellitus, and psoriasis [3]. Furthermore, an association between Human Leukocyte Antigen (HLA)-DQ7 allele and LS has been established, strengthening the autoimmune hypothesis [8].

With the high incidence of disease in prepubertal and postmenopausal women, hormonal factors in the etiology of the disease have been explored. The low estrogen state of these patient populations suggests there could be a link, however, no studies have proven this theory to be significant [3]. Local testosterone deficiency has been considered, as testosterone has been used in the treatment of local disease, but minimal evidence has proven this theory significant as well [3].

Bacterial, *Borrelia burgdorferi*, and viral, hepatitis C and Human Papilloma Virus, pathogens have been implicated in the etiology of lichen sclerosus. The results of the studies have been conflicting [3, 9]. Other factors that have been shown as possible contributors to the disease involve local skin irritation, such as trauma and friction causing the Koebner phenomenon (Koebnerization). Koebnerization is described as the development of new skin lesions secondary to trauma on normal skin [10]. It has been associated with psoriasis, vitiligo, and lichen planus in addition to LS [10].

The pathophysiology of lichen sclerosus involves inflammation and infiltration with activated T-cells. The T-cells release TGF-β and IL-4 which subsequently lead to fibroblast activation and fibrosis [11]. Mast cells and macrophages have also been implicated in the pathogenesis of LS [11]. Classic histopathological findings of LS include thinning of the epidermis, hyperkeratosis, papillary dermis fibrosis, basal cell degeneration, and loss of rete pegs [3].

When diagnosing lichen sclerosus, it is essential to rule out other disorders with similar presenting symptoms. Diagnoses including lichen simplex chronicus, estrogen deficiency, dermatitis, candidiasis, lichen planus, vitiligo, psoriasis, and vitiligo should be explored [9, 11]. The diagnosis is generally made clinically, so careful history and physical exam are necessary. Punch biopsy may be performed to confirm diagnosis or when there is clinical suspicion for malignant transformation. Dermoscopy of the white areas in LS indicates epidermal atrophy and hyperkeratosis with possible telangiectasias [9].

Treatment

Treatment for LS is multimodal with a goal of decreasing pruritus. It includes topical therapies, systemic therapy, minimizing scratching, and good hygiene. Topical hormone therapy, including estrogen, testosterone, and progesterone, has been an effective treatment clinically. Estrogen has been used to decrease vaginal dryness in postmenopausal women with dyspareunia, or epidermal atrophy. Furthermore, 2% testosterone and progesterone can decrease inflammation of LS, but significant side effects have been noted [9]. First-line treatment includes potent topical corticosteroids, like clobetasol propionate 0.05% [9]. Patients should be instructed to apply the cream once a day for a month, then every other day for the next month, then twice a week for the third month. For maintenance therapy, patients can apply the cream 1–3 times/week [11]. Patients should be informed of the side effects of topical corticosteroids like skin atrophy, telangiectasias, and striae formation. Topical calcineurin inhibitors, such as tacrolimus 0.1% and pimecrolimus 0.1%, can be applied 2 times/day for up to 6 months for treatment and twice/week thereafter for maintenance therapy [11]. The calcineurin inhibitors help to decrease inflammation and pruritus. The typical amount that should be applied is ½ a fingertip's amount/dose [11].

There are a variety of treatments used for systemic therapy if topical treatment does not control symptoms. Acitretin 20–30 mg or isotretinoin 0.5–1 mg/kg can be taken once/day [11]. Retinoids can be helpful by decreasing fibroblast function, the size of sebaceous glands, sebum production, and abnormal keratinization [9]. Methotrexate 15 mg/week or cyclosporine 4 mg/kg for 3 months are also options to treat LS [11]. Potassium para-aminobenzoate has been shown to be clinically beneficial in some patients as an antifibrinolytic [9].

Surgical intervention may be indicated in complicated cases like vulvar intraepithelial neoplasia, malignancy, or with severe anatomic distortion. For example, extensive urethral involvement causing disturbances with micturition or sexual dysfunction may qualify for surgical intervention [12]. Current recommendations for surgery include postponing the procedure until disease activity is minimal. Surgery is more commonly recommended in penile lichen sclerosus and in patients whose medical management has failed [12].

Key Points

- Lichen sclerosus (LS) is a chronic inflammatory dermatologic condition typically involving the vulvar, anogenital, or extragenital regions.
- The clinical appearance of the lesions is a thin, atrophic white patch with a shiny appearance. The most common symptoms include pruritus, soreness, dysuria, anal discomfort, dyspareunia, and may even include incontinence.
- The pathophysiology of lichen sclerosus involves inflammation and infiltration with activated T-cells.
- Treatment includes topical therapies like corticosteroids but can move towards systemic therapies with retained emphasis on minimizing scratching and appropriate hygiene.

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Chapter 12
26-Year-Old Female with Itchy, Blisters on the Bilateral Arms and Buttocks

Natasha Baah, Austin Cusick, and Shannon C. Trotter

A 26-year-old female presented with itchy blisters on her bilateral arms and buttocks for about 2 years. She reported scratching them and they would pop easily. She was diagnosed with eczema in the past and treated unsuccessfully with topical steroids. She also noted that she lost about 15 pounds over the year and has bouts of diarrhea. She stated that her sister was just diagnosed with gluten sensitivity, and she wonders if she has the same issue.

On physical examination, there were multiple excoriated pink papules on the extensor surfaces of her arms and the buttocks. A few excoriated papules were also noted in her posterior hairline. A biopsy was performed and showed a subepidermal multilocular blister with papillary neutrophilic microabscesses and a mixed dermal infiltrate. Karyorrhexis was noted in the dermis. Direct immunofluorescence evaluation of the tissue demonstrated granular IgA deposits in the dermal papillae (Fig. 12.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Scabies
2. Linear IgA dermatosis
3. Poison ivy
4. Dermatitis Herpetiformis

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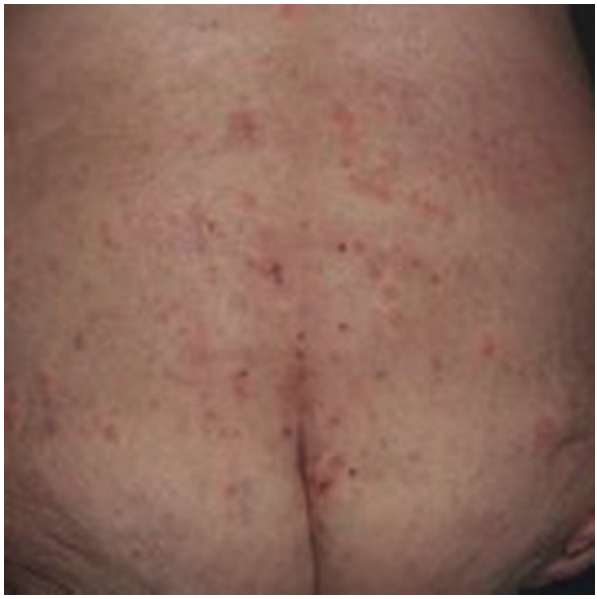

Fig. 12.1 Excoriated pink papules on the buttocks. Courtesy of Dr. Matthew Zirwas

Diagnosis

Dermatitis Herpetiformis.

Discussion

Dermatitis herpetiformis (DH) is an intensely pruritic, autoimmune disease that leads to secondary erosions and excoriations in affected areas. The clinical presentation of DH is unique to this dermatologic manifestation. Primary lesions are grouped, erythematous, and papulovesicular in nature. These lesions then erupt on the extensor surfaces of the upper and lower extremities, elbow, knees, scalp, nuchal area, and buttocks [1]. Less common areas of appearance include the upper back, groin [1], and rarely, the face [2]. DH may also be accompanied by other manifestations including mucosal ulcerations and dental abnormalities. The dental findings may include weakened enamel with noticeable color shifts [1].

DH, also known as Duhring-Brocq dermatitis, was first described by Louis Duhring in 1884 [1]. DH primarily affects males from Northern European descent in about a 2:1 ratio to females, most often during the fourth decade of adulthood [3]. Celiac disease (CD) is a common disease that has been associated with the formation of DH. Ironically, CD is more prevalent in females with ratios ranging from 2:1 to 4:1 in comparison to males [1]. Asian and African American populations are very rarely affected by CD [3]. The etiology of DH is multifactorial, but genetic

influences are significant. In patients with DH, about 85% are positive for the human leukocyte antigen (HLA)-DQ2 allele, while 15% contain the HLA-DQ8 allele [4]. In addition, 5–10% of DH patients have a first-degree relative affected by DH or CD [4]. DH is characterized by the deposition of IgA immunoglobulin autoantibodies against epidermal transglutaminases in a granular pattern at the top of the dermal papilla. More specifically, deposition occurs in the sublamina densa, a component of the epidermal basement membrane [5]. Deposition at the basement membrane components triggers an inflammatory response along the gut-skin axis that is not fully understood [4]. DH is linked to gluten intolerance, and as a result, is the primary cutaneous manifestation of CD, also known as gluten-sensitive enteropathy (GSE).

CD is a gastrointestinal disease characterized by the atrophy of small intestine mucosa secondary to a gluten-containing diet [6]. Examples of gluten-containing foods are wheat, barley, oat, malt, and rye. CD is triggered by the gluten's gliadin component at the N-terminus [6]. Small bowel biopsies are not necessary for DH diagnosis, but if taken, CD-like villous atrophy is present in almost all patients [7]. It is important to note that all DH patients will be gluten intolerant, but only less than 10% will have CD-like symptoms, which include diarrhea, cramps, and malabsorption [6]. Commonly with mild gastrointestinal disease, the only findings that are present could be an iron deficiency or pernicious anemia [1]. Other environmental factors causing DH include iodine exposure and tobacco smoking [3]. Other DH-associated autoimmune disorders include hypothyroidism, type 1 diabetes, vitiligo, Sjogren syndrome, rheumatoid arthritis, lupus erythematosus, and rarely Addison disease [1].

While pruritus is a significant symptom for DH and cause for the secondary manifestations, it is not certain the exact mechanism in the development of this symptomatology. Cytokine-based inflammation is considered one of the primary mechanisms behind pruritus from DH. Murine models with overexpression of IL-31 evoked pruritus with subsequent inflammatory cell accumulation [4]. In DH individuals, significant elevation of IL-31 levels in serum, with subsequent overexpression in the skin, help strengthen the possible role of this cytokine in itch [4]. Confirming the role of IL-31 in pruritus will help develop specific treatments for this often-refractory symptom.

A diagnostic algorithm for DH can utilize several laboratory techniques to determine the extent of involvement. In a patient with classic clinical symptoms of DH, a perilesional skin biopsy using direct immunofluorescence (DIF) will be used to analyze granular IgA deposits in the dermal papillae. With successful DIF, serum analysis of anti-tTG antibodies should be evaluated [8]. With both positive antibodies and DIF, the diagnosis of DH can be assured. If antibody testing yields a negative response, evaluation for HLA DQ2/DQ8 could help further direct future investigation. With positive HLA alleles, further analysis of anti-endomysium antibodies or anti-deamidated synthetic gliadin-derived peptides (DGP) could isolate a possible previous false-negative antibody assay. Another negative response then suggests evaluating for CD with a duodenal biopsy [8]. Recent investigation

suggests that epidermal transglutaminase (eTG) may be a more specific marker for DH; however, current diagnostic algorithms do not endorse this investigation [8].

While investigating DH lesions, other skin disorders that are closely related need to be ruled out. Linear IgA dermatosis should be considered, especially with the resembling clinical formation and histopathological overlap. Bullous pemphigoid must also be considered since it is also an autoimmune disease with vesicular lesion formation [1]. Other more common considerations for this differential should include atopic dermatitis, contact dermatitis, urticaria, and scabies [1].

Treatment

DH treatment consists of a combination of patient education and counseling, collaboration with a nutritionist, and close follow up with a healthcare professional. The gold standard for DH treatment is strict adherence to a gluten-free diet. Due to the slow, but progressive, course of treatment needed for skin resolution, most patients add dapsone 25–150 mg and topical corticosteroids daily to help manage the inflammation and severe pruritus [3, 8]. Due to the hematologic side effects of dapsone that include hemolysis, methemoglobinemia, and agranulocytosis, patients must undergo routine blood tests before and during treatment [3]. A major contraindication to dapsone use includes patients with glucose-6-phosphate deficiency (G6PD); however, topical formulation does not interact to the same degree as oral therapy [3].

The mechanism of dapsone in the use of skin manifestations is heavily debated. One possible mechanism is described as a reduction in reactive oxygen species. Dapsone based inhibition of calcium influx decreases oxygen radical formation intracellularly. Reactive species formation also has been investigated across several immune cells with varying results in correlation [9]. Dapsone is also hypothesized to directly inhibit myeloperoxidase. Inhibition of this enzyme prevents reactive oxygen species formation downstream [9]. Another investigation suggests evidence that dapsone inhibits integrin expression, decreasing neutrophil margination [9]. Other possible mechanisms of dapsone's therapeutic effect include TNF-α modification, IL-8 limited expression, and decreased production of COX pathway products [9].

Current literature findings and case reports suggest that colchicine, cyclosporine A, azathioprine, tetracyclines, and heparin have shown some efficacy in treating the rash in its acute stages [4]. It is possible that colchicine may be effective as second-line to the anti-neutrophilic effects it provides [4]. IL-31 based management may potentially provide widespread relief. Current investigation is to determine the possible effectiveness regarding IL-31 inhibitors and the role in treating atopic dermatitis [10]. As of now, the management of pruritus is reliant on overall disease suppression.

Key Points

- Dermatitis herpetiformis (DH) is a cutaneous manifestation of celiac disease associated with HLA-DQ2 and DQ8.
- DH's clinical presentation is a severe pruritic papulovesicular rash on the extensor surfaces of the elbows, knees, and buttocks.
- DH is classically associated with CD, but skin manifestations and gastrointestinal disease do not always correlate with one another well. Other common autoimmune conditions associated include hypothyroidism, type 1 diabetes mellitus, and Sjogren's disease.
- Diagnosis of DF can be made using direct immunofluorescence showing IgA in the papillary dermis with the presence of IgA anti-tissue transglutaminase (tTG) in the serum.
- Gold standard to treat DH is a multidisciplinary approach to care including, strict life-long adherence to a gluten-free diet, dapsone, corticosteroids, and patient education.

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Chapter 13
38-Year-Old Female with Intensely Itchy, Erythematous Scalp and Muscle Weakness

Ian McArdle, Pankaj Bansal, Austin Cusick, and Shannon C. Trotter

A 38-year-old female presented with itching and erythema of the scalp. She had been treated with antifungal shampoos and topical steroids with little improvement. She also reported a rash on the sun-exposed sites of her chest and back that would also itch. The rashes were treated with topical steroids and improved but would typically recur, especially after sun exposure. She reported difficulty with getting out of a chair and walking upstairs. She stated that her muscles just felt fatigued at times; she could not complete basic activities. In addition, she reported difficulty swallowing, joint pain, and fatigue.

On physical examination, there were scaly, erythematous patches on the scalp and poikilodermatous patches on the chest and back. There were flesh-toned papules noted on the metacarpophalangeal joints. A skin biopsy of the poikilodermatous eruption showed an interface dermatitis with an atrophic epidermis and a sparse perivascular lymphocytic infiltrate with increased dermal mucin. A direct immunofluorescence test of the tissue was negative for IgG, IgA, and IgM. A more detailed workup showed positive ANA, anti-Jo antibodies, elevated creatine kinase, and aldolase. A muscle biopsy showed perivascular and perimysial inflammation with perifascicular necrosis (Figs. 13.1 and 13.2).

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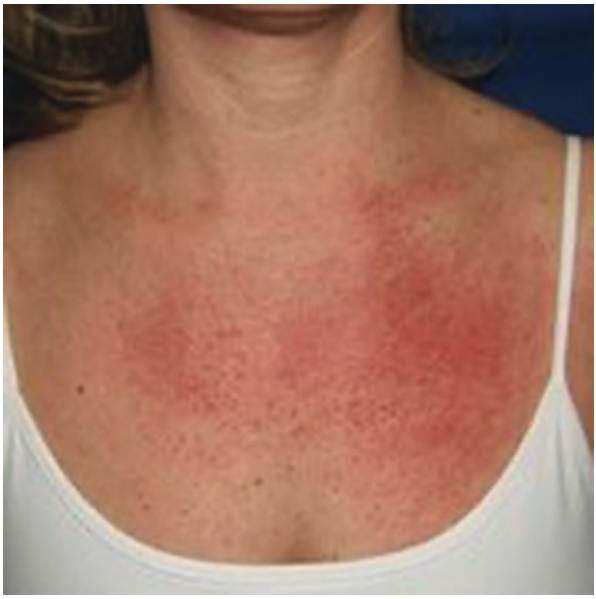

Fig. 13.1 Pokiolodermic patches on the chest. Courtesy of Dr. Matthew Zirwas

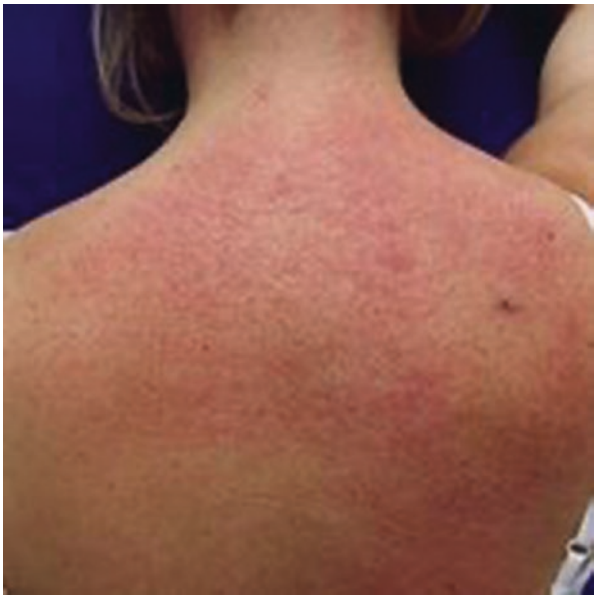

Fig. 13.2 Pokiolodermic patches on the back. Courtesy of Dr. Matthew Zirwas

Based on the clinical case description, what is the most likely diagnosis?

1. Polymyalgia rheumatica
2. Dermatomyositis
3. Lichen planus
4. Systemic lupus erythematosus

Diagnosis

Dermatomyositis.

Discussion

Dermatomyositis (DM) is an inflammatory muscle disorder and is described as an autoimmune disease. The incidence of dermatomyositis is approximately 2 per 100,000 in the general population with a female predominance of two to one [1]. The estimated prevalence of DM is cited from 5 to 22 per 100,000 [2]. The exact cause of DM is not completely understood; however, several genetic and environmental factors, including other diseases, are thought to play a role. Approximately 7–30% of DM is associated with various cancers including ovarian, breast, and lung as the most common system malignancies [3]. There is also a genetic aspect of DM which is linked to HLA-DRB1, and HLA-DQA1 serotypes in Caucasian individuals. With respect to Asian populations, HLA-B7 is predominantly linked to DM manifestation [4].

DM is a multifaceted disease that presents with a wide variety of clinical manifestations. The predominant clinical manifestations are muscle weakness and characteristic skin findings. Besides the typical muscle and cutaneous involvement, DM can involve other organ systems leading to pathologies including interstitial lung disease, myocarditis, inflammatory arthritis, and neuropathies. Proximal muscle weakness is typical, with the most common muscles affected being deltoids and hip flexors [5]. Muscle weakness is a shared characteristic of both DM and a related disease, polymyositis. However, skin manifestations are not typically seen in polymyositis. Approximately, 50–60% of patients with DM will show skin manifestations [5]. The two skin manifestations that are most common, and are considered pathognomonic for DM, are Gottron papules and a heliotrope rash. These cutaneous lesions are often pruritic as well. The Gottron papules are erythematous to violaceous slightly scaly plaques predominantly found on the metacarpophalangeal

joints and proximal/distal interphalangeal joints. The heliotrope rash is a purplish or lilac to erythematous rash involving the periorbital region, with or without edema [6]. Histopathologically, these photosensitive cutaneous lesions exhibit vacuolar interface dermatitis with increased dermal mucin.

Diagnostic testing for DM should include electromyography (EMG) and muscle biopsy in addition to other laboratory tests. With DM muscle involvement, EMG may reveal sharp waveforms with possible fibrillations. Affected nerves often recruit quickly with increased irritability [7]. Muscle biopsy of affected muscles will reveal mononuclear cell infiltration with necrosis. Cell infiltration can be found around the perimysial and endomysial sections with further perivascular infiltration as well [7]. Laboratory findings that assist in making the diagnosis of DM include elevated creatine kinase, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase [7].

The diagnosis of DM is based on the following criteria:

1. Symmetric proximal muscle weakness on physical exam.
2. Elevation of serum skeletal muscle enzymes such as creatinine kinase and aldolase, serum glutamate oxaloacetate, pyruvate transaminases, and lactate dehydrogenase.
3. Electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and neuronal irritability; and high-frequency repetitive discharges.
4. Muscle biopsy specimen abnormalities of degeneration, regeneration, necrosis, phagocytosis, and interstitial mononuclear infiltrate.
5. Typical skin rash of dermatomyositis, including a heliotrope rash and Gottron papules.

Diagnosis of traditional dermatomyositis is broken into three categories: definitive, probable, and possible. Using the above criteria, a definitive diagnosis is positive for all of 1–4, probable diagnosis is positive for three of 1–4, or possible diagnosis is positive for two of 1–4. Patients can also be definitively diagnosed with DM if they are positive for criteria number 5 plus three of criteria 1–4, probable if positive for criteria number 5 plus any two of criteria 1–4, or possible if positive for criteria 5 plus any one of criteria 1–4 [8]. Amyotrophic dermatomyositis is DM that is composed of skin manifestations without the typical muscle involvement. Criteria number five listed above helps isolate the possible causes of amyotrophic DM [8].

In addition to the above criteria, there are several autoantibodies associated with DM. Patients with DM are often positive for antinuclear antibodies (ANA), aminoacyl-tRNA synthetase antibodies, antibodies against histidine-tRNA ligase, or also known as anti-Jo-1 antibody, antibodies against signal recognition particle (SRP), and anti-Mi-2 antibodies [9].

The pathophysiology of the pruritus is not fully understood. Though, according to a 2018 study, there does seem to be an association between interleukin-31(IL-31) and dermatomyositis. The study showed a link between “itchy DM patients” and upregulation of IL-31. IL-31 takes part in numerous biological functions in the

body. IL-31 is an immunoregulator, a signal protein, a proinflammatory cytokine, a regulator of cell proliferation, and a component of propagating pruritic sensation [10]. More research is necessary to definitively determine the cause of pruritus in the disease.

DM is a complex disease with many associations varying from cancer to genetics. With that said, the proper diagnosis of DM is pertinent to patient care, especially when an underlying cancer diagnosis is a possibility. DM, with or without associated malignancy, can be life threatening. Delays in treatment may lead to musculature damage to the esophagus and diaphragm. Such damage can lead to severe dysphagia and respiratory distress resulting in the need for tube feedings and mechanical ventilation. Prompt diagnosis and aggressive treatment is of utmost importance and can prevent these severe outcomes.

Treatment

First, with the possibilities of malignancy in DM, all patients should be screened for common cancers associated, such as colon, ovarian, breast, and lung cancers. Age-related cancer screenings are essential to keep up to date to aid in screening DM patients.

There is no cure for DM, but there are many treatment options for the disease. Most treatment options for DM involve immune modulation and symptomatic control. The mainstay of treatment is glucocorticoid therapy [11]. Immunosuppressive agents should be initiated, along with steroids, with the goal to achieve steroid-free remission. Methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, cyclophosphamide, and rituximab have all been shown to be effective [12]. In patients who have life-threatening weakness or have severe dysphagia with aspiration risk, intravenous immune globulin can be used [13]. Antimalarials/disease-modifying anti-rheumatic drugs such as hydroxychloroquine have also proven to be effective in the treatment of the skin manifestations of DM [14].

Pruritus is often a significant complaint in patients with DM. There are a number of treatments that have shown efficacy in the treatment of pruritus including photoprotection, topical antipruritic agents, and oral antipruritic agents. Like most cutaneous disorders, photoprotection with sunscreens and limiting sun exposure is integral to management. Topical antipruritic agents such as pramoxine, menthol, lidocaine, or camphor have shown to give temporary relief [15]. The use of sedating antihistamines such as hydroxyzine, or cyproheptadine are also efficacious [16]. Oral antidepressants such as mirtazapine, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants have been shown to reduce pruritus in DM patients [17]. Calcineurin inhibitors such as tacrolimus have shown to be effective in the treatment of DM when pruritus is refractory to the previously described treatments [18]. Lastly, there have been advancements in the treatment of cutaneous DM. With the new era of biological treatments, medications such as rituximab, and others have shown varying degrees of success in the treatment of cutaneous DM [19].

Key Points

- DM is an autoimmune disease associated with muscular weakness in the proximal muscles and cutaneous symptoms.
- Diagnosis of DM is reliant on several factors including laboratory findings, classic skin manifestations, muscle biopsy, EMG, and clinical muscle weakness.
- DM is associated with several genetic alleles including HLA-DRB or HLA-DQA1 and the presence of several possible autoantibodies including Anti-Jo-1 and anti-Mi-2.
- Treatment is reliant on the use of corticosteroids and DMARD therapy with the goal of maintaining disease without steroids in the future.
- While relatively unknown, IL-31 is strongly associated with pruritus in DM. Treatment, beyond overall disease attenuation, includes topical anti-pruritic agents, antihistamines, SSRI's and tricyclic agents.

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Chapter 14
52-Year-Old Female with Itchy Skin After Showering and Red Palms

Michael Goldenberg, Ashwin Kumar, Daniel Manzanillo, Austin Cusick, and Shannon C. Trotter

A 52-year-old female presented to the clinic with a chief complaint of diffuse, intractable itching for the past 10 years. She reported that the itching is worse after she uses her hot tub as well as after taking hot showers. She noticed that after she scratches to alleviate the itching, she often creates red excoriation marks on her skin that take a while to resolve. The patient stated that she does not take any medications and is in good health otherwise.

On physical examination, her skin appeared normal overall. She had a few areas on her back where the skin was dry in texture. Her palms were red and blanched easily. Routine lab work was ordered. A CBC showed elevated levels of hemoglobin, red blood cells, and platelets. However, her erythropoietin levels were low (Fig. 14.1).

Based on the clinical case description, what is the most likely diagnosis?

1. Hot tub folliculitis
2. Irritant contact dermatitis
3. Polycythemia vera
4. Systemic lupus erythematosus

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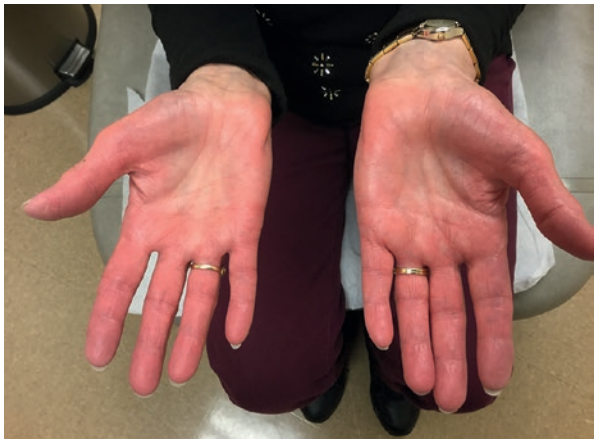

Fig. 14.1 Palmar erythema found on physical examination

Diagnosis

Polycythemia vera.

Discussion

Polycythemia Vera (PV) is a Philadelphia chromosome-negative, malignant, hematological neoplasm. PV usually results from JAK2 mutations, often *JAK2V617F* or *JAK2* exon 12 [1]. These mutations result in enhanced kinase activity with constitutive activation of downstream pathways including the MAPK pathway [2]. This results in resistance to apoptosis in hematologic cell lines [2]. The pooled rate of incidence for PV is less than 1%, with a median age of diagnosis of 61 years of age [3]. PV is the most common myeloproliferative neoplasm seen worldwide [4]. Approximately 40% of patients with PV have aquagenic pruritus (AP), which is itching, tingling, burning, or stinging associated with exposure to water. Notably, these patients will present without visible skin lesions. Current studies suggest JAK2 mutations have been shown to be more often associated with AP [1]. Classically, PV presents with increases in hematologic cell lines predisposing patients to complications [4]. The median survival rate for patients with PV diagnosed after the age of 60 years old is 14 years, while the median survival for patients diagnosed prior to the age of 60 is 33 years [5]. The leading causes of death in patients with PV include acute leukemia, secondary malignancies, thrombotic complications (including both venous and arterial), and heart failure [3].

The exact mechanisms of pruritus in PV are unknown, but there have been several theories suggested. Altered platelets and prostaglandins are possible components of the pruritic mechanism in PV [1]. This proposed mechanism is likely due to altered platelet-derived serotonin [1]. A serotonin-based mechanism reinforces

the effectiveness of selective serotonin reuptake inhibitors (SSRI) as antipruritic agents in PV [1]. There is also evidence that patients with PV have increased numbers of mast cells. Mast cells mediate the inflammatory and pruritic response through IgE allergic responses, release of histamine, tryptase, prostaglandins, and leukotrienes [2]. Although there is evidence that histamine plays a role in pruritus of PV, antihistamines have shown variable effectiveness in management [1]. In contrast, evidence suggests that pruritus correlated with increased levels of papillary dermal mast cells, rather than systemic histamine release. [2].

Although about half of patients with PV had AP prior to diagnosis, only a small percentage of physicians considered PV as a possible cause for the pruritus [1]. Unfortunately, patients can develop aquaphobia resulting in significant decreases in quality of life [1].

Differential Diagnoses

Unlike other myeloproliferative neoplasms, PV has high morbidity and mortality related to arterial and venous thrombosis [4]. Patients with PV often will have an increase in red blood cell mass, plasma volume, and total blood volume. Alterations in plasma volume and total blood volume may mask an abnormal hematocrit [4]. Persistent elevation of red blood cell count, hemoglobin, or hematocrit necessitates serum erythropoietin level evaluation. If the erythropoietin level is elevated, then various etiologies of absolute erythrocytosis can be considered. These include hypoxia, renal disease, EPO-producing tumors, drugs, and EPO receptor mutations. Likewise, causes of relative erythrocytosis also need to be considered including acute fluid loss or chronic contraction of plasma volume [4]. However, if the erythropoietin levels are normal or low, then a JAK2 genetic test should be performed. A negative JAK2 mutation may not rule out PV but may point to other absolute causes [4]. Diagnostic criteria for PV also include bone marrow biopsies to assess for hypercellularity of prominent erythroid, granulocytic, and megakaryocytic cells [3]. Other myeloproliferative disorders to consider include essential thrombocytopenia, chronic myeloid leukemia, and primary myelofibrosis.

Treatment

Primary goals of PV treatment include controlling symptoms and reducing the risk of thromboembolic events. The first line treatment for PV is phlebotomy accompanied with 40–100 mg of aspirin daily [5]. Phlebotomy acts by decreasing red blood cells, which subsequently reduces blood viscosity, to achieve an appropriate hemoglobin level [6]. Aspirin, as an adjunctive treatment, works by decreasing platelet aggregation and inhibiting prostaglandins, decreasing the overall risk of thrombosis [1]. Phlebotomy is usually well tolerated with limited side effects related to mild

fatigue. For patients who have a history of thrombosis, or who are over the age of 60, should be treated with hydroxyurea 500 mg twice daily. Hydroxyurea works by inhibiting ribonucleotide reductase, resulting in stunted DNA synthesis and cell growth [7]. If the patient cannot tolerate hydroxyurea, treatment includes pegylated interferon-α (IFN-α) or busulfan [5]. IFN-α reduces red blood cell proliferation, while busulfan is an alkylating chemotherapeutic agent that inhibits hematopoiesis [5, 8]. Although IFN-α has shown similar efficacy to hydroxyurea, it has a higher toxicity rate [5]. Ruxolitinib, a newer medication targeting JAK2, can also be considered as an option for hydroxyurea refractory PV, but long-term safety is still undetermined. Further, it has not shown molecular remission, unlike pegylated IFN-α or busulfan [5] (Fig. 14.2).

However, if the pruritus associated with PV is not resolved by treating the disease systemically, then more targeted therapy may be warranted. Other treatments specifically aimed at the pruritus can also include antihistamines, SSRIs, clopidogrel, anagrelide, pregabalin, IFN-α, and narrow-band ultraviolet B phototherapy

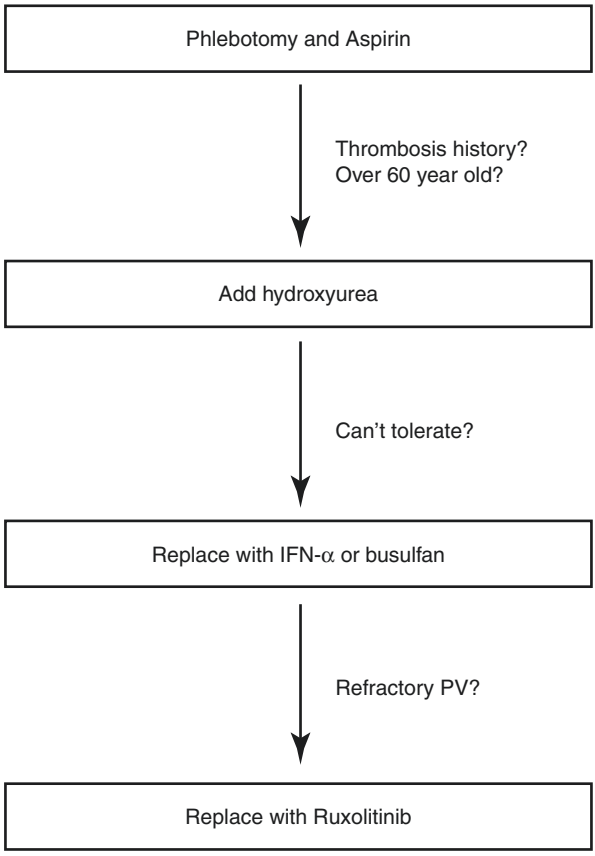

Fig. 14.2 Treatment algorithm for treating PV

[3, 5, 9]. Antihistamines have variable efficacy in aquagenic pruritus [10]. Some evidence suggests efficacy of SSRIs in PV-induced pruritus. SSRIs have been hypothesized to mediate serotonin release by mast cells [10]. Clopidogrel works as an antiplatelet drug by irreversibly antagonizing ADP receptors, preventing platelet aggregation [11]. Anagrelide inhibits megakaryocyte differentiation into platelets [12]. Pregabalin acts by decreasing calcium influx in nerve endings, affecting neurotransmission [10]. Phototherapy may help with itching by decreasing the number of peripheral nerve endings with calcitonin gene-related peptide (CGRP) receptors, which is especially effective in inflammatory conditions [10].

In order to prevent complications such as pruritus, it is important to also educate patients with PV to avoid scratching their skin, bathing in cold water and less frequently, avoiding hot tubs, and keeping the skin well moisturized [13].

Key Points

- Polycythemia Vera is a hematological, neoplastic, myeloproliferative disorder associated with JAK2 mutations that can present with pruritus in approximately 40% of patients.
- Patients with persistently elevated red blood cell mass, hemoglobin, or hematocrit should be considered for a workup of PV, especially if they have low erythropoietin.
- First line treatment for PV should include phlebotomy and aspirin, with hydroxyurea added in most refractory cases.
- If pruritus is not sufficiently treated with overall disease management, consider antihistamines, SSRIs, and JAK2 inhibitors like ruxolitinib.

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Chapter 15
31-Year-Old Female with Diffuse Itchy Skin and Nail Changes

Abbey Cusick, Amandeep Goyal, Austin Cusick, and Shannon C. Trotter

A 31-year-old female presented with diffuse itching for about 6 months. She expressed frustration because she had seen three different doctors who told her that her itching is because of her anxiety. She reported heavy periods, which she had for years. She also mentioned frustration with her fingernails and stated they have become thin over time. She wondered if her nail changes were related to using acrylic nails. Her medications included sertraline for the past 6 years.

On physical examination, her skin appeared normal overall. She had no evidence of rash but demonstrated excoriation marks on the arms and legs. Her nails had raised ridges and were thin and curved inward, consistent with koilonychia. A laboratory workup showed a microcytic anemia and low ferritin.

Based on the clinical case description, what is the most likely diagnosis to explain her itch?

1. Iron deficiency anemia
2. Irritant contact dermatitis

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3. Polycythemia vera
4. Medication-induced itching

Diagnosis

Iron deficiency anemia.

Discussion

Anemia is classically described as a reduced quantity and quality of red blood cells. Hemoglobin levels typically fall below two standard deviations the accepted mean for an individual's gender and age [1, 2]. An estimated 25% of the global population is affected by anemia, half of which are diagnosed with iron deficiency anemia (IDA) [2]. Iron serves as a crucial component of hemoglobin production; therefore, patients with insufficient levels of available iron in their bodies are unable to produce enough hemoglobin to sustain normal function. Ultimately, affected individuals' red blood cells become microcytic and hypochromic, with a concomitant decrease in reticulocyte count [2]. Consequently, the body does not have the ability to efficiently oxygenate the blood, potentially causing significant issues such as high-output heart failure, impaired mental or physical development, decreased learning ability, preterm labor, and compromised cell-mediated immunity [3].

IDA is a multifactorial disease. There are numerous methods by which the body can become iron deficient leading to IDA including blood loss, increased iron demand, inadequate dietary intake, and malabsorption [4]. Blood losses causing IDA usually occur in obvious manners, easily distinguishable to clinicians. These include traumatic hemorrhage, hematemesis, hemoptysis, excessive menstrual bleeding, child delivery, and hematuria. However, the onset of IDA may be attributed to forms of bleeding that are not as apparent, such as frequent blood donation, significant diagnostic testing, hemodialysis, gastrointestinal bleeding, and gastrointestinal parasites [4]. In addition to hemoglobin production, iron is crucial in various enzymatic processes including DNA synthesis, and mitochondrial energy generation. Thus, individuals subject to rapid growth, like infants, children, adolescents, and pregnant women, experience an increased iron demand. In these states, the body's maximum daily iron absorption is likely below the amount required for maintenance functioning; therefore, iron deficiency, and subsequent anemia, may develop [4]. There are two main forms of dietary iron, heme and non-heme. Heme iron is present in animal sources like red meat, poultry, and seafood. It is the most readily absorbed form of iron as it accounts for over 40% of total absorbed iron. Non-heme iron is associated with plant diets in sources like black tea, cereals, and dried fruits; however, it is not as readily absorbed by the body [4]. Therefore, individuals following plant-based diets are missing a staple source of iron. Iron

malabsorption is commonly induced by specific gastrointestinal issues or modifications including celiac disease, gastrectomy, gastric bypass surgery, and *Heliobacter pylori* infections [4]. Additionally, malabsorption may be induced by medications that decrease stomach acidity such as proton pump inhibitors and H2 receptor antagonists [4].

The prevalence of each cause is based on the population's age, gender, and socioeconomic status [2]. In underdeveloped areas, individuals are most at risk for insufficient dietary intake and blood loss due to parasitic infections [5]. Meanwhile, developed countries are most susceptible via iron-lacking nutrition, chronic blood loss, or malabsorption [5]. Additionally, women are more likely to be affected by IDA than men [1]. Overall, infants, adolescents, women of menstruating age, vegetarians, and older adults have an increased risk by being exposed to one or more of the potential causes for a long period of time [5].

Iron deficient and subclinical IDA patients may be asymptomatic or experience relatively nonspecific symptoms [4]. As IDA progresses, the symptoms heighten in frequency and intensity. The most common symptoms are noticeable pallor of the skin and nail beds due to the diminished red blood cells, chronic fatigue, dyspnea, and headache. However, these symptoms can sometimes be confused as signs of other conditions [4]. Therefore, it is important to be aware of other frequent but lesser-known symptoms to provide a more accurate diagnosis such as sporadic to moderate alopecia, restless leg syndrome, tachycardia, arrhythmia, pica, and koilonychia [4]. Additionally, IDA patients may present with dry, rough skin and a generalized but persistent sensation of pruritus as denoted in the case of interest. Pruritus is a common symptom of multiple systemic diseases and its direct connection to IDA remains ambiguous. Based on previous case studies, researchers have postulated potential hypotheses regarding the relationship between pruritus and IDA. One thought rationalizes that the combination of abnormalities in epithelial tissues and potential for neuropathy, caused by iron deficiency, may induce pruritus [6]. A different theory addresses the possibility IDA triggers the onset of cutaneous xerosis, a highly accepted pruritus origin [7]. As previously mentioned, iron deficiency obstructs DNA synthesis potentially limiting cutaneous cell replacement and skin thickness. Moreover, decreased levels of serum iron may cause errors in the dermis' elastic fibers, thus forming the foundation of cutaneous xerosis [7]. Additionally, iron has a role in wound healing and collagen formation. Therefore, iron deficiency may lead to decreased skin healing and further xerosis [8]. In all cases, iron loading can alleviate pruritus, reducing the need for further research on the link between IDA and pruritus [6, 7].

Treatment

Standard IDA treatment consists of a two-step process. The first step is to identify the specific cause of the condition and correct it when possible. After the source is identified and managed, the patient will undergo some form of iron replacement

therapy [9]. The type of therapy prescribed to the patient depends on the severity of the disease and medical history. The first type, oral iron supplements, are available in a wide variety of formulations such as ferrous sulfate, ferrous citrate, ferrous gluconate, ferrous chloride, ferrous ascorbate, and carbonyl iron [9]. The goal of these supplements is to provide 100 mg of additional iron daily. Traditionally, these supplements are prescribed for multiple doses a day [9]. However, more current studies are finding that iron supplementation in single doses and on alternating days has significantly increased iron absorption over traditional patterns [10]. The second most utilized iron therapy is intravenous (IV) iron supplementation [9]. Once again, there are multiple formulas with the same clinical effectiveness including ferric carboxymaltose (FCM), ferric gluconate (FG), ferumoxytol, iron sucrose (IS), ferric derisomaltose, and low molecular weight iron dextran (LMW ID). The goal of IV iron is to deliver 1000 mg of elemental iron to the patient in each dose [9]. The third treatment is the use of blood transfusions only to be used in critical situations where all other available treatments are inadequate or in circumstances where patients are actively bleeding [11].

Currently, there is debate over the use of oral iron versus IV iron for IDA patients. Therefore, it is important to note the advantages and disadvantages of each therapy to ensure clinicians utilize the most beneficial course of action based on the patients' circumstances. Oral iron is known as an inexpensive and convenient method of iron replacement as it is available over the counter and can be taken from home [11]. However, this method is impeded by significant gastrointestinal side effects and the limited maximum daily absorption capabilities of the intestines. Additionally, individuals who suffer from malabsorption-induced IDA cannot be treated with oral iron. IV iron provides a faster source of iron repletion and proves effective in absorption-impaired patients [11]. Negatively, it is more costly as it carries the burden of requiring a healthcare professional for administration and imposes a risk of anaphylaxis [11].

IDA patients experiencing cutaneous xerosis and pruritus may utilize additional treatments for symptom management until iron therapy corrects the issue. Initially, a series of nonpharmacological actions are recommended to reduce the chance of exacerbation. These methods include eliminating potential skin irritants like harsh cleansers, maintaining a cool environment for skin, and avoiding scratching [12]. Additionally, daily use of moisturizers is highly advised [13]. These products help the skin retain moisture and improve barrier protection [13]. If the symptoms persist or worsen and inflammation occurs at the affected sites, topical glucocorticoids are prescribed [12]. IDA results in the abnormalities of red blood cells and their ability to carry oxygen. Consequently, the condition results in decreased overall function in several cellular mechanisms which manifest in symptoms such as fatigue, pallor, arrhythmias, and others. Ideally, iron supplementation is the mechanism of choice in remedying all symptoms of IDA.

Key Points

- IDA is the most common form of anemia. Several factors can predispose a patient to IDA including pathological causes, diet factors, and medication causes.
- Several theories exist on the mechasim of ruritus linked to IDA.
- The best treatment for IDA includes iron replacement therapy.
- If pruritus is refractory, other measures can be taken to reduce this sensation. Ointments, avoiding irritating skin environments, and topical corticosteroids can be beneficial.

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Chapter 16
73-Year-Old Male with Diffuse, Itchy Skin

Ashwin Kumar, Daniel Manzanillo, Austin Cusick, and Shannon C. Trotter

A 73-year-old male presented with a 10-year history of diffuse, intractable itching. He described the itching as migratory in nature with varied intensity. He stated that he has tried multiple medications including over the counter emollients, antihistamines, topical, and oral steroids. The patient had a medical history of controlled hypertension and type II diabetes mellitus. He stopped his medications for several weeks at the instruction of his primary care physician, but reported no improvement in itch. He denied having a thorough laboratory evaluation for his profuse itching. He reported being up to date on all age-appropriate cancer screening and routine labs.

On physical examination, his skin appeared normal with the exception of xerosis on the lower extremities. He had excoriation marks on the arms and upper back. A laboratory workup was initiated. Complete blood count, thyroid function, liver function, and kidney function were all within normal limits. Copies of his PSA value and colonoscopy report were reviewed, and the results were non-contributory. A hepatitis panel showed positive HCV antibodies and was subsequently confirmed with a positive HCV RNA test. He was referred to infectious disease and started on therapy.

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Based on the clinical case description, what is the most likely diagnosis to explain his itching?

1. Medication-induced itching
2. Generalized xerosis
3. Chronic hepatitis C infection
4. Idiopathic itch

Diagnosis

Chronic Hepatitis C infection.

Discussion

Hepatitis is a broad diagnosis that stems from viral, autoimmune, or idiopathic etiologies. Despite its numerous causes, viral hepatitis is the most common with an estimated worldwide 1.4 million deaths yearly [1]. Composed of a group of families of viruses, the main culprits of the disease include hepatitis A, B, C, D, and E virus. Hepatitis can lead to cholestasis, cirrhosis, and hepatocellular carcinoma, making early diagnosis and intervention necessary [1].

Hepatitis-induced pruritus is a common condition seen to affect patients most commonly with hepatitis C (HCV). Extrahepatic manifestations of hepatitis C include renal disease, vasculitis, and cutaneous manifestations. Pruritus can be used as an important prognostic factor, as its presence is shown to increase the propensity for the development of chronic viral infection [2]. The currently proposed mechanism stems from an accumulation of bile acids that trigger the activation of G-protein coupled receptors (GPCR) which activate the downstream protein vanilloid 1 (TRPV1) ultimately resulting in widespread itching [2]. Further studies have suggested that hepatitis C viral infection can cause pruritus through both direct and indirect mechanisms. The direct mechanisms include the production of proinflammatory chemokines and cytokines, which include IL-8, CCL2, and CXCL5 [2]. Indirect mechanisms for itching center around cholestasis as a consequence of chronic HCV infection. Cholestasis leads to autotaxin accumulation, which in turn converts lysophosphatidic choline into lysophosphatidic acid (LPA). There is a suggestion that LPA is known to be associated with the development of chronic liver disease and causes pruritus through the stimulation and sensitization of epidermal nerve endings [2].

Treatment

Treatment of pruritus in HCV is complex and currently without routine guidelines. It is recommended to attempt to use trial by error for medications in these patients and that distinction needs to be made between patients with cholestatic and non-cholestatic disease. For patients with cholestatic disease, first-line treatment often involves ursodeoxycholic acid (UDCA) to treat the underlying disease in a dose of 10–15 mg/kg/day is a medication that binds bile acids and increases excretion via upregulation of calcium and protein kinase C dependent mechanisms [3, 4]. UDCA is a well-tolerated medication with minimal side effects mainly related to gastrointestinal distress being reported.

The first-line agent should be a bile acid sequestrant such as cholestyramine at an initial dosage of 4 g/day [5]. Bile acid sequestrants reduce enterohepatic uptake of bile salts thereby decreasing their concentration in the body. Most common side effects include constipation and unpleasant taste. In patients in which cholestyramine is ineffective, rifampicin, an anti-tuberculosis drug, may be used.

As a second-line agent, rifampicin acts by inducing cytochrome P-450 enzymes as well as detoxification enzymes within the hepatocytes [3]. Upregulation of these enzymes results in increased excretion and detoxification. By inducing drug-metabolizing enzymes and transporters such as the pregnane X receptor, the drug enhances the metabolism of pruritogens [6]. Furthermore, autotaxin (ATX) is an enzyme that is elevated in serum concentrations of patients with cholestasis induced itching [3]. Rifampicin reduces ATX levels at the DNA synthesis transcription phase. Doses start at 150 mg and can be increased to a maximum of 600 mg daily. Rifampicin can be hepatotoxic and cause hepatitis, which requires a follow-up liver profile and stoppage if there is an elevation of liver enzymes [6]. Of note, it is also important to monitor INR in these patients as the drug can affect vitamin K metabolism [3]. Serious but rare side effects include hemolytic anemia, thrombocytopenia, and renal impairment. Patients should also be warned of discoloration of tears, urine, and other bodily secretions to a red, orange, or brown color during their treatment [7, 8].

In patients with refractory itching, naltrexone the μ-opioid antagonist may be used. Opiate receptors are ubiquitous within the epidermis and binding of low dose naltrexone results in reduced pruritus. Studies have suggested the initiation of naltrexone at low dosage (12.5 mg) and increasing to an eventual daily dose of 50 mg [3, 9]. High levels of naltrexone are associated with hepatocyte injury, elevated liver function tests, withdrawal, and gastrointestinal distress. Also, sertraline, a selective serotonin reuptake inhibitor (SSRI) may be used as a fourth-line treatment. At a dosage of 75–100 mg/day, it has been shown to have moderate antipruritic effects [3]. However, the usage of sertraline should be cautioned as it is mainly metabolized in the liver and therefore reduction in frequency, as well as dosage, should be considered in patients with advanced disease [3].

The previous four medications have been extensively studied and have proven efficacy in the treatment of pruritus. Patients who continue to show resistance may be treated with drugs and modalities with anecdotal support. The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) have made recommendations that experimental approaches may be used if the previous four medications all fail. This includes ultraviolet phototherapy. Studies have shown that patients that undergo ultraviolet therapy for itching may have anywhere from a 60–80% reduction in itching [10]. The likely mechanism while incompletely described is due to influence of itch nerve endings. Patients generally tolerate phototherapy with minimal to no side effects. Further studies are needed to investigate its long-term efficacy [3]. Invasive modalities that have shown some efficacy in treating refractory pruritus include plasmapheresis and albumin dialysis. Plasmapheresis has appeared to have a transient, short-lived effect that aims to remove pruritogens from the body. Albumin dialysis clears bile acids, bilirubin, and any other albumin-bound substances that contribute to intractable pruritus [11]. Although it has been shown to be effective in providing transient relief of pruritic symptoms, Albumen dialysis is extremely time-consuming and expensive. Nasobiliary drainage (NBD) has shown some effectiveness in treating pruritus refractory to standard medications. Nasobiliary drainage is carried out through the placement of a nasobiliary catheter into the common bile duct during endoscopic retrograde cholangiopancreatography. The bile is drained via the external end of the catheter for continuous drainage. In a study conducted that sought to determine the efficacy and safety of nasobiliary drainage, the results showed that the median percentage decrease in pruritus using the Visual Analogue Scale (VAS) was 94% in post-NBD patients. Also, the study showed that the median duration of treatment response was 50 days. However, adverse effects such as post-ERCP pancreatitis and post-ERCP acute cholangitis were seen in 34% of patients following nasobiliary drainage [12]. Although it has been shown to provide transient relief in cholestatic pruritus, it is an invasive procedure that frequently is associated with serious complications. If all the above options have failed, liver transplant is an effective means of eliminating pruritus. However, issues may arise regarding organ allocation priority in patients with HCV-induced pruritus [6].

Key Points

- Hepatitis is a group of diseases with numerous etiologies. Most common is viral hepatitis with an estimated 1.4 million deaths worldwide yearly.
- Hepatitis is concerning for its propensity to develop chronic liver disease and potentially hepatocellular carcinoma.
- Pruritus secondary to hepatitis is most seen with hepatitis C virus. Itching can be used as a prognostic factor and that the development of chronic liver disease is associated with itching.
- There are numerous treatment methods for pruritus, however, no universal guidelines exist.

- At this time, medications such as cholestyramine, naltrexone, sertraline, and rifampicin should be used toward the treatment of hepatitis C pruritus with Cholestyramine being used as a first-line agent due to its proven efficacy.
- Patients refractory to standard treatment may be treated via experimental approaches. This includes ultraviolet phototherapy, plasmapheresis, albumen dialysis, and nasobiliary drainage.

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Chapter 17
49-Year-Old Male with Itchy Skin and Abnormal Liver Function Tests After Antibiotic Use

Harsh Patel, Ziyue Wang, Austin Cusick, and Shannon C. Trotter

A 49-year-old male presented for follow up on his acne. He had been taking doxycycline for the past 4 months as well as a multivitamin, turmeric, cinnamon, and garlic supplements. He reported that his skin has a yellow tone and he had been itching over the past few weeks. He denied abdominal pain.

On physical examination, his skin was jaundiced but there was no evidence of rash. Due to his appearance and itching, an immediate referral to gastroenterology was made. A laboratory workup was also initiated. His liver enzymes were abnormal. Viral hepatitis and autoimmune hepatitis serologies were negative. A magnetic resonance cholangiogram was normal. Repeat liver function tests showed bilirubin levels continued to increase. A liver biopsy was performed and demonstrated cholestatic hepatitis.

Based on the clinical case description, what is the most likely diagnosis to explain his itching?

1. Drug-induced cholestasis
2. Acne vulgaris
3. Alcohol-induced hepatitis
4. Peptic ulcer disease

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Diagnosis

Drug-induced cholestasis.

Discussion

Cholestasis occurs when there is impairment of bile secretion from the hepatobiliary system. Further, accumulation of bile in the hepatobiliary system and/or systemic circulation may precipitate downstream symptoms including pruritus. Drug-induced cholestasis can be precipitated by alterations in various hepatocellular and bile canaliculi dynamics [1]. Drugs can adversely inhibit exportation of bile salts via the export pumps into the canaliculi. Therefore, a possible mechanism for drug-induced cholestasis involves bile salt export pumps (BSEP) [2]. Drugs, and subsequent metabolites, inhibit the cytoplasmic side of the protein leading to cholestasis. In addition, it has been hypothesized that drugs may affect the transcription of the *ABCB11* gene and BSEP proteins. As a result, drug-induced cholestasis may be a combination of both BSEP repression and inhibition [2, 3].

The risk factors for drug-induced cholestasis are poorly understood. Age over 60 years has been identified as an independent risk factor, irrespective of the drug. The age-related physiologic changes in the volume of distribution, body-fat content, and gene expression can contribute to cholestasis [4]. Genetic studies have identified strong associations between human leukocyte antigen (HLA) B*5701 and flucloxacillin-induced cholestasis. Associations between amoxicillin clavulanate-induced stasis and HLA haplotypes-DRB and -DQB have also been documented [4]. Furthermore, tetracycline-induced cholestasis has been associated with large intravenous doses and dose-dependent oral forms. Overall, the incidence of tetracycline-induced liver injury is relatively rare, accounting for 1.5 cases per 100,000 prescriptions or 3.7 cases per 100,000 users with a generally good prognosis [5, 6]. One particular reported case described a farmer with depersonalization and derealization syndrome ingesting 1 g of doxycycline per day for more than 12 years [7]. The patient reported having hepatocellular necrosis with cholestasis, leukopenia, anemia, nephrotoxicity, sporadic Wenckebach heart block, and skin hyperpigmentation. Interestingly, he did not present with the common side-effects of doxycycline that are photosensitivity, esophagitis, colic, and abdominal discomfort [7].

Drug-induced cholestasis usually presents with unpredictable, idiosyncratic reactions. Generally, most patients remain asymptomatic, but they can present with vague symptoms such as nausea, malaise, fatigue, and anorexia. Painless jaundice, with or without pruritus, can also be observed and resolves after drug withdrawal [4]. In elderly patients, severe pruritus has been linked with sleep deprivation and psychological abnormalities [8]. Cancer drugs are also well known for inducing cholestasis and having adverse reactions including facial/scalp eruptions, alopecia,

and pruritus [9]. One of the studied drugs is sorafenib (a kidney/thyroid/liver chemotherapy), which induces adverse cutaneous reactions by mast cell degranulation [9]. The drug seems to stimulate mature mast cells only, as it did not induce proliferation or apoptosis of mast cells [9].

While herbal supplements seem to have an overall protective effect on the liver, there has not been a distinct association made between a patient's supplements and cholestatic liver injury. Epidemiologically, the incidence of herbal and dietary supplements seems to be increasing. Recent investigation suggests supplements accounted for 20% of liver injury in 2014 [10].

Even though the pathophysiological mechanism for pruritus remains unknown, possible mechanisms included high concentrations of bile salts in tissues and serum, increased opioidergic tone, alteration of serotonin neurotransmitters, and lysophosphatidic acid [8].

There has been conflicting evidence reported for bile acids as a possible trigger mechanism for pruritus. Experimentally, when normal volunteers are injected with bile acids intracutaneously, they report local itch. When a synthetic bile acid, i.e., cholylsarcosine is administered to patients with primary biliary cirrhosis, worsening pruritus was reported. On the other hand, patients with liver failure whose bile acids are elevated tend to report disappearance of pruritus. Also, not all patients with high serum bile acids concentration report pruritus, and those who do, have fluctuating levels of serum concentrations of bile acids [11].

The role of serotonin is not well defined in pruritus, but the treatment with selective serotonin reuptake inhibitors (SSRIs) is discussed under the treatment section. Therefore, the positive outcome of treatments with SSRIs suggests that serotonergic pathways are important in the pathophysiology of pruritus. Increased histamine levels have been reported in patients with cholestasis and pruritus, but the skin of these patients does not show classic erythema and edema associated with histamine-mediated reaction. Antihistamines, specifically hydroxyzine, does provide relief to some of these patients. However, it has been hypothesized that the sedative effect, and not the antipruritic effect, provides relief for patients [11].

Lysophosphatidic acid (LPA) has also been associated with the pruritus of cholestasis. LPA induces nociception by releasing substance P from the peripheral nerve endings. Autotaxin is the enzyme that produces LPA. Furthermore, autotaxin activity has been reported to be higher in pregnant patients with cholestasis and patients with cholestasis and pruritus from liver disease. The activity of this enzyme decreases in patients who are treated with rifampin antibiotics, suggesting that rifampin decreases the activity of autotaxin and pruritus [11].

Substance P is an excitatory neurotransmitter synthesized and released by the primary afferent nociceptors with the action via the neurokinin (NK)-1 receptor in the spinal cord. The increased opioidergic tone associated with cholestasis may promote nociception instead of analgesia in part by the NK-1 receptor activity. The enhanced nociception may also be perceived as pruritus in part by substance P activity. Research has shown that the concentration of two endogenous opioids (Met-enkephalin and Leu-enkephalin) increases significantly in livers from rats and patients with cholestasis and liver disease, respectively. This theory is further

supported by triggering opiate withdrawal-like reaction in patients when given an opiate antagonist [11]. In rat models, the mu and delta receptors are also downregulated in the brains of rats with cholestasis. Meta-analysis investigating naltrexone, nalmefene, and intravenous naloxone concluded that the opiate antagonists lead to a significant decrease in pruritus of cholestasis [12]. Positive outcomes of opioid antagonists strengthen the plausibility of the opioid receptor's role in the pathophysiology (Fig. 17.1).

Treatment

Treatment for drug-induced cholestasis includes removal of the offending drug and symptomatic management. Ursodeoxycholic acid can be prescribed as a potential treatment for cholestasis as the drug protects against cytotoxicity secondary to bile salts accumulation. It also has a protective effect on the hepatobiliary system as it stimulates secretion, enhances glutathione production, and provides antioxidative property [14]. Associated mild pruritus can often be managed with emollients, warm baths, and/or histamine 1-receptor blockers. For moderate to severe pruritus, bile acid resins, i.e., cholestyramine or colestipol are considered first-line treatment [8]. Other treatments include rifampin, opioid analogs, and phenobarbital. Ultraviolet B phototherapy and plasmapheresis have also been reserved for drug-resistant treatment [13].

When the offending agent cannot be discontinued, for example, aggressive chemotherapy, there has been a management algorithm that can be used for reference [15]. Prophylactically, gentle skincare including moisturizer and proper cleaning is recommended. The management for pruritus usually starts with topical antipruritic and topical steroids, for non-controllable pruritus, oral antihistamines are added. The next step in management is the addition of systemic treatments including [15] GABA agonists, pregabalin, gabapentin, doxepin, aprepitant, or corticosteroids [15].

Randomized placebo-controlled studies, investigating the association between SSRIs use and relief of cholestatic pruritus, highlighted a unique treatment possibility. The study concluded that sertraline provided relief from pruritus and showed improvement of skin of the patients on physical exam [16]. The authors also proposed a couple of hypotheses for sertraline induced relief. Sertraline may mediate the serotonergic signals of the itch pathways in the central nervous system by providing inhibitory signals. With respect to psychosocial stressors and pruritus, sertraline's role in inhibiting stress may also improve pruritus [16]. In addition, SSRIs have been reported to decrease pruritus associated with polycythemia vera, multifactorial malignancy pruritus, and in patients with nocturnal itch from skin diseases [11].

Disease	Potential drug-induced cholestasis offend-ers
Bacterial Infection	Penicillins
	Sulfonamides
	Fluoroquinolones
	Tetracyclines
	Clindamycin
Fungal Infection	Terbinafine
	Griseofulvin
	Ketoconazole
	Itraconazole
Viral infection	Stavudine
	Didanosine
	Nevirapine
Inflammatory disease/acute injury	Diclofenac
	Sulindac
	Piroxicam
	Ibuprofen
	Phenylbutazone
	Gold
	Penicillamine
	Allopurinol
	Azathioprine
Psychiatric disease	Chlorpromazine
	Prochlorperazine
	Fluphenazine
	Thioridazine
	Tricyclic antidepressants
	Risperidone
	Duloxetine
	Benzodiazepines
	Diazepam
Others	Oral contraceptives
	Anabolic steroids
	Warfarin
	Thiabendazole

Fig. 17.1 Common agents that induce cholestasis [8, 13]

Key Points

- Drug-induced cholestasis is caused by gene expression alteration and direct protein inhibition of BSEP leading to accumulation of bile salts within tissues and serum.
- It is usually asymptomatic but can present as pruritus, jaundice, and/or other vague symptoms. While the risk factors are poorly understood, there has been a strong association made with HLA-B*5701.
- While the exact interaction between cholestasis and pruritus is unknown, several mechanism components have been suggested including substance P, serotonin, and LPA.
- Treatment usually warrants removal of the offending agent and the associated pruritus can be treated with emollients, antihistamines, and bile acid resins.

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Chapter 18
65-Year-Old Male with Itchy, Dry Skin

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A 65-year-old male presented with itchy, dry skin on the trunk and extremities. He reported that the itching was worse on his lower extremities and tops of his feet. He had a history significant for hypertension and type two diabetes mellitus with diabetic neuropathy.

On physical examination, his skin was diffusely dry, especially on the lower extremities. He had excoriation marks on the shins and dorsal feet. A laboratory workup for itching was within normal limits. His hemoglobin A1C was 7.9. He was up to date on age-appropriate cancer screening.

Based on the clinical case description, what is the most likely diagnosis to explain his itching?

1. Diabetes mellitus and diabetic neuropathy
2. Tinea corporis
3. Allergic contact dermatitis
4. Hypertension

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Diagnosis

Diabetes mellitus and diabetic neuropathy.

Discussion

Diabetes mellitus (DM) is defined as a group of metabolic disorders that arise from abnormalities in insulin secretion, action, or a combination of the two [1]. Insulin is an anabolic peptide hormone secreted from pancreatic β cells found in the islets of Langerhans [2]. It plays a crucial role in blood glucose maintenance and macromolecule metabolism in the body. In healthy individuals, insulin is secreted in counterbalance with glucagon as a response to physiologic changes in blood glucose. The primary role of insulin is to facilitate intracellular transport of blood serum glucose so it can be utilized as an energy source for various tissues including muscle and adipose [2]. By doing so, the body suppresses the need for triglyceride hydrolysis or gluconeogenesis by promoting glycogen synthesis and carbohydrate use instead [2]. Therefore, due to insulin dysfunction, diabetic individuals are unable to properly access or utilize their blood glucose causing them to suffer from chronic hyperglycemia. If not controlled properly, this condition is associated with an extensive list of symptoms and comorbidities including glaucoma, vision loss, heart failure, ketoacidosis, coma, or even death [1]. In 2019, it was estimated that 463 million adults from 20–79 years of age are living with diabetes, translating to approximately 9.3% of the global population [3]. Additionally, 1.1 million individuals below the age of 20 are diagnosed diabetics. It is projected that by the year 2045 over 700 million adults will be affected by DM in some capacity [3].

Every disorder within DM is characterized by the onset of chronic hyperglycemia; however, each is unique in pathogenesis, symptoms, and specialized treatments. Moreover, understanding each classification of diabetes mellitus and its respective manifestations is pivotal in providing proper care. Type 2 diabetes (T2D), occasionally referred to as adulthood diabetes, is the most common form of the condition [1]. This disease has a multifactorial pathogenesis and usually results as a combination of issues in insulin secretion and action. Traditionally, individuals develop insulin resistance, usually because of genetic predisposition being exacerbated by environmental factors such as poor diet or lack of exercise [1]. In response, the pancreas heightens insulin production to rid the body of excess glucose, but the intracellular transport pathway is inhibited. As time progresses, the body cannot sustain this increased rate of insulin production and directly causes β cell failure [1]. T2D may also be the consequence of other malfunctions such as impaired insulin processing or mitochondrial functionality issues; however, it still presents the same consequences [4, 5]. Type 1 diabetes (T1D), referred to as childhood diabetes, is an autoimmune disorder that targets the pancreatic insulin-secreting cells. It accounts for 5–10% of all diabetes diagnoses and 80–90% of diabetes in children and

adolescence [6, 7]. While the exact mechanism of this destruction is unclear, it is understood that β cell-specific autoantibodies attack the pancreas via T-cell mediated inflammatory response and the humoral immune response [1]. These autoantibodies include autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD), protein tyrosine phosphatase, and zinc transporter protein [1]. Ultimately, the pancreas undergoes irreparable damage rendering it unable to synthesize or secrete insulin entirely. While these two groupings are the most prevalent classifications of DM, it is important to recognize that there are additional, sometimes transient, types of DM that can display some of the complications commonly witnessed in typical diabetics. These categories include prediabetics, gestational diabetics, and monogenic diabetics [1].

Each category of diabetes displays its own set of symptoms that depends on pathogenesis, progression, severity, and management. In the early stages of DM, it is common for patients to be asymptomatic [8]. As the conditions progress, the classical signs of hyperglycemia emerge including polyuria, polydipsia, nocturia, and fatigue [9]. Additionally, it is common for Type 1 diabetics to report unintentional weight loss [8]. If not properly managed, the diseases place individuals at high risk for developing further complications including neuropathy, retinopathy, impaired wound healing, depression, and frequent infections [9]. T1D has the potential to develop into diabetic ketoacidosis. As a result, patients report fruity breath and lethargy; however, this is distinctly uncommon in T2D [10, 11]. While this progression is considered the status quo, there are other potential manifestations related to DM. One of the commonly overlooked associations is the relationship between DM and pruritus. Generalized pruritus in diabetic patients has been studied for many years. It is mostly reported as a sensation presented on the trunk, extremities, and scalp with or without cutaneous indications [12]. The exact pathophysiology mechanism is not well characterized; currently, diabetes-associated pruritus is thought to be a result of diabetic neuropathy, anhidrosis, or a secondary complication of renal failure depending on the person and their condition [12]. In additional studies, diabetic women have reported high frequencies of pruritus of the vulvae; however, this is believed to result from an entirely separate pathway. As the body attempts to excrete excess glucose via urination, an optimal, local environment for *Candida albicans* to cultivate is created and itching then manifests [12].

Beyond the increased infectious etiologies possible, pruritus in the setting of DM can manifest secondary to longstanding nerve damage with DM progression. While a prior association of diabetes and pruritus was loose, recent investigation helped better link diabetic polyneuropathy (DPN) to truncal pruritus of unknown origin (TPUO). TPUO was significantly associated with signs of DPN including areflexia and acral numbness. Therefore, TPUO can then be advanced as a possible complication of early DPN [13]. By realizing this connection, understanding the pathology of neuropathy can help explain diabetic origins of pruritus.

Pain sensation is transmitted via nerves categorized as unmyelinated C-fibers and thinly myelinated axons A-delta fibers. When damage targets either of these nerve fibers, the manifestation is termed small-fiber polyneuropathy (SFPN). While several causes can lead to SFPN including toxicities, drugs, and cancers, DM

remains the most common cause in developed countries. Currently, diabetic neuropathy, more specifically SFPN, is reliant on a clinical diagnosis; however, some laboratory investigation can be employed to aid in diagnosis. Skin biopsy with the purpose of evaluating axonal number may be used to support the diagnosis. The ideal site for skin-biopsy should be taken from healthy tissue proximal to the lateral malleolus. Specimens are then immediately fixed and sent to appropriate laboratories that then stain with antibodies against PGP9.5 for axonal counts [14]. Of note, several other forms of diabetic neuropathy exist, but these forms are not closely linked to pruritus formation.

Treatment

Management of diabetic neuropathy, and therefore pruritus, in DM, requires a multifaceted approach in both lifestyle intervention and medical therapy. Initially, the goal must be to improve glycemic control. Strict glycemic control with lifestyle modification, diet, and exercise limits the progression of sequelae in T1D, and possibly T2D. While lifestyle modification has not shown a reversal of DPN, it has proven effects on slowing progression in T2D [15]. Additionally, lifestyle modifications reduce the overall severity of neuropathic pain experienced. Furthermore, medications that induce hyperglycemia will need to be replaced as an additive measure in improving glycemic control [16]. Overall, T1D-induced DPN responds more favorably to glucose control than T2D. While less evidence supports successful neuropathic damage treatment with glycemic control in T2D, lifestyle modification is still widely accepted as the initial step [16]. Medications for glycemic control may also be advantageous to limit the progression of DPN; however, a description of these medications in detail goes beyond the extent of this chapter. Further DPN medication intervention can be separated into two broad categories that include pathological medications and symptomatic medications.

Several medications can help treat the various pathological mechanisms described in DPN development. Hyperglycemia pathology begins by inducing reactive oxygen species formation. Reactive oxygen species then eventually overwhelm antioxidant pathways and lead to microvascular damage, DPN, and pruritus. Therefore, the use of α-lipoic acid can alleviate oxidative stress by way of neutralizing free radicals. While used in various parts of the world, approval by regulatory committees has not been attained in the United States [16]. While evidence is scant, there is some support for angiotensin-converting enzyme inhibitors in reducing neuropathy progression. Several other therapies including C-peptide, ruboxistaurin, and actovegin [16]. While significant research continues on all of the previously mentioned medications, none are currently used in the United States for routine DPN treatment.

Beyond treating the pathologic mechanism, several medication classes can operate in the role of mitigating DPN and pruritus symptoms (Fig. 18.1). Several medications promote symptomatic management, and the order of use is varied across

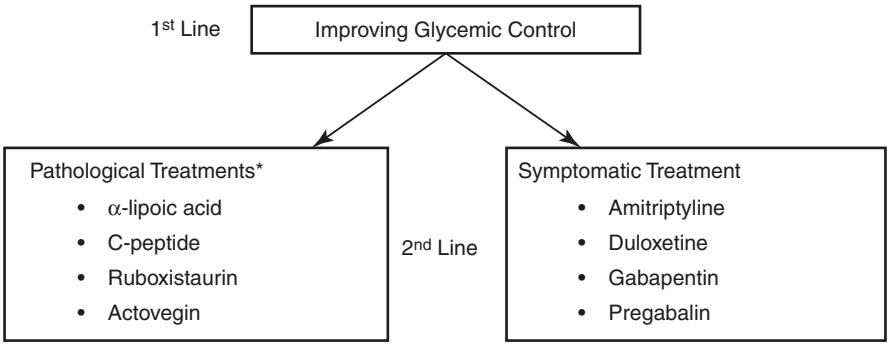

Fig. 18.1 Treatment algorithm with examples in treating diabetes-induced pruritus. * = pathological treatments are not recommended in the United States [15, 16]

recommending bodies. The first medication class commonly used includes tricyclic antidepressants (TCA) such as amitriptyline. In past management, these medications were often considered first-line for neuropathic pain but have fallen out of favor due to significant anticholinergic side effects and safer alternatives. While the mechanism on neuropathic pain is unknown, the class has a neuronal effect on various neurotransmitters that are different based on TCA that is used [16]. Neuropathic medicine can also be treated with serotonin-norepinephrine inhibitor class medications. The mechanism is reliant on blocking the reuptake of both serotonin and norepinephrine in the synaptic cleft after release. This blockade then causes an increase in central descending inhibition and ultimately neuropathic pain relief [16]. Duloxetine is the only medication in this class that the Food and Drug Administration approved in the United States for neuropathic pain [16]. While the side effect profile is more tolerable than TCA's, there is still a chance to have possible constipation, somnolence, and metabolic derangement in glucose and lipids [16].

Continuing with symptomatic management, anti-convulsant medications can often serve a vital role in reducing DPN burden. Gabapentin is a medication in this category that is commonly used in neuropathic pain management. The mechanism of gabapentin, and other related medications, works through inhibition of presynaptic calcium channels. There is significant evidence supporting the use of gabapentin in DPN, often being considered as the safest and most efficacious by comparison [16]. Pregabalin is a newer medication like gabapentin, in structure and action, with greater potency. The efficacy of pregabalin provides significant DPN relief in a dose-dependent manner. Notably, with higher potency, pregabalin tends to accompany more significant possible side effects including sedation and mood disturbance. Encephalopathy and cerebral edema are both also possible after abrupt cessation of therapy. With respect to the considerable efficacy of gabapentin and pregabalin, both retain indications for the treatment of DPN in both the United States and the United Kingdom [16]. In the direct comparison of gabapentin to pregabalin, a cost comparative analysis determined decreased healthcare costs associated with pregabalin therapy for DPN treatment [17]. Other medications that have

been evaluated in the treatment of DPN include opioids and topical capsaicin. Although not FDA approved, topical gabapentin or topical TCAs may be a viable option for localized areas [16].

Key Points

- Diabetes mellitus (DM) is defined as a group of metabolic disorders that arise from abnormalities in insulin secretion, action, or a combination of the two.
- DM can be further divided into T1D and T2D. T1D is the autoimmune destruction of insulin-secreting cells of the pancreas resulting in decreased production. T2D is a reduction of insulin action on cells and then further decrease in insulin production.
- Diabetic patients are at an increased risk for several pathologic sequelae which includes DPN. Pruritus has been linked as a manifestation of DPN specifically SFPN.
- Intensive lifestyle modifications and glycemic control are crucial in early limitation of DPN progression in T1D and possibly T2D.
- Beyond glycemic control, first line therapy of DPN is consistent with symptomatic control using medications such as amitriptyline, duloxetine, gabapentin, and pregabalin.

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Chapter 19
56-Year-Old Female with Itchy, Dry Skin and Hair Loss

Erica Haught, Ian McArdle, Austin Cusick, and Shannon C. Trotter

A 56-year-old female presented with itchy, dry skin on the trunk and extremities. She reported a long history of dry skin and itch but stated it has worsened significantly over the past year. She also complained of constipation, mood changes, and fatigue. In addition, she reported hair thinning over the last 7 months. She attributed her symptoms to menopause.

On physical examination, her skin was diffusely dry but worse on the back. Her scalp skin was normal but there was sparse hair loss. No discrete patches were noted. Laboratory evaluation showed positive TPO antibodies and elevated TSH and low free T4. Hormonal labs were consistent with menopause. CBC, liver function, kidney function, thyroid function, and hepatitis screen were within normal limits. She was up to date on age-appropriate cancer screening. She refused an HIV test.

Based on the clinical case description, what is the most likely diagnosis to explain her itching?

1. Polycystic ovarian syndrome
2. Hypothyroidism
3. Chronic fatigue syndrome
4. Depression

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Diagnosis

Hypothyroidism.

Discussion

Hypothyroidism, or low levels of circulating thyroid hormone, can be caused by primary thyroid disease or hypothalamic-pituitary axis dysfunction. Hypothyroidism can often be identified by cutaneous manifestations including pruritus. Pruritus associated with thyroid dysfunction can be due to coarsened and scaly skin, myxedema, and xerosis. A more thorough list of cutaneous manifestations of hypothyroidism (Table 19.1). Xerosis is the most common cutaneous manifestation, occurring in 57% of individuals with hypothyroidism [1]. Myxedema is seen in 4% of patients with Grave's disease and has rarely been described in Hashimoto's thyroiditis [2, 3].

The pathophysiology of cutaneous manifestations from thyroid dysfunction can be divided into three categories including direct action of thyroid hormone on skin, skin responding to direct thyroid hormone on non-skin tissues, and autoimmune phenomena [4]. Xerosis, myxedema, and coarsened, scaly skin can be a result of decreased levels of thyroid hormone that act directly on the epidermis and dermis [4].

Thyroid hormone binds receptors directly in keratinocytes, skin fibroblasts, and sebaceous gland cells. Triiodothyronine (T3) has been known to stimulate the proliferation of epidermal keratinocyte and dermal fibroblasts [5]. With low levels of thyroid hormone, skin homeostasis can become unbalanced and lead to epidermal changes such as coarse, thin, scaly skin. Dermal changes that lead to pruritus include myxedema, which is a non-pitting edema that occurs in the pretibial region but can arise in the feet or rarely the upper extremities. In myxedema, hyaluronic acid accumulates in the dermis, and its synthesis is normally inhibited by thyroid hormone [6].

Xerosis in hypothyroidism is caused by decreased eccrine gland secretion with unknown etiology; although, there is evidence of atrophied glands associated with decreased levels of thyroid hormone [4]. In xerosis, the epidermis becomes thin and

Table 19.1 Cutaneous manifestations of hypothyroidism

Xerosis
Myxedema
Coarsened skin changes
Scaly skin
Mottled skin
Cold skin
Brittle, sparse hair
Lateral third eyebrow thinning

hyperkeratotic with follicular plugging in addition to stratum corneum dehydration [7]. Hypothyroidism may also affect the development of lamellar granules, which play an important role in maintaining a normal stratum corneum [8].

Given the detrimental effects that hypothyroidism can have on one's health, it is important for clinicians to be cognizant of the range of cutaneous manifestations of hypothyroidism in order to make an early diagnosis and provide appropriate intervention.

Treatment

The mainstay of treatment for hypothyroidism is levothyroxine which is synthetic thyroxine (T4). It has a favorable side effect profile, half-life, and cost [9]. It is favored due to its efficacy in treating symptoms of hypothyroidism, including cutaneous manifestations. Levothyroxine is a pro-hormone T4 that is converted to T3 in the body by D1 and D2 deiodinases at the target cell [10]. T3 acts on its nuclear receptor in various organs including the skin. While the goal is to maintain normal circulating thyrotropin (thyroid-stimulating hormone) levels and a euthyroid state, the long half-life allows for dosing once a day. Levothyroxine replacement therapy should be aimed to reduce hypothyroid symptoms while avoiding overdosing or thyrotoxicosis. Levothyroxine dosage should be titrated to increasing levels toward the therapeutic goal, with thyrotropin level assessment 4–6 weeks after the change in dose [9].

Although controversial, T4 and T3 combination therapy is an option in patients who have not improved on levothyroxine since having a thyroidectomy, ablative therapy with radioiodine, or those who have serum T3 below the reference range. Combination therapy is not recommended for routine use, and the combination ratio must mimic the normal physiologic ratio of T4 to T3 13:1 to 16:1. Another option is desiccated thyroid extract (T4 to T3 ratio of 4:1); in a double-blind, crossover trial comparing desiccated thyroid extract to T4 alone, there was no difference in symptom improvement [11]. However, the extract is not routinely recommended because high-quality long-term studies regarding efficacy and safety are lacking [9].

While treating the underlying hypothyroidism is the mainstay of intervention for treating cutaneous manifestations such as xeroderma, myxedema, coarsened and scaly skin changes, there are interventions that target each of these. Treatment for xerosis includes the use of mild cleansers such as synthetic detergent cleansers with a low pH to compliment the normally acidic pH of the skin [12]. Alkaline soaps can exacerbate pruritus by worsening xerosis. Acidic soaps may be helpful since they inhibit, serine proteases involved in pruritus [13]. Another recommendation is to avoid excessive skin washing, especially with hot water, which can worsen xerosis. The use of skin moisturizers that contain lactic acid, topical urea, glycerin, and petroleum are recommended to maintain a hydrated epidermis [14, 15].

Indications to treat pretibial myxedema are pruritus, discomfort, and cosmetics. Aside from managing thyroid function, nonpharmacologic risk factor control includes avoiding tobacco and reducing weight. Normalizing thyroid function might not improve existing pretibial myxedema but may prevent further worsening of the myxedema [16]. Compression stockings have also been shown to improve lymphedema [3]. Pharmacologic therapy for pretibial myxedema includes medium to high potency topical corticosteroids covered by an occlusive dressing changed nightly to every other night [17]. An example of a topical corticosteroid is 0.025% fluocinolone acetonide. If there is no improvement after 4–12 weeks, intralesional corticosteroid injections can be administered [18]. In resistant pretibial myxedema, pentoxifylline, which prevents the proliferation of fibroblasts, has been reported to be beneficial [19]. Rituximab and plasmapheresis, as well as intravenous immunoglobulin, has been reported to help in severe cases [20–22]. Treatments that have been successful in improving the lesions of pretibial myxedema include intralesional injections of insulin-like growth factor-1 receptor blocking monoclonal antibody to reduce the secretion of hyaluronic acid [23].

The mainstay of treatment for hypothyroidism, and its cutaneous manifestations, is levothyroxine therapy. Treating each individual cutaneous manifestation such as xerosis, myxedema, and scaly skin changes can reduce pruritus and improve quality of life.

Key Points

- Pruritus in hypothyroidism is a result of cutaneous manifestations such as xerosis, pretibial myxedema, coarsened, and scaly skin changes.
- The mainstay of treatment for hypothyroidism and its cutaneous manifestations is levothyroxine.
- Supplemental treatments such as acidic cleansers and moisturizers containing lactic acid, topical urea, glycerin, petroleum can benefit xerosis in hypothyroidism.
- Supplemental treatments such as compression stockings, topical or injection corticosteroids, and pentoxifylline can benefit pretibial myxedema.

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Chapter 20
59-Year-Old Female with Diffuse Itchy Skin on Dialysis

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A 59-year-old female presented with a known history of stage IV kidney disease and dialysis therapy. She reported increased diffuse itching that was better right after dialysis but intensified 1–2 days after dialysis treatment. She said her itching interfered with sleep and caused her to feel depressed at times.

On physical examination, her skin was dry. She had excoriation marks on her arms, upper back, and abdomen. Her nails lacked a lunula and had a proximal white color to the nail plate and a distal brownish red area, consistent with Terry's nails. CBC, liver function, thyroid function, and hepatitis screen were within normal limits. She was up to date on age-appropriate cancer screenings. Her BUN and creatinine were elevated.

Based on the clinical case description, what is the most likely diagnosis?

1. Hepatic pruritus
2. Medication induced pruritus
3. Uremic pruritus
4. Depression

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Diagnosis

Uremic pruritus.

Discussion

Uremic pruritus (UP) is a distressing form of itchiness found in 40% of patients with chronic kidney disease [1]. UP can be severely debilitating with patients reporting severely decreased quality of life [1]. UP often affects large areas of the skin in a symmetrical distribution with symptoms predominating at night [1]. UP is not associated with primary skin lesions, thus does not follow a dermatomal distribution [2]. Although there are variable presentations, these may warrant workup of other causes of pruritus [1]. Demographically, UP is often associated with hepatitis C, smoking, dialysis, and age [3].

The exact mechanism of UP is unknown, but several theories propose a multifactorial approach. UP may be associated with: increased systemic inflammation with IL-31 and C-reactive protein; abnormal levels of serum calcium, phosphorus, and parathyroid hormone; a neuropathic process; or an opiate receptor imbalance [1, 3, 4]. UP is also associated with: lower dialysis adequacy; xerosis; using low-flux dialysis membranes; low levels of serum albumin; and high ferritin [3]. There are certain abnormalities associated with uremia that can activate itch fibers. Such abnormalities include hyperparathyroid-induced bone disease, dehydration-related structural skin changes, and overall immune dysregulation [1]. These changes may affect the unmyelinated C fibers, which are slow-conducting, and histamine-dependent. However, the aforementioned abnormalities may also affect various other non-histamine dependent neurons associated with itching [1]. UP may be associated with neuropathic pain related to alteration of nociceptive receptors both peripherally and centrally [1]. The overall level of uremic toxins positively correlates with the degree of pruritus, suggesting their role in the pathophysiology of UP. Interestingly, the GFR does not correlate with the degree of pruritus [1].

Differential Diagnosis

Various skin pathologies can be found in patients with renal insufficiency. Although UP does not present with primary skin lesions, it can still present with secondary skin lesions. It is necessary to distinguish these manifestations from other pathologies [5, 6]. Besides uremic pruritus, common conditions found in end-stage renal disease can include calciphylaxis and perforating dermatoses [7]. These pathologies must be discussed to understand the full scope of uremic pruritus.

Xerosis is dry and thickened skin with ichthyosiform scaling often found on the trunk and extensor surfaces. Xerosis is found in about 50–60% of patients with end-stage renal disease and may be found concurrently with UP [5, 6]. Xerosis in renal failure may develop due to fragmented elastic fibers, atrophy of eccrine and sebaceous glands, and excess vitamin A. This results in alterations of stratum corneum composition and maturational process [5].

Prurigo nodules are hyperkeratotic nodules with erosion that present in a symmetric distribution [6]. They develop because of neuronal sensitization to itch from continuous scratching [6]. Scratching promotes inflammatory markers such as nerve growth factor, which promotes neuronal hyperplasia, causing pruritus [8].

Calciphylaxis is a condition where microvascular calcifications cause painful net-like skin lesions such as plaques, nodules, livedo, or purpura. These lesions can present with induration, erythema, and a dusky appearance representing imminent necrosis [9]. Calciphylaxis typically presents as multiple, bilateral lesions with surrounding skin that has a leathery texture [9]. The initial lesions can quickly progress to stellate, malodorous painful ulcers with black eschars, which advance to sepsis and death [9].

Perforating dermatoses present as small, pruritic, hyperkeratotic papules or nodules in the buttocks or extremities. These lesions may coalesce into plaques with a linear pattern due to Koebnerization [5, 6]. These lesions appear in areas where cellular debris and altered dermal connective tissue extrude through the epidermis [5]. Several perforating dermatoses are associated with renal failure and diabetes, with much overlap. These include reactive Kyrle's disease, perforating collagenosis, acquired perforating dermatosis, and perforating folliculitis [5, 6]. Perforating dermatoses and UP are not mutually exclusive and can appear together, but require a biopsy to confirm the presence of a perforating dermatosis [10]. Reactive perforating collagenosis is a rare, autosomal dominant or recessive genodermatosis that may also be acquired in adults with chronic renal disease or diabetes. In this condition, altered collagen is eliminated transdermally [6]. Reactive perforating collagenosis presents on the face and extremities as pruritic brown or pink papules or plaques that can be keratotic, umbilicated, nodular, or verrucous [6]. The papules initially become umbilicated over 3–5 weeks before regressing to leave a scar that forms over 6–8 weeks, with lesions presenting in various stages simultaneously [6]. Perforating folliculitis presents similarly to the other perforating dermatoses both histologically and clinically with the addition of degenerated follicular units [6].

Other causes of pruritus such as eczema, inflammatory conditions, infective conditions, and neoplastic conditions should also be considered. These conditions are not specifically associated with renal insufficiency and often have some defining primary skin lesions, unlike UP [7]. A notable exception is polycythemia vera (PV), which also does not present with primary skin lesions. The way to differentiate UP from PV includes assessing for elevated erythropoiesis, such as an elevated hematocrit or hemoglobin and the presence of a JAK2 Kinase mutation [11].

Treatment

Several long-standing treatments for UP that are believed to be better than placebo include optimizing dialysis, emollients, gabapentin, capsaicin, mast cell stabilizers, and parathyroidectomy (in the case of hyperparathyroidism) [2, 6]. Newer investigative treatments that have shown to be superior to placebo include activated charcoal, thalidomide, UV-B phototherapy, opioid antagonists, cholestyramine, pramoxine lotion, and montelukast [2, 6]. However, kidney transplants have been the ultimate treatment for uremic pruritus, although only a small portion of patients qualify for a kidney transplant [5, 6].

Despite variable efficacy in reducing pruritus, the first-line treatment is dialysis [2]. Studies have shown that the severity of pruritus was lower in patients on peritoneal dialysis than on hemodialysis, indicating that peritoneal dialysis may be a better treatment modality [4].

In addition to dialysis, first-line treatments include topical therapy, especially in patients with dry skin [6]. Emollients with high-water content such as γ-linolenic acid may have anti-inflammatory properties [6]. Topical capsaicin blocks painful and pruritic signals by depleting substance P from peripheral neurons and should be reserved for patients with a small affected areas Capsaicin's side effects include localized stinging, burning, and erythema [6] Topical pramoxine lotion, an anesthetic, has been shown to be effective as well [2].

A systemic first-line agent is gabapentin, which is an anticonvulsant that is also used to treat neuropathic pain [6, 12]. Important side effects of gabapentin include dizziness and sedation, so it is important to consider the effects of polypharmacy before initiation [6].

Although histamine has been shown to be part of the pathogenesis of UP, antihistamines have not been shown to reduce pruritus better than placebo [6]. Meanwhile, cromolyn sodium, a mast cell stabilizer, has been shown to be effective. Side effects of cromolyn sodium include flatulence [6, 12]. Montelukast, a leukotriene receptor antagonist, has also been shown to be effective with no adverse effects [6].

One study showed that thalidomide reduced pruritus by 50%, although it is contraindicated in women of reproductive age due to teratogenic effects [2, 6, 12].

Two small clinical trials showed that activated charcoal is cost-effective, has limited side effects, and is effective at reducing pruritus. Activated charcoal works by binding pruritogens in the intestinal lumen [6]. Another trial showed that cholestyramine reduced pruritus better than placebo in 80% of patients and had a similar mechanism of activation to activated charcoal [2, 6, 13].

Several studies have shown that broad band ultraviolet (UV)-B light is more effective than UV-A light in reducing pruritus. UV-B has short-term side effects such as sunburn and tanning, as well as long-term side effects such as photoaging and cancers [2, 6].

Nalbuphine is a novel k-opioid and μ-opioid receptor antagonist that was shown to reduce the intensity of itching in hemodialysis patients in one study [6].

Alternatively, acupuncture has also been shown to be effective with minimal side effects, although it is debated whether there is enough evidence to support using acupuncture for uremic pruritus [2, 3, 12].

Key Points

- UP is the most common cause of pruritus in patients with end-stage renal disease.
- UP does not present with primary skin lesions, but it can present with secondary skin lesions such as excoriations, xerosis, eczema, and prurigo nodules.
- First-line treatments for UP include adequate dialysis, topicals like γ-linolenic acid or pramoxine, and gabapentin, with renal transplant being the definitive treatment.

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Chapter 21
72-Year-Old Male with Diffuse Itching

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A 72-year-old male presented with diffuse itching of about 1-year duration. He did not see a family physician and had no known medical history or prescription medications. He took ibuprofen on occasion for arthritis pain.

On physical examination, his skin was dry in some areas but no rash was present. There were excoriation marks on the arms and abdomen. Laboratory workup was initiated. Liver function, kidney function, thyroid function, PSA, and hepatitis screen were within normal limits. He refused a colonoscopy. His CBC was consistent with an absolute lymphocytosis and clonality was confirmed with flow cytometry. A peripheral smear confirmed the diagnosis.

Based on the clinical case description, what is the most likely diagnosis to explain his itching?

1. Chronic lymphocytic leukemia (CLL)
2. Medication-induced pruritus
3. Arthritis
4. Prostate cancer

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Diagnosis

Chronic lymphocytic leukemia (CLL).

Discussion

Non-Hodgkin Lymphoma (NHL) is the most common cause of hematologic malignancy worldwide. NHL can present as either a B- or T-cell malignancy with B cell cancers predominating [1]. NHL has a propensity to affect patients in developed countries with NHL affecting women at a slightly higher rate [2]. NHL commonly presents in mid-adulthood with an overall median age of presentation of 42 years [1]. Numerous studies have been undergone to identify risk factors for the development of the disease. Family history, autoimmune diseases, and alcohol consumption are associated with an increased risk of disease overall [2]. Smoking has been shown to be a primary risk factor for Follicular Lymphoma specifically [2]. NHL has numerous subtypes with the most common being diffuse large B-cell lymphoma, Burkitt lymphoma, follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma [2].

Patients typically complain of lymphadenopathy within the groin, axillary, or neck region [2]. Patients may also present nonspecifically with symptoms related to fever, night sweats, abdominal pain, and weight loss [2]. Patients that have underlying immunosuppression such as transplant, autoimmune, and HIV patients are at increased risk for NHL. Most NHL cases will present with CD10 and 20 positive antigens and commonly undergo genetic rearrangement and chromosomal translocations [2]. Overall survival depends on staging and most patients will live past 5 years after diagnosis [2].

Chronic lymphocytic leukemia (CLL) is B-cell malignancy classically characterized by CD5 B-cells [3]. CLL can be divided into two main types depending upon their expression of mutated immunoglobulin heavy chain proteins with unmutated patients having a more aggressive disease [3]. CLL affects men at a disproportionate rate with a median age of diagnosis between 70 and 72 years of age [3]. Current estimates suggest that CLL incidence is less than one percent in both women and men [3]. Genetic factors contributing to the disease include family history and monozygotic twins [3]. Environmental factors that contribute to the disease include Agent Orange and insecticide exposure [3]. Further evidence suggests that ionizing radiation is no longer a risk factor for disease [3].

CLL patients commonly present with fatigue, weight loss, and night sweats. Patients can also develop lymphadenopathy which allows CLL to be considered small lymphocytic lymphoma (SLL), a type of NHL [3]. Patients commonly develop hypogammaglobulinemia, the most common cause of death.

Hodgkin Lymphoma (HL) is an uncommon malignancy that stems from B-lymphocytes. HL can be further distinguished between nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (CHL) accounting for 95% of cases [4]. CHL can further be divided into further histologic types including lymphocyte rich, nodular sclerosis, mixed cellularity, and lymphocyte depleted.

HL has a bimodal distribution of age ranges with young (15–34) and older adults (50 and older) being affected. The age ranges also have a predilection for CHL subtypes with young adults presenting with nodular sclerosis type, and older adults presenting with mixed cellularity. Incidence rates are higher in males and the developed world [4]. HL is characterized by the presence of Reed-Sternberg tumor cells histologically, with these cells deriving from germinal center B-cells undergoing genetic rearrangement [5]. HL cells predominantly express CD30, with a reduced number expressing CD15, CD50, and PAX5 proteins [6].

Risk factors for the development of HL include increased fetal growth, Epstein Barr Virus (EBV), and immunosuppression [7, 8]. Notably, the treatment of HL shows an increased risk for the development of further cancer both hematological and solid in nature. Overall, this forms the largest cause of mortality in survivors [7].

HL presents systemically with the involvement of lymph node enlargement mainly cervical, supraclavicular, and mediastinal. Extranodal involvement is rare but can be widespread including spleen, bone, and liver involvement. Bone involvement may be either primary in nature or due to hematogenous or contiguous spread [9]. Sternal involvement has been also reported [9]. Symptoms involve lymphadenopathy and B-symptoms including fever, night sweats, weight loss, pruritus, and increased infections but may not always be seen leading to a lack of diagnosis [10].

HL-induced pruritus is seen as a paraneoplastic sign manifestation of disease with a prevalence of 30% [11]. HL pruritus often manifests itself after ingestion of alcohol or exposure to high temperatures such as after bathing. Patients can present with eczematous lesions or ichthyosiform skin changes [11]. Overall, the severity of pruritus corresponds with decreased quality of life. Currently, there is no consensus treatment. Common medications include steroids and aprepitant, a neurokinin-1 antagonist.

Current understanding of pruritus in malignancy is poorly understood. Multiple theories have been described including the effects of inflammation both systemically and locally, the usage of antineoplastic medications, and the disruptions of the hepatobiliary and renal clearance systems [12]. Hepatobiliary system involvement may induce pruritus secondary to the accumulation of bile acid and salts accumulation [12]. Renal involvement may be secondary to uremic itch or cytokine dysregulation [12]. Further studies have suggested that specifically related to hematologic malignancies, opioid receptors may be implicated as patients who are prescribed opiate medications show a decrease in pruritus [12]. Other studies describe the variations in cytokine expressions as being implicated as well [12].

Treatment

HL Patients are classified based on disease severity and various scoring systems. Intervention and treatment, therefore, depend on score. For patients with early-stage HL, the variant with the best prognosis, patient receive combination therapy of involves site radiation therapy (ISRT) and treatment with chemotherapeutic agents adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) [13]. Treatment with chemotherapy is challenging due to various side effects from bone marrow suppression to irreversible cardiotoxicity, depending upon the agent. Early unfavorable stage HL is associated with a worse prognosis. These patients may have elevated erythrocyte sedimentation rates, multiple nodal involvement, and mediastinal masses [13]. These patients typically undergo four to six cycles of ABVD therapy followed by ISRT [13]. Advanced disease is generally treated with chemotherapy alone. Furthermore, elderly patients, who represent 15–30% of HL cases, are associated with poor prognosis. Despite this, the standard of care is ABVD therapy. However, these patients have an increased predisposition to the development of lung toxicity from bleomycin which further increases their mortality. Studies have shown that patients who do not use bleomycin have no different long-term survival rates [13].

Current treatment guidelines for NHL include the usage of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment protocol [14]. Early-stage disease is treated with R-CHOP followed by radiotherapy [14]. Whereas patients with more aggressive disease are treated with R-CHOP therapy alone [14]. Side effects associated with R-CHOP therapy involve hematological disturbances such as leukocytopenia [15].

There are currently no routine guidelines surrounding the treatment of pruritus in HL. Itching in HL may be related to the release of histamine as HL patients respond to histamine blockers [16]. Furthermore, studies have shown that eosinophilia may be seen as well [16]. Hydroxyzine (50–100 mg/day) and doxepin (25–75 mg/day) have both been reported to be effective secondary to their antihistamine effects [17]. Some patients may even respond to μ-opioid antagonists naltrexone (25–50 mg/day) and butorphanol (1–4 mg/day) [17]. A subset of patients may require the use of antidepressants including mirtazapine (15 mg/day) and paroxetine [17]. Finally, inhibitors of central and peripheral itch pathways gabapentin (up to 3200 mg/day) and pregabalin (150–300 mg/day) may be used [17].

Aprepitant is a neurokinin-1 receptor antagonist that blocks substance P to downregulate its effects. Substance P is involved in several processes including pain, depression, and itching. Mechanism of action involves the downregulation of neurokinin-1 receptor in keratinocytes and thereby preventing substance P release of inflammatory cells that lead to pruritus [18]. HL Patients taking this drug have experienced considerable relief of symptoms with short term use. The current dosage recommendation is 80 mg daily for 2 weeks [18]. Side effects are mild with patients reporting fatigue, diarrhea, dyspepsia, and abdominal pain. The drug also can increase liver function tests so they should be monitored during treatment.

Key Points

- Hodgkin's lymphoma is an uncommon malignancy with a bimodal age distribution. Risk factors include EBV, radiation exposure, and increased fetal growth. Non-Hodgkin's lymphoma is comprised of several different subtypes with varying risk factors.
- HL pruritus is a paraneoplastic syndrome that can often present with eczematous lesions.
- Treatment of HL and NHL generally involves combination therapy. This includes ABVD chemotherapy in conjunction with radiation therapy for HL and R-CHOP for NHL.
- Treatment of pruritus in HL and NHL generally involves the use of a myriad of drugs. In a subset of patients, the use of the neurokinin-1 receptor antagonist Aprepitant has been shown to be effective.

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Chapter 22
47-Year-Old Female with Diffuse Itching Not Alleviated with Scratching

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A 47-year-old female presented with diffuse itching that would come and go for the past 2 years. She described it as a traveling itch that would start at one area like her arms, and then move to other areas of the body like her back, scalp, or legs. The itch was intense but tended to be short-lived, lasting a few seconds to a few minutes. Scratching did not alleviate the itching but cool compresses seemed to help her symptoms. Occasionally the itching was mixed with a pins and needles sensation. Her medical history is significant for migraine headaches, depression, and multiple sclerosis (MS).

On physical examination, her skin was dry in some areas, but no rash was present. Laboratory workup was initiated. CBC, liver function, kidney function, thyroid function, and hepatitis screen were within normal limits. She was up to date on age-appropriate cancer screening.

Based on the clinical case description, which one of her conditions likely is responsible for her itching?

1. Migraine headache
2. Medication-induced pruritus
3. Multiple sclerosis
4. Depression

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Diagnosis

Multiple sclerosis.

Discussion

Multiple sclerosis (MS) is a central nervous system chronic inflammatory disease leading to neuronal demyelination. Oligodendrocytes and axons are destroyed by autoreactive T-lymphocytes to myelin, resulting in CNS lesions and sclerotic plaque formation. Nerve impulse transmission and brain functions become increasingly impaired and compromised as the disease progresses, resulting in a decline in both health and quality of life. The symptoms of MS are distinguished by their relapsing and remitting pattern. These include, but are not limited to, visual, sensation, muscle, and balance deterioration, fatigue, bladder and bowel incontinence, and cognitive and emotional impairment [1]. Classically, four subtypes of MS generally categorized most disease courses [2]. First, primary progressive MS is described as a steadily worsening neurologic function that is without relapses or remissions. Second is relapsing-remitting MS which is described as an acute worsening of neurological functioning that shows relative recovery without further progression. Third is secondary progressive MS that typically follows a relapsing-remitting subtype as steadily worsening neurologic functioning. Lastly, progressive relapsing MS is similar to primary progressive except there is the presence of occasional relapses in this subtype. The progressive relapsing subtype is now considered obsolete. Also, of note, newer definitions of these subtypes further classify disease based on activity and overall progression. More recently, clinically isolated syndrome MS can be a CNS lesion formation that then may develop into MS with progression [2].

Recent research implicates both autoimmune humoral and T-cell mediated damage in combination with infectious etiologies, environmental etiologies, and genetic predisposition [1]. Decreased blood levels of both linoleic and arachidonic acid, fatty acid precursors for pro-inflammatory eicosanoid production, have been shown in patients with MS. Decreased levels of these fatty acids then lead to a dysfunctional inflammatory response with surrounding tissue damage [3, 4]. MS is associated with the presence of the HLA-DRB*1501 allele, as well as elevations in serum levels of cytokines IL-17 and IL-2 [5]. Environmental risk factors include decreased vitamin D, stress, smoking, and infections. Infectious agents implicated include Epstein Barr Virus, human herpesvirus 6, *Chlamydia pneumoniae*, and *Helicobacter pylori* [1, 6].

Many central and peripheral nervous system disorders that cause neuropathic pain also create an associated neuropathic itch (NI). While being implicated in many neuropathic pain disorders such as sensory polyneuropathies, radiculopathy, herpes zoster, and stroke, NI is also associated with MS [7]. It develops from either increased peripheral neuronal firing or decreased central inhibition of neurons

associated with the itch pathway. The exact mechanism is poorly understood, but recent research implicates itch mediators such as gastrin-releasing peptide, certain receptors such as neurokinin 1 (NK-1), and certain pathways such as Janus kinase. Presentation of NI varies with different subtypes for the associated disorder [7]. Itching associated with MS is thought to be caused by partially demyelinated neuronal lesions in the CNS. The activation spreads transversely via ephaptic activation [8].

In animal studies, brain natriuretic peptide (BNP) was identified as an itch-selective neuropeptide. It has been shown to increase both central and peripheral levels of spinal relay of itch signaling to the skin [9]. Another animal study in 2019 found similar results. By blocking itch-selective neuropeptide, such as neuropeptide NPPB receptors, researchers were able to attenuate the itch response in mice. By blocking the human and murine NPR1 (natriuretic peptide receptor 1), both acute and chronic itch behavioral responses were attenuated [10]. Drug development, with respect for these targets, could potentially alleviate itch in some patients.

Research from 2015 suggests that immunohistochemical and pharmacological interventions regulating both BNP and gastrin-releasing peptide (GRP) receptors could attenuate the itch response. It was found that administration of either BNP or GRP receptor antagonists may have beneficial antipruritic effects. However, due to the location in the dorsal horn, these would only provide benefits in central pruritus, not peripheral [11].

Clinically, pruritus is a paroxysmal complaint in patients with MS, affecting about 5% of patients [12]. The itching associated with MS follows a similar relapsing and remitting pattern, tending to be only minutes, starting and ending abruptly, but occurring multiple times per day [13]. This paroxysmal pattern of itch can be spontaneous, especially during sleep, or aggravated by movements, eliciting a painful sensation. This can often be the presenting complaint and initial presentation of a patient with MS [14]. Along with being paroxysmal, the itch pattern is often symmetrical and segmental in nature, supporting the idea that it has a neurological origin [14]. For example, localized spinal cord lesions can cause pruritus in the same dermatome associated with the lesions [15].

Treatment

Treatment of MS requires targeting the disease from several different standpoints. Ultimately, treatment should focus on limiting progression, exacerbations, and symptomology. With respect to relapse, the formation of new symptomology over a period of time, high dose corticosteroid administration is paramount in improving recovery and reducing symptomology [16]. Evidence supported dosages include intravenous administration days of methylprednisolone 1 g/day for 3 days. This is then tapered with oral prednisone across 11 days. The relapsing symptom of optic neuritis improved more rapidly when using this regimen. Pregnant patients may require intravenous immunoglobulin (IVIG) due to established safety [16].

In limiting progression, disease-modifying therapies (DMT) is used for the group's close action to MS immunologic pathophysiology. These therapies target T-cell activation with newer therapies targeting B-cell activation. Most common use of DMT is in the relapsing-remitting subtype of MS. One of many classic medications used is interferon beta-1 (IFN-β) which can be delivered in various dosages, formulations, and schedules. Flu-like illness can be a common adverse effect with sustained therapy. Additionally, decreased responsiveness overtime may be due to antibody development to the treatments itself [16]. Another classic medication is glatiramer acetate (GA). In relapsing-remitting MS, GA has allowed for delay of the next exacerbation and radiologic evidence of slowed progression. Of note, GA injection is associated with post-injection reactions that include flushing, chest pain, urticaria, and pharyngeal constriction [16]. Combination therapy of IFN-β and GA showed significant benefit than IFN-β monotherapy but did not limit clinical progression to the degree of GA monotherapy.

Oral medications used in MS include dimethyl fumarate and its derivatives. The mechanism is thought to upregulate protective oxidative mechanisms for added protection. While effective, it is not without side-effects including anaphylaxis, angioedema, and progressive multifocal leukoencephalopathy (PML) to a lesser degree [16]. Fingolimod is another oral medication with proven superiority over IFN-β dosed every week. The mechanism is reliant on reducing lymphocyte migration of naïve T-cells and reduce further damage. This medication has significant drug interactions and adverse effects that require monitoring. A cardiac workup is necessary to monitor for possible bradycardia or atrioventricular blockade. Other adverse effects may include hepatic toxicity and increased risk for infections [16].

More recent drug development has created monoclonal antibodies including alemtuzumab and natalizumab. Alemtuzumab is a monoclonal antibody used to lyse reactive T-cells and other components of the immune system. This is not without significant side effects including the development of secondary autoimmune disease and cytopenia [16]. Natalizumab is specific in limiting T-cell migration across the blood-brain barrier through blockade of integrin of immune cells. Integrin is a component of cells used for cell adhesion and migration. Secondary to this mechanism, MS relapse is possible with drug discontinuation [16]. Furthermore, a black box warning for natalizumab was issued for an increased risk of PML. Rituximab is another monoclonal that can be used in treating MS, but it is considered off-label. Lastly, there are newer emerging therapies with promising clinical trial results that include ocrelizumab and daclizumab. Ocrelizumab is a monoclonal antibody against CD20, and daclizumab is an antibody against the CD25 receptor of T-cells [16].

MS-induced pruritus is often considered as a type of neuropathic itch; therefore, it is important to review the medications that can be used in neuropathic itch. Ultimately, treatment of the underlying disease will help mediate the underlying pruritus. If pruritus persists, methods for limiting neuropathic itch can be employed. Conservative measures include creating barriers and preventing propagation of the itch-scratch cycle. The next step would be the use of topical anesthetics and topical capsaicin to help reduce nerve excitation and itch. Systemic therapies can be used but have weaker evidence supporting their use. Oral medications suggested can

include antiepileptics and some tricyclic antidepressants [17]. Overall, mediation of overall disease is paramount to treating pruritic symptomology. However, in the event of refractory causes, we suggest neuropathic itch medications may be trialed to help remedy the symptoms.

Key Points

- MS is a neurologic disease that presents with neurologic impairment that's progression can be classified into several different categories.
- Pathogenesis of MS is linked to autoimmune T-cell destruction of central nervous system myelin. However, the humoral immune system may also be implicated.
- Management of neuropathic itch has mainly included symptomatic relief, risk factor management, and treatment of MS with corticosteroids, IVIG, and DMT.
- Recently, novel research has been targeted at itch-specific neural pathways such as BNP, GRP, NK-1, and Janus Kinase receptors. Treating MS will help alleviate neuropathic itch, but other methods can be used to help alleviate refractory cases.

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Chapter 23
64-Year-Old Male with Diffuse Itching After Starting Amlodipine

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A 64-year-old male presented with diffuse itching over the past 6 weeks. He reported taking amlodipine for the first time about 1–2 weeks before his itching started. His medications also include aspirin 81 mg and acetaminophen as needed for pain. He is not on any other medications. He has a history of diverticulosis. He denied any rash with his itching. He reported excoriation marks where he had been scratching.

On physical examination, there was no evidence of rash but scattered excoriation marks on the trunk and arms. CBC, liver function, kidney function, thyroid function, and hepatitis screen were within normal limits. He was up to date on age-appropriate cancer screening.

Based on the clinical case description, which one of his conditions likely is responsible for his itching?

1. Arthritis
2. Medication-induced pruritus
3. Thyroid dysfunction
4. Diverticulosis

Diagnosis

Medication-induced pruritus.

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Discussion

The disease presentation of drug-induced pruritus varies, and it is important for a clinician to be able to recognize the many forms of presentation. Drug-induced pruritus presents either with or without skin lesions. Often, a new drug-induced reaction will have no obvious indications on the skin, but in cases of chronic pruritus, defined as over 6 weeks duration, a patient may present with lesions secondary to the scratching behaviors such as lichenification and prurigo nodularis [1]. Most commonly, a diagnosis of drug-induced pruritus will not have these conditions [2]. The severity of the pruritus also may vary, with presentations possibly consisting of localized or systemic pruritus. Several variables often need to be considered including administration timing, type of medication, drug-drug interactions, presence of primary skin lesions, and medication dose. Some patients may experience pruritic symptoms directly upon starting a new regimen, whereas others may find the sensation to begin after a specific loading dose is achieved [2].

Recent investigation of over one million patients demonstrated about 1% of patients experienced pruritus from drug administration within 3 months [3]. Females were more likely to experience pruritus, and black patients reported experiencing it more commonly. The medications most likely to cause pruritus were heparin, sulfamethoxazole-trimethoprim (TMP-SMX), and calcium channel blockers respectively [3]. These most likely medications exhibited an occurrence rate of around 1% [3]. Chemotherapeutic agents have also been linked to pruritus development. These patients most commonly ranged between 50 and 79 years of age. Geriatric populations are possibly more likely to experience pruritus due to their higher rates of medication usage. Geriatric pruritus is compounded with increased neurodegenerative disorders and reduced epidermal repair rates [4].

Focusing on drug-induced pruritus without primary skin lesions, timelines describing the pruritus are acute and chronic pruritus with 6 weeks duration being the marker [5]. Acute pruritus is described in the setting of rapid itch sensation less than 6 weeks duration. Commonly this mechanism is described in several different medication classes most notably being antimalarial agents, serotonin reuptake inhibitors, and opioids. Itching that lasts greater than 6 weeks is considered chronic [5]. Several medications have been described in both settings making clinician history important for successful diagnosis.

The pathophysiology behind most drug-induced pruritus manifestations is not completely understood. The mechanism of the need to itch is the same as with other forms of pruritus and has a significant central nervous system involvement [6]. Furthermore, other pruritic etiologies can vary and include hypersensitivity reactions (type I and IV), cholestasis, hepatotoxicity, phototoxicity. Beyond this, the drug-induced release of pruritogens and altered biochemical mechanisms can create

a pruritic sensation. Lastly, the drug-induced formation of primary skin lesions also carries its specific sensation of pruritus [2]. Despite increasing attention, due to an increasingly older population, little is understood about the specific mechanisms [6]. Based on cancer drugs that induce itching, it is possible some of the mechanisms may have to do with epidermal growth factor receptor inhibition [2]. In unique cases, aromatic anticonvulsants may be associated with the interplay of virus and drug in the immune system when started 3 weeks to 3 months before symptoms of pruritus. These cases may present with a rash and systemic pruritus. This is most common in patients infected by cytomegalovirus (CMV), human herpesvirus-6 (HHV-6), HHV-7, and Ebstein Barr virus (EBV) [7].

Some medications that induced pruritus have been well studied creating a significant understanding of possible mechanisms and treatment. Antimalarial-induced pruritus, more specifically chloroquine, is well described as an acute agent in disease development. While the presentation may vary between acral, generalized, or aquagenic, it is agreed that the black population is described as more susceptible with 60–70% reporting pruritic sensation. Possibilities attempting to describe this manifestation include genetic basis, variance in pharmacokinetics, and glucose-6-phosphate dehydrogenase deficiency presence [5]. Biochemical molecules more recently implicated include histamine release, and endogenous μ-opioid peptide release [2].

Opioid-induced pruritus is also commonly associated and well-studied. This manifestation is often with acute administration of these agents [5]. More specifically, opioid-induced pruritus has a high association with intrathecal delivery. The mechanism is commonly thought to be by way of μ-opioid receptor modulation from the central nervous system. This is strengthened by an increased sensation described in medications with higher affinity to these opioid receptors [2]. Nevertheless, oral administration has shown possible development of opioid-induced pruritus as well [5].

In cases of medication initiation that induce cholestasis, the pruritus is a secondary effect. The direct mechanism of the itching is from the cholestasis causing epidermal deposits [2]. This phenomenon is discussed in Chap. 17 of this book.

In terms of pruritus secondary to medication, a large differential diagnosis accompanies based on the presentation of illness and accompanying laboratory studies. It is significant other causes of pruritus from drug-induced pruritus as management often varies to a degree. One important example to separate and keep as a differential diagnosis is the development of an immediate drug-induced allergic reaction. Generalized rapid itching after administration may often be a presenting sign before the development of urticaria and anaphylaxis, requiring prompt treatment and discontinuation [2]. Beyond this, other drug-induced cutaneous reactions may give rise to pruritus. These manifestations include fixed drug eruption, steven

johnson syndrome/toxic epidermal necrolysis, erythema multiforme, erythroderma, red man syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) Syndrome, and photosensitivity [2]. Further and thorough evaluation of the skin is pertinent to isolate a possible diagnosis.

Treatment

Linking drug initiation to the development of pruritus is difficult but crucial to the management of symptoms. Further management then surrounds removal or reduction, in cases where cessation increases the risk from another condition. A complication of isolating a medication as the cause of new-onset pruritus is the need to differentiate it from stress-induced pruritus. Oftentimes a new diagnosis leads to a new drug prescription alongside an increased anxiety state in a patient, both of which can cause pruritus. Anxiety induced pruritus must not be blamed on a new medication regimen, nor the other way around [8]. Accompanying disorders of sleep disturbances and mental symptoms should be considered.

Unsurprisingly, the mainstay of treatment, after isolating the drug as the cause, is to either completely stop the medication, reduce doses, or switch the patient to another medication entirely [2]. If a medication cannot be stopped, such as in the cases of chemotherapy, it is important to provide effective supportive antipruritic options to the patient [2]. Common options include antihistamines, antidepressants, antipsychotics, and antiepileptics. The mechanism of the antipsychotics and antiepileptics center around changing the neuropsychological threshold for itching, acting to decrease triggers or intensity [8]. If itching continues after the drug stoppage, initiate antipruritic therapies [2]. This can include classical medications including opioids [8].

In cases of anti-cancer chemotherapies, there cessation of the offending agent is not an option. The pruritus likely is unavoidable for these patients, and there is promising work showing psychoactive drugs that influence the CNS may be able to alleviate the irritation in these patient populations. Specifically, these include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), Chlorpromazine, and Perphenazine [8]. Their itch may also be compounded by a paraneoplastic pruritus that accompanies their cancer diagnosis.

For more common etiologies of drug-induced pruritus, treatment regimens are described in cases of persistent pruritus after drug discontinuation. Chloroquine-induced pruritus is often treated initially with antihistamine agents leaving μ-receptor antagonists and prednisolone as second and third-line agents [5]. Opioid-induced

pruritus is often treated with first-line medications acting on the μ-opioid receptor including nalbuphine and naloxone [5]. Nalbuphine is often described as superior due to the reduction of pruritus without curtailment of analgesia [9]. If refractory, further addition of dopamine 2 antagonists, like droperidol, and serotonin receptor antagonist, like ondansetron, can be utilized [5].

Since there is an expansive list of drugs that can possibly induce pruritus without primary skin lesions (Fig. 23.1), a generalized protocol is described [5]. If pruritus persists after drug discontinuation, initial management with antihistamines should be used as first-line treatment. Further refractory management should employ μ-receptor antagonists as second-line. Other medications to consider, if needed, include medications with neuropathic action like gabapentin and amitriptyline (Fig. 23.2) [5].

PATIENT CONDITION	POTENTIAL PRURITUS OFFENDER
Heart failure, hypertension	Lisinopril, captopril: ACE Inhibitors
	β-blockers, diltiazem, nifedipine, verapamil
Arrhythmia	Amiodarone, disopyramide, flecainide
Anxiety	Diazepam, oxazepam
Infection	Penicillins, tetracyclines
Hypercoagulation	Ticlopidine
Epilepsy	Carbamazepine, clonazepam, gabapentin, lamotrigine
Gout	Allopurinol, colchicine, probenecid
Malaria	Various malaria medications
Birth control or hormone replacement	Estrogens, oral contraceptives
Pain	Codeine, fentanyl, morphine
Cancer	Cetuximab, vemurafenib, erlotinib, panitumumab, bleomycin, peplomycin
Diabetes	Insulin
Tuberculosis	Isoniazid, rifampicin
Psychosis	Haloperidol, risperidone, chlorpromazine

Fig. 23.1 Medications implicated in drug-induced pruritus organized by disease state [2, 3]

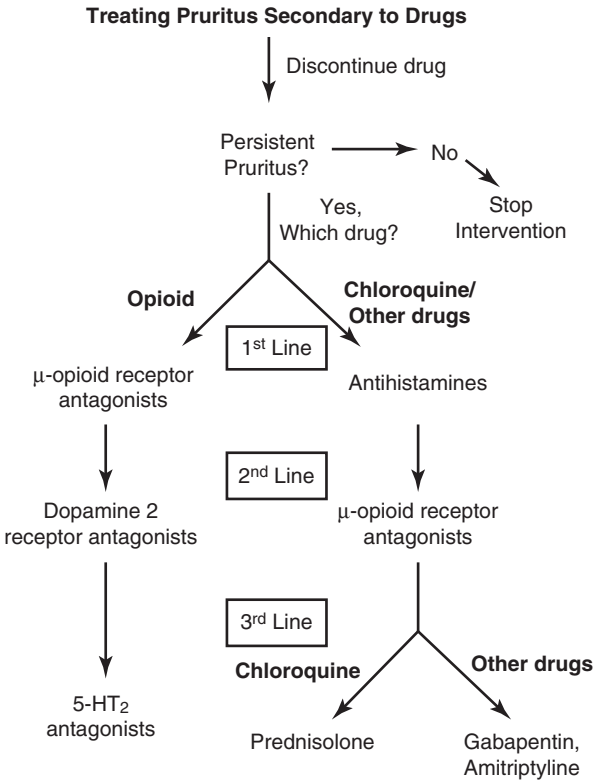

Fig. 23.2 Drug-induced pruritus treatment algorithm [5]

Key Points

- Drug-induced pruritus is a rare but present manifestation with recent estimates of about 1% occurrence overall.
- While little is known about the mechanism of action, some understood potential parts in pathogenesis may include opioid receptors, cholestasis, epidermal accumulation, or generalized age changes.
- First-line therapy is drug continuation. If the pruritic sensation is refractory or the drug cannot be discontinued, management should be continued with antihistamines, opioid antagonists, and neuropathic medications.

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Chapter 24
27-Year-Old Pregnant Female with a Pruritic Eruption on the Trunk and Extremities

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A 27-year-old Caucasian female gravida two, 32 weeks gestation presented with a 6-week history of a diffuse, pruritic eruption. She reported large blisters forming on her skin over the past several days. The patient was referred by her primary care physician who diagnosed her with rhus dermatitis. She was put on a 12-day prednisone taper starting at 30 mg that provided initial relief. However, the eruption persisted, and her pruritus returned once she finished her taper.

On physical exam, she had generalized urticarial, annular plaques with overlying bullae across her abdomen, back, flanks, chest, forearms, and legs (Fig. 24.1). Yellow crusting was present in some areas as well.

Two biopsies were performed to confirm the diagnosis. An H&E biopsy showed subepidermal vesicles, perivascular infiltrate of lymphocytes, eosinophils, and histiocytes in the dermis and papillary dermal edema. A direct immunofluorescence (DIF) staining was positive for linear C3 deposition at the basement membrane zone [1].

What is the most likely diagnosis?

1. Chronic urticaria
2. Intrahepatic cholestasis of pregnancy
3. Polymorphic eruption of pregnancy
4. Pemphigoid gestationis

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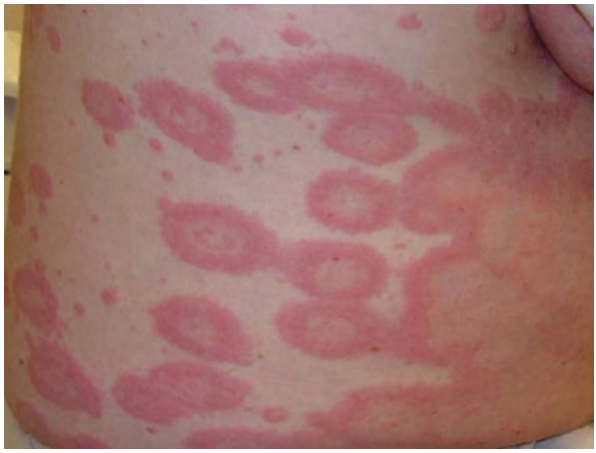

Fig. 24.1 Urticarial plaques with overlying vesicles on patient flank and abdomen. Reprinted with permission from *Cutis*. 2011;88:21–26. ©2011, Frontline Medical Communications Inc. [1]

Diagnosis

Pemphigoid gestationis.

Discussion

Pemphigoid gestationis (PG) is an autoimmune vesiculobullous dermatosis of pregnancy [2]. This rare disease was historically called herpes gestationis and gestational pemphigoid. Incidence is estimated at 1 in 50,000 pregnancies [3]. There is an increased incidence of PG in individuals with human leukocyte antigen (HLA) subtypes HLA-DR3 and HLA-DR4 [4].

The classic pattern is a pregnant woman in her second or third trimester to present with an acute pruritic rash [5]. Lesions characteristically start around the umbilicus and spread outward, and often with sparing of the mucous membranes and face. Primary lesions can be polymorphic and evolve over time. Initially, lesions are often urticarial patches or targetoid in nature. As the disease progresses, vesiculobullous lesions appear [6].

However, clinical presentations often vary with respect to time of onset, lesion morphology, and course of the disease. Some patients may not develop lesions until after delivery. Many patients experience a postpartum recurrence of PG at the time of menstruation, initiation of hormonal contraceptives, and subsequent pregnancies [3]. Lesions of some patients never progress to the blistering stage. While most cases resolve spontaneously weeks after delivery, other patients have lesions that persist for years after delivery [7]. Other possible features of the disease course include excoriations, peripheral eosinophilia, and pregnancy complications.

This disease impacts not only the mother but also the fetus. Approximately, 5–10% of neonates from PG mothers will have a transient bullous eruption at delivery [8]. Additionally, the fetus is at an increased risk of preterm birth and low birth weight secondary to mild placental insufficiency. Interestingly, this risk is correlated to the severity of the mother's disease [9].

The pathogenesis of PG is similar to that of bullous pemphigoid (BP) in that both result in the production of autoantibodies against the hemidesmosome protein BP180 (also known as collagen XVII) [2]. In PG specifically, placental expression of major histocompatibility complex (MHC) class II molecules presenting collagen XVII antigens triggers a humoral response. The resulting antibodies targeting the placental basement membrane zone (BMZ), will circulate and fix on the same components in the cutaneous BMZ [2]. The IgG autoantibodies activate the complement system, and the resulting complement deposition at the BMZ leads to clinical disease [10]. Linear complement deposition at the BMZ can be visualized using DIF; which is the diagnostic and pathognomonic hallmark of both PG and BP.

The mechanism of itch in PG has not been fully investigated, but it could parallel that of BP. Current evidence points to eosinophil degranulation as a mediator of tissue damage in PG [11]. BP research has shown a similar pattern of injury, with further studies observing eosinophils releasing higher levels of interleukin-31 (IL-31) [12]. Elevated levels of IL-31 have been found in other pruritic conditions including atopic dermatitis, prurigo nodularis, and cutaneous lymphoma [13]. This interleukin is a well-described itch mediator between the skin, immune system, and nervous system [14]. IL-31 is produced by type 2 helper T-cells, mast cells, and eosinophils [13]. Receptors for IL-31 are found on cutaneous neurons, keratinocytes, and histiocytes [13]. IL-31's function is still under investigation; however current research supports a role in initiating the sensation of pruritus [15]. Phase II clinical trials with a monoclonal antibody against the IL-31 receptor A, nemolizumab, showed that inhibition of the IL-31 pathway reduces pruritus in patients with atopic dermatitis [15]. Future studies should investigate how IL-31 contributes to the pathogenesis of PG, as therapies targeting the IL-31 pathway may be an effective treatment option.

The differential for a pregnant patient with pruritus should include the more common dermatoses associated with pregnancy polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy (AEP), (Fig. 24.2) [16, 17]. Proper diagnosis is important because ICP and PG have an increased risk to the fetus [16]. ICP can be ruled out with a low total serum bilirubin level. PEP occurs in the third trimester with polymorphic lesions within the striae, but the lesions lack bullae. AEP occurs in the first trimester in a patient with an atopic diathesis. While being pregnant may influence the differential diagnoses, it is pertinent to consider etiologies unassociated with gestation. Other manifestations to include are acute urticaria, erythema multiforme, drug eruption, and dermatitis herpetiformis to name a few [17].

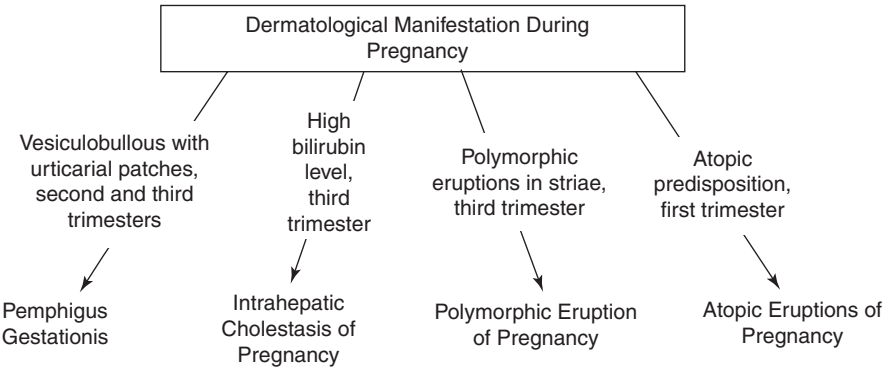

Fig. 24.2 Dermatoses of pregnancy

Treatment

Managing patients with PG should focus on two goals: preventing further blistering and relieving pruritus. Treatment will vary based on the severity of disease, whether the patient has delivered yet, and the mother's desire to breastfeed. Mild disease can be managed with potent topical corticosteroids alone [18]. However, most patients will require additional systemic steroids. Most patients respond to daily low dosages (30–40 mg) of prednisolone [5]. If new lesions continue to form 3 days after starting treatment, the dose of systemic steroids should be increased [19]. Some patients experience a flare of PG with delivery or the return of their menstrual cycle postpartum, which can be treated with additional steroid tapers. Treatment of PG with systemic corticosteroids has been found to have no risk to the fetus [20].

Pruritus can be managed with first or second-generation antihistamines. First-generation antihistamines, diphenhydramine, cyproheptadine, and chlorpheniramine, are preferred due to the amount of safety data supporting their use in the first trimester [21]. If the patient decides to use a nonsedating antihistamine such as loratadine or cetirizine [21].

Treatment for steroid-resistant PG is dependent on whether the patient has given birth. Management prior to delivery can be with intravenous immunoglobulin G (IVIG) infusions, plasmapheresis, or cyclosporine [22]. Postpartum treatment can include dapsone, cyclophosphamide, azathioprine, and rituximab [22]. Interestingly, rituximab has also been used to prevent recurrences in one patient with a history of PG and miscarriages during subsequent gestations [23].

The patient in the case presentation was initially treated with a regimen of triamcinolone acetonide cream 0.1%, 60 mg prednisone tapered over 30 days, oral cyproheptadine hydrochloride (to decrease pruritus), and oral erythromycin with topical mupirocin (for secondary impetigo). Within 2 weeks of treatment, her lesions disappeared. At 38 weeks gestation, she delivered without any immediate symptom relapse. At birth, the infant had no rash or evidence of adrenal suppression. The eruption did reappear 1 week after delivery and again at the onset of her first

menstruation. The eruption cleared both times with the same 60 mg prednisone taper. To date, she has had no recurrence of PG.

Key Points

- Pemphigoid gestationis (PG) is an autoimmune vesiculobullous disease estimated to affect 1 in 50,000 pregnancies. There is an increased incidence associated with human leukocyte antigen (HLA) subtypes HLA-DR3 and HLA-DR4.
- The pathogenesis of PG mimics bullous pemphigoid (BP) with autoantibodies against the hemidesmosome protein BP180 (collagen XVII). In PG specifically, placental expression and presentation of collagen XVII antigens triggers a humoral response and antibodies that then target the cutaneous basement membrane zone (BMZ).
- Treatment of PG includes use of topical and systemic steroid regimens. These can be used for initial presentation during pregnancy and for recurrences after delivery.
- The pruritic component of the disease may be secondary to interlukin-31 (IL-31), and can be treated reliably with a first-generation antihistamine and treatment of PG.

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Chapter 25
50-Year-Old Male with Diffuse Itching

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A 50-year-old male presented with diffuse itching over the past 2–3 months. He recalled having a viral-like illness a few months back with a fever, rash, pharyngitis, and generalized aches and pains. He stated that it resolved on its own. He admitted to having unprotected sex with five partners over the last year. He denied recreational drug use.

On physical examination, there was no evidence of rash but scattered excoriation marks on the trunk and arms. CBC, liver function, kidney function, thyroid function, and hepatitis screen were within normal limits. He was up to date on age appropriate cancer screening.

Based on the clinical case description, what additional testing should be done to investigate his itching?

1. Vitamin D levels
2. HIV screen
3. Colonoscopy
4. Chest X-ray

Diagnostic Test

HIV screen.

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Discussion and Treatment

The CDC estimates the prevalence of Human Immunodeficiency Virus (HIV) in the United States to be at 1.1 million people [1]. Skin conditions are extremely common in individuals infected with HIV. Before highly active antiretroviral therapy (HAART), 90% of HIV positive (HIV+) patients developed a skin condition during their disease course [2]. The skin conditions associated with HIV are numerous and of diverse etiologies including infectious, malignancy such lymphoproliferative disorders and solid tumors, and drug reactions. A common symptom of HIV+ patients face is chronic pruritus. One survey from a clinic in the Southeast United States found a 45% prevalence of chronic pruritus in HIV positive patients [3]. The patient's pruritus was objectively measured using a visual analog scale, and patients with a higher visual analog score also reported a significantly decreased quality of life (QOL) overall [3]. To help improve the QOL of HIV+ patients, it is important for dermatologists to relieve a patient's pruritus, if present. Difficulty in pruritus management stems from the vast array of causes in both HIV+ and HIV−. Initial investigation of pruritus should be separated into the following: pruritus with primary skin lesions and pruritus without primary skin lesions [4].

If there are no primary skin lesions present, then the itch is secondary to a nondermatologic etiology. The pruritic sensation triggers the patient to scratch, resulting in a disruption of the skin barrier, causing secondary skin lesions. Examples of secondary lesions include excoriations, post-inflammatory hyperpigmentation, and/or prurigo nodularis lesions. Discussing all nondermatologic causes of the itch is outside of the scope of this chapter. However, in general, there are three general categories that nondermatologic itch can fall under: systemic, neuropathic, and psychogenic [4]. Systemic causes include primary HIV infection, Hodgkin lymphoma, liver disease, chronic kidney disease, and thyroid disease. Neuropathic causes include postherpetic itch and neuropathic itch syndromes [5]. Psychogenic causes include substance use disorder, OCD, and delusions of parasitosis [4].

Conditions with primary skin lesions indicate a condition that is localized to the dermis/epidermis [4]. Disorders that are not unique (in etiology or presentation) to a patient's HIV status will not be focused on in this chapter; this includes xerosis, contact dermatitis, arthropod bites, lichen planus, psoriasis, and more. Instead, the focus is on entities special to HIV+ individuals: pruritic papular eruption of HIV and HIV-associated eosinophilic folliculitis. Atopic dermatitis, seborrheic dermatitis, and scabies will also be explored further because of their unique presentation in HIV+ patients (Fig. 25.1).

Pruritic papular eruption of HIV (PPE) is a chronic, nonfollicular, papular eruption with a generalized distribution across the extremities and trunk [6]. These papules are often excoriated because of the intense pruritus associated with the lesions. Histologically, the lesions resemble arthropod bites with a wedge-shaped infiltrate of eosinophils and lymphocytes [6]. PPE is hypothesized to be an abnormal immune reaction to arthropod antigen [7]. This idea is supported by the biopsy of PPE mimicking arthropod bites, peripheral eosinophilia, and higher prevalence in tropical

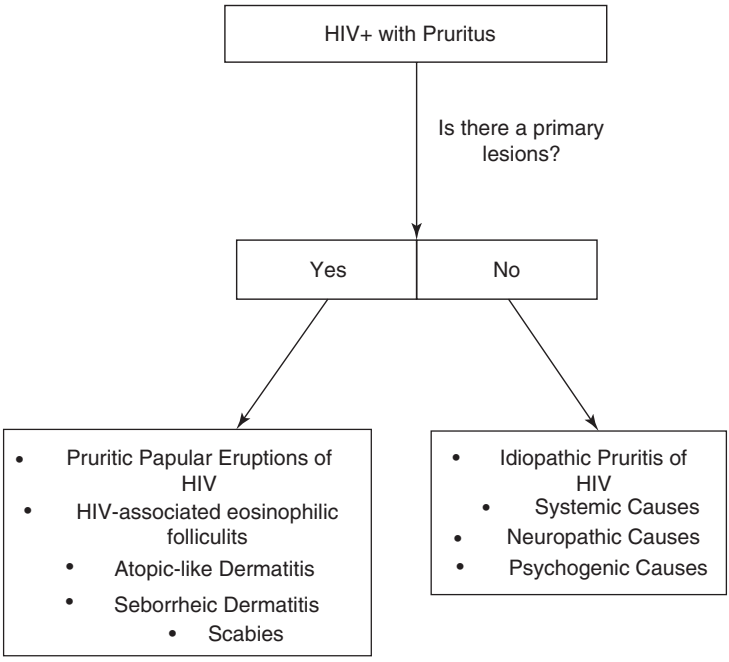

Fig. 25.1 Differential Diagnosis of HIV-associated pruritus

areas of the world [6]. This eruption has been documented occurring at any point in the time course of HIV, but most patients will have a CD4+ T-cell count less than 100/mm^3 [8]. PPE is often resistant to treatment, especially if HAART is not initiated [9]. Initial treatment often uses oral antihistamines and potent topical corticosteroids [10]. One study found that oral antihistamines statistically improved itching in PPE patients compared to topical steroids [11]. For refractory cases, phototherapy, dapsone, and oral thalidomide have been anecdotally useful [10].

HIV-associated eosinophilic folliculitis (HIV EF) shares some commonalities with PPE in that it is a chronic, erythematous, pruritic, papular eruption with peripheral eosinophilia seen in HIV+ individuals [11]. HIV EF most commonly happens in an HIV+ individual with a CD4+ T-cell count less than 300 cells/mm^3 [12]. HIV EF differs from PPE in that the papules are follicular-based, and lesions are absent below the chest [4]. Biopsy shows a follicular based spongiosis and infiltrates of primarily eosinophils with other leukocytes. The current working hypothesis is that HIV EF is due to a hypersensitivity reaction to skin flora, *Malassezia* or *Demodex*, in the pilosebaceous unit leading to eosinophilic chemotaxis and recruitment [13]. HIV EF is difficult to treat just like PPE, and often can use the same treatments such as topical corticosteroids, oral antihistamines and phototherapy [11]. Treatments that are additionally used to treat HIV EF include oral metronidazole, antifungals, and retinoids [11].

Atopic-like Dermatitis is a condition of HIV+ adults that is phenotypically identical to the typical atopic dermatitis (AD), except it is in an individual with no history of childhood eczema [14]. Patients will have lichenified lesions in the typical atopic distribution [11]. A predominant type 2 helper T-cell (Th2) cytokine profile is seen in both AD and HIV+ atopic-like dermatitis individuals; resulting in an increased peripheral eosinophil count, IgE level, and Th2 interleukins [14]. This unbalanced immune profile is what likely predisposes both populations to express this common cutaneous eruption. It is no surprise that patients with a history of atopy and HIV can experience an eczema exacerbation or recurrence due to a shift towards the Th2 profile [15]. This imbalance has been studied in children with perinatally acquired HIV which showed there was a significantly increased prevalence of AD [16]. Histology and treatment of atopic-like dermatitis is the same as AD in an HIV− patient.

Seborrheic dermatitis (SD) is an extremely common condition in patients infected with HIV [17]. SD is estimated to impact 35% of patients with early HIV infection who have a CD4+ T-cell count greater than 500 cells/mm^3, and 85% of patients with AIDS [17]. Two patterns of SD should trigger a workup for possible HIV. The first pattern is noted in a patient with the normal disease distribution of yellow, greasy scale on an erythematous background across the scalp, nasolabial folds, eyebrows, and postauricular area, but their rash is resistant to typical treatments [11]. Alternatively, patients can develop a more generalized form of SD that involves additional areas such as the whole face, chest, back, and axilla [11]. Biopsy of SD would reveal nonspecific perivascular infiltrate of lymphocytes and histiocytes, spongiosis, psoriasiform hyperplasia, and shoulder parakeratosis [18]. The pathophysiology of SD is a complex interaction between *Malassezia*, sebaceous gland secretions, and an individual's susceptibility [18]. Factors that contribute to an individual's susceptibility include epidermal barrier defects, genetics, neurogenic factors, environmental factors, and immune system function [18]. This last factor can explain why patients with HIV are more likely to have SD. SD is directly linked to decreased cell-mediated immunity which is prevalent in HIV infection [18]. Treatment of SD is the same regardless of the patient's HIV status, with most patients being treated with topical corticosteroids and/or topical antifungals [11]. However, HIV+ patients should be counseled that their SD is more likely to be treatment-resistant and more likely to relapse [19]. Overall, HAART can decrease SD prevalence in addition to reducing the frequency and severity of disease in HIV+ individuals [20, 21].

The presentation of scabies in an HIV+ individual depends on their level of immunosuppression [11]. Classic scabies can be seen early on when the patient still has a high CD4+ T-cell count or if the patient is on HAART [11]. The patient will have erythematous papulonodular lesions on the fingers, wrist, genitals, axillae, trunk, and nipples. Often, interdigital burrows may be present on physical exam [22]. These lesions will be extremely pruritic and classically worse at night [22]. This presentation is thought to represent a hypersensitivity reaction to mite antigens [11]. As the patient's CD4+ T-cell count falls, the disease presentation of scabies

will shift [11]. Rather than classic scabies, patients with a low CD4+ T-cell count will present with crusted scabies. Hyperkeratotic plaques often appear in the same distribution of classic scabies, like the hands, genitals, and axilla [11]. Crusted scabies affects other areas such as the scalp and face. The scale classically has a dirty appearance [11]. Interestingly, this form of scabies is often nonpruritic; possibly due to the lack of inflammatory response to the mites [22]. Diagnosis of any form of scabies is through examining the skin scrapings using a microscope to look for mites, eggs, or fecal matter [11]. Treatment of crusted scabies requires a more aggressive approach using a combination of topical scabicides, topical keratolytic to help remove the scale, and multiple courses of oral ivermectin [11]. Another important component of treatment is to treat everyone who lives in the patient's household, treat the patient's sexual partners, and wash all clothes and sheets in hot water [22].

Of note, one diagnosis that does not fit into any of the three categories is idiopathic pruritus of HIV, which is a diagnosis of exclusion [11]. Most often, a dermatologic (such as xerosis) or systemic condition (like lymphoma) can be identified as the cause of a patient's pruritus [11]. Therefore, this diagnosis should be reserved for patients who have no identifiable cause of pruritus and a normal workup. A standard workup includes history and physical exam, complete metabolic panel to evaluate kidney and liver function, hepatitis serologies, and complete blood count with differential [11]. Without a definitive diagnosis, treating a patient with idiopathic HIV pruritus is difficult. Interestingly, one therapy that may provide symptom relief is phototherapy [11].

Key Points

- Pruritus in an HIV+ patient should be organized as pruritus with primary skin lesions and pruritus without primary skin lesions.
- Pruritic papular eruption of HIV (PPE) is a generalized, nonfollicular eruption composed primarily of papules. Initial treatment is with antihistamines and topical steroids.
- HIV-associated eosinophilic folliculitis (HIV EF) is an erythematous, papular eruption with follicular-based lesions and peripheral eosinophilia. Initial treatment is with antihistamines and topical steroids.
- Atopic-like dermatitis is clinically identical to atopic dermatitis, except it is in an HIV+ patient with no history of atopy. Treatment is the same as atopic dermatitis in HIV− patients.
- Seborrheic dermatitis (SD) can present as a typical SD that is treatment-resistant or as a generalized across the face, trunk, and axilla. Patients with either of these variants of SD should be tested for HIV. Treatment is with topical steroids, topical antifungals, and HAART if the patient is not on a drug regimen.
- Scabies can present as a typical, localized disease in patients with high CD4+ T-cell count, or as hyperkeratotic, nonpruritic plaques in patients with low CD4+ T-cell count. Treatment is with topical scabicides, keratolytic, and oral ivermectin.

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