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Prurigo
Diagnosis and Management

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Contents

Abstract

Prurigo is a condition of nodular cutaneous lesions that itch (*pruire*) intensely. Although the acute form can be caused by insect stings, most of the subacute and chronic forms appear to be idiopathic. Toxic agents deposited in the skin by exogenous factors such as parasites, bacteria, or topically or orally administered drugs can induce itch. In susceptible individuals, physical mechanisms such as UV light can induce changes in epidermal innervation that result both in itch generally and in prurigo lesions. Prurigo is sometimes associated with atopy, pregnancy, internal diseases, malabsorption, or malignancy. Some forms of prurigo may be secondary to scratching. Emotional factors can also influence the perception of itch and induce prurigo by provoking scratching. These are the various specialized forms of prurigo, and there are certain others, such as prurigo pigmentosa, that have some ethnic preference. Topical treatments by corticosteroids, coal tar, bath photochemotherapy, UVB, cryotherapy, or capsaicin, as well as systemic regimens involving use of psoralen + UVA (PUVA), erythromycin, arotinoid acid, cyclosporine, chloroquine, dapsone, minocycline, naltrexone, azathio-

prine or thalidomide are used for the treatment of this condition. Psychotherapeutic agents to treat problems of mood that deteriorate prurigo are also prescribed. Combined sequential treatments for generalized, therapy-resistant cases need to be tailored to the exacerbations that occur and to provide maintenance treatment in order to enable the patient to withstand the intolerable itch.

The term prurigo, originating from the Latin *pruire*, meaning to itch, was coined by Ferdinand von Hebra in characterizing intensely itching papules and nodules (figure 1). When von Hebra founded the first Department of Dermatology and Pathologic Anatomy in Vienna in 1850, prurigo was one of the most frequent forms of skin disease in Europe, the acute form being associated with stings and bites from parasites, especially fleas and mites. The improved social and hygienic conditions since then have cut down the frequency of prurigo to a very large extent.[1]

In 1974, Shelly wrote, "Know this disease for what it is: a terrible, tormenting, relentless itch".[2] Itch is conducted by mechano-insensitive C-fibers with excessive terminal branching in the epidermis and upper dermis. Upon nerve stimulation, neurotransmitters are released, resulting in neurogenic inflammation, a process other inflammatory mediators can augment. The cell bodies of cutaneous sensory nerve fibers are located in the dorsal root ganglia, their axons terminating in the dorsal horn of the spinal cord.[3] Inflammation at this level can enhance neuronal excitability, causing repetitive activation of C-fibers. Aberrant peripheral and spinal nerve transmission can lead to neuropathic itch. Contralateral spinothalamic neurons sensitive to histamine conduct signals to the medulla oblongata, inducing reflex scratching. The signals are transmitted from there to the thalamus, which is responsible for the emotional processing of itch. The central neuronal pathways involved terminate in the somato-sensory cortex and in the motor areas that lead to conscious scratching.[4] Continuous inhibitory signals directed in the retrograde direction, originating at several levels in the spinal cord, as well as in the thalamus and the cortex, stop some of the influx of sensory information from the skin. However, tissue injury at different signal transmission levels or alterations in neurotransmitter concentrations, as seen in various psychogenic disorders, can allow neuronal activity from the periphery connected with itching to progress to the medulla oblongata and to the cerebrum, so that itching which would not otherwise have been perceived is experienced.

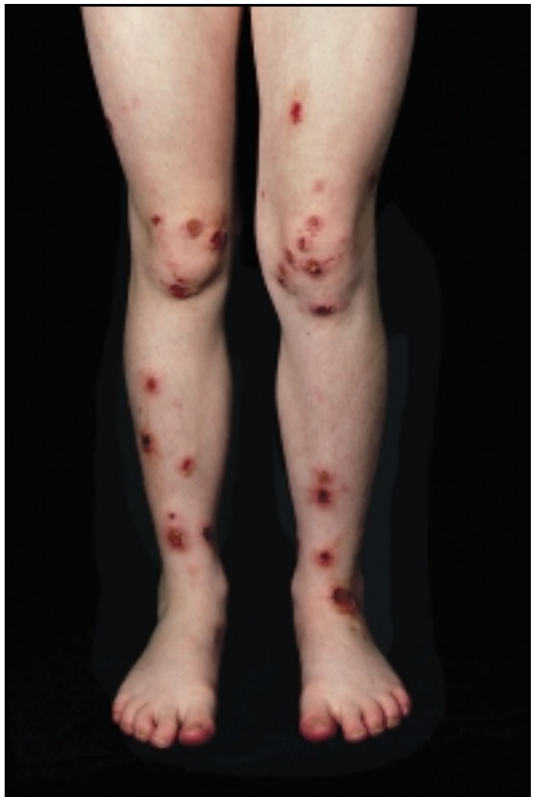

Fig. 1. Prurigo nodules of the legs.

Both peripheral and central nervous factors have been suggested to be etiological factors in prurigo. Histological evidence speaks for prurigo having a peripheral etiology. Psychogenic and emotional factors, however, are also known to worsen the symptoms, which indicates that central nervous mechanisms are also involved.[2]

1. Nomenclature of Prurigo and its Differential Diagnoses

The categorization of prurigo reflects the history of dermatology in general. During the 19th century and the first half of the 20th century, dermatology was morphologic, the eponyms of the prurigos being various leading dermatologists who first described them. The use of hundreds of eponyms in the classification of prurigo has been a detriment to communication between dermatologists regarding it. A working classification in which prurigo is divided into acute, subacute and chronic forms, the older eponymal groupings being included in these categories, has been reviewed by Jorizzo et al.[1] Different types of prurigo and their etiological or associated factors are summarized in table I.

Table I. Different types of prurigo and their etiological or associated factors

Type of prurigo	Etiology or associated factors
Acute prurigo	Insect stings or bites,[5] atopy[6]
Subacute prurigo	Emotional stress[7]
Chronic prurigo	Atopy,[8] internal diseases,[8,9] malabsorption,[10] malignancy,[11,12] collagen diseases,[13,14] emotional stress,[8,15] infections,[16,17] parasitoses[16,18]
Prurigo of pregnancy	Pregnancy in atopic women[19]
Pemphigoid nodularis	Pemphigoid[20,21]
Actinic prurigo	Native North and South American Indians, associated with sun exposure[22]
Hutchinson summer prurigo	Described in Europe, identical to actinic prurigo[23]
Sutton summer prurigo	Atopic eczema in children[24]
Prurigo pigmentosa	Onset in summer, mainly in Japan[25] but also in Turkey and Sicily
"Papular eruption in black men"	Occurs in Black skin, etiology unknown[26]

1.1 Acute Prurigo

The acute form of prurigo (prurigo simplex acuta) is identical to strophulus, which many authors connect with urticaria. Other names used for this condition are prurigo mitis, lichen urticatus, and papular urticaria.[5] The condition occurs principally in young children. The primary lesions can be papules, vesicles, and/or urticarial lesions that persist for a period of about a week. The lesions are scattered, occurring mainly on the trunk and the proximal extremities. Secondary excoriational changes are often present. The chronic eczematized, lichenified, and impetiginized form of strophulus is the prurigo Hebra, which Hebra himself called prurigo ferox. His patients were often children with atopic eczema, whose intensely pruritic papules were accompanied by lymphadenopathy. The incidence of this condition was highest in areas of poor hygiene and malnutrition. This condition has now become very rare.[1] Prurigo simplex temporanea (Tommasolo) is the adult form of acute prurigo, occurring mainly in young adults. Most authors agree that the stings or bites of insects cause the primary lesions here.[1] Differential diagnoses of the condition are those of pediculosis corporis, scabies, dermatitis herpetiformis, and urticaria. The usual histopathological finding is that of a heavy infiltration of lymphocytes and eosinophils, primarily around middermal blood vessels and appendages, accompanied by dermal edema.[1]

1.2 Subacute Prurigo

Eponyms such as Kogoj prurigo subacuta, Darier prurigo vulgaris, Lutz prurigo multiforme, and Vidal lichen urticatus, flourish in the subacute group of prurigos. Urticaria papulosa chronica perstans and itchy red bump disease are other names involved.[7] These variants are virtually identical in the clinical picture they present, even when combined with eczema. Another form of prurigo that can be described here is dermographic prurigo. This is a severe form of symptomatic dermographism in which urticarial wheals and excoriations occur at sites of clothing pressure or rubbing. Neurotic excoriations, characterized by erosions or ulcers rather than by papules, may in a few cases be an element of nodular prurigo. These forms of prurigo tend to occur in middle-aged patients, especially women.[7] Psychogenic or emotional factors in subacute prurigo are common. The differential diagnoses are those of dermatitis herpetiformis, transient or persistent acantholytic dermatosis, and scabies. Biopsies reveal acanthosis, hyperkeratosis, a proliferation of nerve fibers, and focal spongiosis, a moderate chronic perivascular inflammatory infiltrate being present.[7]

1.3 Chronic Prurigo

The genuine chronic form of prurigo is the prurigo nodularis of Hyde, who in 1909 coined the term.[27] Other previously described entities included in this category are keratosis verrucosa, lichen obtusus corneus, and urticaria perstans verrucosa. Since prurigo nodularis is probably the entity to which most dermatologists apply the term prurigo, a careful description of it is worthwhile.

The lesion involved is a hemispherical, often irregular node with a horny, rhagadiform or crateriform depressed surface. It may be as much as several centimeters in diameter. The lesions may be single, grouped, or disseminated. They are mainly located on extensor surfaces of the extremities, although the trunk, face and even the palms can likewise be affected.[27] In cases that are long lasting, large, irregular, keratotic, often excoriated plaques are seen and scars show changes in pigmentation. Chronic prurigo can occur at any age, although mainly from 20 to 60 years, both sexes being affected equally. Patients are affected by a pruritus of intense severity. New nodules develop from time to time, and

existing nodules may remain pruritic indefinitely, although some may regress spontaneously to leave scars.

The usual histopathological finding is one of pronounced acanthosis and papillomatosis[27] (figure 2). There is a proliferation of small vessels and nodular polymorphic infiltrate containing mast cells and eosinophil granulocytes in the upper and middle layers of the dermis. The most impressive and pathognomonic finding is the presence of thick nerve fiber bundles and fine, reticularly arranged terminal nerve fibers. In 1899, Johnston wrote that the number of hypertrophic nerve fibers in prurigo lesions is increased.[28]

The cause of chronic prurigo is unknown, although around 65–80% of the patients are atopic.[8] In these patients the age of onset may be earlier, even if no eczematous eruptions are present. Emotional stress seems to be a contributory factor in many cases.[8]

The clinical and pathological characteristics of prurigo nodularis are readily identified, the diagnosis being easily made. The main differential diagnoses are those of chronic prurigo associated with internal disorders (see section 3.1).

2. Pathophysiology of Prurigo

During the 19th century, there was much discussion between leading dermatologists about whether the prurigo lesion appears first and produces an urge to scratch or whether its appearance is only secondary to scratching.[27]

According to Hebra, who introduced the term, it is the prurigo papule that appears first. The application of new histological markers and the use of immunofluorescence methods have thrown new light on the prurigo papule.[27]

S-100 protein staining has shown there to be an increase in the number of nerve fibers in the papillary dermis of patients with prurigo nodularis. Occlusion with elastic bandages for 4 weeks improves the clinical picture, so that no enlarged nerve fibers or neurinoma-like structures are visible. This appears to indicate that the prurigo nodularis lesion is secondary to traumatization. However, the thick nerve fiber bundles found in the lesional skin of prurigo nodularis do not occur in other forms of itching skin, such as in lichenified eczema. The nerve fibers in the lesional skin of prurigo nodularis show immunoreactivity for calcitonin gene-related peptide and substance P, both known as sensory neuropeptides.[29] Studies of skin biopsies of prurigo reveal an increase in the number of mast cells, not only in the dermis but also in the epidermis.[30] An invasion of the cutaneous nerve fiber bundles in the dermis by mast cells has also been shown.[31] Mast cells and sensory nerve fibers constitute a unit. Neuropeptides and histamine cooperate in neurogenic inflammation and in the induction and transmission of itch. In addition, the number of Merkel cells, functioning as specific slowly adapting sensory touch receptors, has been found to be increased in prurigo nodularis at the basal cell layer.[32] Dermal nerve fibers are occasionally observed in biopsies of the prurigo nodularis to be in close proximity to Merkel cells. This suggests that the proliferation of sensory nerve fibers, mast cells, and Merkel cells, may together be responsible for the abnormal perception of itch and of touch that creates the prurigo nodulus found in susceptible individuals.

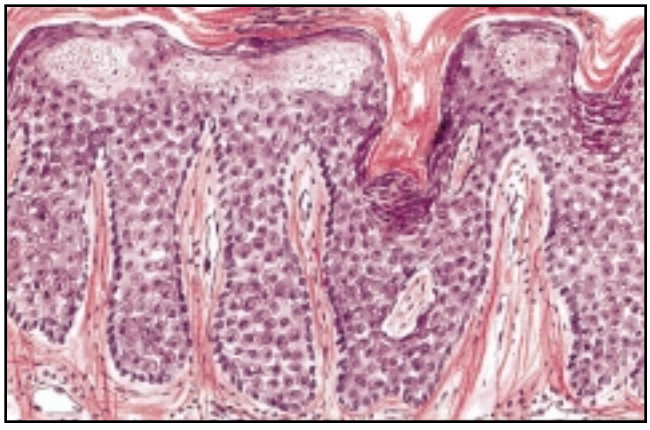

Fig. 2. Histopathology of nodular prurigo in aquarelle. There is hyperkeratosis, parakeratosis, a very marked acanthosis and an epidermal necrosis due to picking. (Courtesy of Dr A. Bjornberg and Dr E. Tegner.)

3. Specialized Forms of Prurigo and their Etiology

The term prurigo originates from a time when dermatology was a descriptive discipline. Today dermatology has become investigative and there is an urge for a categorization based on pathophysiological mechanisms. In this light, prurigo may be regarded as an archaic term, as pointed out by Mascaro.[33]

The prurigo nodule is a cutaneous pattern associated with itch. Some endogenous substances found in excessive amounts such as the histamine in atopic patients, biliary salts in pregnancy or in hepatobiliary cirrhosis, or uric acid in uremia may sometimes cause local reactions in the skin producing prurigo lesions identical to the primary lesion of acute, subacute, or chronic prurigo. Some specialized forms of prurigo are more often found in certain ethnic groups.

Emotional and environmental factors may also change the perception of itch, inducing scratching and provoking a prurigo lesion. Several exogenous factors such as parasites, bacteria, topically or orally administered allergens, or toxic agents deposited in the skin can induce itch as well. Itching is a sensation primordially directed at a mechanical reflex for the removal of ectoparasites. Physical factors such as UV light can induce changes in epidermal innervation that result in itch and in prurigo lesions in susceptible

individuals. Descriptions of the various specialized forms of prurigo associated with endogenous (section 3.1) and exogenous (section 3.2) factors now follow.

3.1 Endogenous Disorders Associated with Prurigo

3.1.1 Atopy

The term Besnier prurigo is still used in continental Europe, being applied to the chronic papular, lichenified form of atopic dermatitis. Many of the original cases of Hebra prurigo probably involved atopic patients living under poor social conditions. Flea bites may have played a role in producing papular lesions. This pruriginous form of atopic dermatitis is a less usual form, found in about 9% of the young adults who have had a chronic form of the disease since childhood.[34] According to Mali, patients with an atopic background develop signs identical to those of subacute prurigo, although they are mainly restricted to the seborrhoic area.[6] The chief complaint of most of these patients is severe itching experienced in attacks that occur especially after physical strain, in hot weather, and during periods of emotional stress. In addition, atopic patients with a history of marked intolerance for psoralen + UVA or UVB (PUVA or PUVB) therapy may develop actinic prurigo (see section 3.2.3).

3.1.2 Internal Diseases

In a clinical study of 46 patients with nodular prurigo or chronic lichenified eczema by Rowland Payne et al., 50% of the patients were found to have a pruritus of metabolic cause.[8] Several internal diseases associated with itch may involve skin lesions that simulate prurigo nodularis, and occasionally prurigo nodularis-like changes due to scratching may appear.

Itch is a very common symptom in patients with chronic renal failure receiving maintenance hemodialysis. Perforating folliculitis with superimposed prurigo nodularis in these patients was described first in 1982.[9] Histological examination reveals a wedge-shaped parakeratotic plug within a widened follicular infundibulum. The thinned wall of the infundibulum ruptures, resulting in the spillage of parakeratotic cells into the dermis, where a granulomatous perifolliculitis appears. Interestingly, the skin lesions of one patient, which had been completely unresponsive to treatments of various kinds, cleared up rapidly within a week after hemodialysis was stopped and a renal allograft transplanted.[9] Acquired reactive perforating collagenosis, a rare disease usually associated with diabetes mellitus or renal failure, may involve prurigo nodularis.[13] In addition, prurigo-like lesions are associated with various other collagen diseases such as disseminated lupus erythematosus (DLE), systemic scleroderma and the adult onset of Still disease.[14] Occasionally prurigo nodularis may be associated with α1-antiprypsin deficiency.[35]

3.1.3 Malabsorption

The association between prurigo nodularis and malabsorption was first observed by Wells in 1962, who described a patient with gluten enteropathy.[10] Since then, seven additional patients with coeliac disease and therapy-resistant prurigo nodularis have been described in the literature. After several months of treatment involving a gluten-free diet supplemented by vitamins and iron, the intestinal symptoms tend to improve and the typical clinical prurigo nodularis tends to diminish, disappear, or be partly improved.

The question is whether there is an etiopathologic link between enteropathy and prurigo nodularis or whether prurigo nodularis is instead a result of the accumulation of pruritogenic metabolites in the skin secondary to fasting. The occurrence of prurigo nodularis in patients with anorexia nervosa favors this last explanation. Itching is a clinical feature of anorexia nervosa associated with low weight, one that disappears with the restoration of weight.[15] 'Scratch prurigo' at the site of the itch also appears to improve with the restoration of weight.[15]

3.1.4 Malignancy

Pruritus, often accompanied by excoriations, can be a nonspecific marker of internal malignant disease. Prurigo has been associated with T-cell lymphoma and visceral neoplasia in the esophagus, the ventricle, the rectum, the liver, and the bile duct. Prurigo of the lymphoma may precede symptoms of malignancy.[11] Malignancy may also appear as diffuse prurigo.[12] The occurrence of prurigo can also be a warning signal for malignant transformation in patients with tumors previously diagnosed as being benign.[12] In the case of malignancy, prurigo nodules are likely to develop secondary to scratching.

3.1.5 Emotional and Psychogenic Factors

In a clinical study of 46 patients with prurigo nodularis by Rowland Payne et al., 50% of the patients were found to have depression, anxiety, or some other psychological disorder requiring medical intervention.[8] The explanation for this association is probably that neurotransmitters of mood such as dopamine, serotonin or opioid peptides modulate sensory perception via the descending spinal pathways. Seventy-two percent of the patients in the study felt that psychosocial problems were of relevance to their skin disease.[8]

3.1.6 Pregnancy

Pruritus is the main cutaneous symptom during pregnancy. Pruritus gravidarum refers to the intense itching that occurs late in pregnancy in the absence of any associated rash or clinical jaundice.[19] The term prurigo of pregnancy or prurigo gestationis was first introduced by Besnier in 1904 to include all patients with pregnancy rash other than herpes gestationis. Prurigo of pregnancy

occurs in about in 2% of all pregnancies. It usually starts at about 25–30 weeks of gestation and disappears soon after delivery, but may also persist postpartum for months. It does not necessarily occur in subsequent pregnancies.[19] It is a benign disorder that influences neither the pregnancy nor the newborn child. Prurigo of pregnancy is characterized by small, erythematous or skin-colored papules that are extremely pruritic, resulting in excoriated lesions, the surrounding skin remaining normal. Acanthosis and a perivascular inflammatory cell infiltrate can be shown histologically. Al-Fares et al. have postulated that prurigo of pregnancy is the result of pruritus gravidarum in atopic women.[19]

3.1.7 Ethnic Predisposition

Prurigo pigmentosa, first reported by Nagashima in 1971, is a distinct clinical entity not at all rare in Japan, where more than 200 cases have been reported.[25] The disorder is less common in non-Japanese patients, although a predisposition to prurigo pigmentosa has been reported recently in the populations of Turkey and Sicily.[36,37] The lesions typical of prurigo pigmentosa are pruritic red papules superseded by reticular hyperpigmented mottling, characteristically on the back, neck, and chest. Histologically, the lesions are lichenoid in character and display certain pigmentary incontinence. The disorder is more common in adult females.[38] Its onset is usually in the spring and summer months. According to Nagashima, physical trauma and friction with clothing may be important in the pathogenesis and for the exacerbation of the disorder in some patients.[38] An association of prurigo pigmentosa with type I diabetes mellitus and anorexia nervosa has been reported in Japan.[25]

Actinic prurigo is a chronic photodermatitis found predominantly in native North and South American Indians.[22] Characteristic clinical features include intense pruritus, prurigo-like papules on light-exposed areas, cheilitis, conjunctivitis, scars, and alopecia of the eyebrows. Generally, the onset is at an early age, and there is usually a family history and a predominant occurrence in females. There is also an association with residence at high altitudes (above 2000 meters), with outdoor occupations, and with a predominance of *HLA-DR4*.

In 1980, Rosen and Algra published a report on what they referred to as "a papular eruption in black men".[26] They described seven young Black patients with persistent papular eruptions usually located on the trunk, the upper part of the arms, and sometimes the face, buttocks, and thighs. Histologically, a dense perivascular inflammatory infiltrate composed of mononuclear cells and many eosinophils can be noted in the upper dermis.

3.1.8 Pemphigoid Nodularis

Pemphigoid nodularis is an unusual disorder that was first described in 1981.[20] Since then, about 20 further cases of pemphigoid nodularis have been described.[21] The disease occurs predominantly in elderly women, although it may occur in men and children as well. Initially, patients present itchy noduli, papules, or plaques. Bullae develop later, sometimes several years after the debut of the noduli. This disorder is considered to be a variant of bullous pemphigoid. Histologically, there is an acanthosis of the epidermis and an inflammatory infiltrate in the dermis. Direct immunofluorescence studies reveal a linear deposition of IgG and C3 in the epidermal basal membrane zone.[20]

3.2 Exogenous Disorders Associated with Prurigo

3.2.1 Infections and Parasitoses

HIV infection is associated with itch, with prurigo being diagnosed in about 6% of patients.[16] The pruriginous lesions may represent either exaggerated or persistent reactions to insect stings or bites or chronic prurigo.[16] In addition, immunosuppressed patients are more susceptible to parasitic and helmintic infections, and the skin reactions are persistent, such as in Norwegian scabies.

Prurigo strophulus can be provoked by stings or bites of fleas, mosquitos, ticks, or dog parasites.

In large parts of the world, such as in Africa, zoonotic and parasitic infections are widespread and are a major cause of morbidity and mortality. Prurigo has been associated with helminthic infections such as toxocara or strongyloidiasis.[18]

Lyme disease may be associated with chronic prurigo (to 24% in a Turkish study).[39] Mycobacteria have been found in association with prurigo nodularis.[17] In addition, there have been sporadic reports of prurigo occurring in association with *Helicobacter pylori* infection and with cutaneous toxoplasmosis.[36,40]

3.2.2 Contact Allergy and Drug Reactions

Contact allergy is usually associated with severe itch. It can occur together with prurigo secondary to scratching. Patients with established prurigo often undergo a variety of topical therapies and are prone to developing a contact allergy to drugs they use. It does not appear, however, that special allergens induce a pruriginous form of cutaneous reaction. In a survey of 199 patients with prurigo nodularis at the Mayo Clinic, Zelickson et al. reported 25 of them to have positive patch test reactions of relevance, the main allergens being neomycin, fragrance, and nickel.[41] Several patients reported a definite improvement or clearing of their condition with avoidance of the allergens.

Patch testing of 42 American Indians with actinic prurigo revealed contact allergy in 13. Nickel allergy was found in 12%, an allergy to colophony in 7%, and an allergy to local plants in 2%. None of them were allergic to poison ivy, which is endemic in the region.[42]

A few perorally administered drugs have been reported to provoke prurigo. Etanercept has been found to induce acute prurigo,[43] carbamazepine to induce subacute prurigo,[44] and etretinate to induce nodular prurigo-like reactions.[45]

3.2.3 Light Eruptions

Hutchinson summer prurigo, described in 1878, occurs in children and young adults. The erythematous papular eruption affects light-exposed areas, most commonly the face.[23] This disease is rarely seen in Europe. It appears to be identical to the actinic prurigo described in American Indians (see section 3.1.8).

Sutton summer prurigo of the elbows appears as a papular eruption, usually limited to the elbows, although it may also affect the knees, hands, or chest.[24] This disease is related to atopic eczema and affects children during the first few weeks of spring or summer and tends to recur for several years.

4. Management of Prurigo

In the case of secondary prurigo, the underlying disease should be treated and external provoking factors avoided. Acute prurigo is accompanied by inflammation and severe itching, which can be successfully treated by topical corticosteroids and by antihistamines. Subacute prurigo is a relapsing disease requiring treatment when exacerbations occur. The course of prurigo nodularis and many types of secondary prurigo is a prolonged one. The major chronic and persistent forms of prurigo are therapy resistant and patients expect to try various types of treatments. Severe, generalized exacerbations can be treated systemically. Maintenance topical therapy can be required too, in order to stop the itch and avoid the scratching that provokes relapses. There are many topical and systemic agents, as well as sequentially combined treatments. The therapeutic regimens suggested in this section are based on experience in our department and on a review of literature obtained on Medline®.

4.1 Topical Treatments

Topical therapies used in the treatment of prurigo and their mode of action are summarized in table II.

In the acute phase we start treating a patient with severe excoriated and discharging prurigo lesions in the same way as Hebra did 150 years ago, by means of a potassium permanganate bath and a 2–5% coal tar bath. The mode of action of coal tar is still unknown, mainly because of the difficulties in evaluating the pharmacodynamics of the collection of chemical compounds of which tar consists. Antiseptic, antipruritic, antiparasitic, antifungal, and antibacterial activities probably result from the phenolic constituents. In practice, coal tar was often used earlier in the treatment in association with UV light. Bath PUVA (a psoralen bath followed by UVA irradiation) is now used instead.[46] Such treatment can be given daily for 1–4 weeks and then for 4 days every second month for 5 months. In a Finnish study of 15 patients with prurigo nodularis, the lesions of all the patients were cleared up by the use of this regimen and the lesions in 13 patients remained healed.[46]

Table II. Topical therapies used in the treatment of prurigo and their mode of action

Topical therapy	Mode of action
Calcipotriol	Anti-inflammatory, antipruritic
Capsaicin	Anti-inflammatory, antipruritic-heat receptors
Coal tar, bath	Antiseptic, antipruritic, antiparasitic, antibacterial
Corticosteroids	Anti-inflammatory, antipruritic
Cryotherapy	Anti-inflammatory, antipruritic, antiproliferative
Cyclosporine	Anti-inflammatory, antipruritic
Lidocaine (lignocaine)	Antipruritic
Menthol	Antipruritic-cold receptors
Potassium permanganate, bath	Anti-inflammatory, antiseptic, antipruritic
Psoralen + UVA (PUVA), bath	Anti-inflammatory, antipruritic
UVB, TL01 phototherapy, Bucky irradiation	Anti-inflammatory, antipruritic

In our department, we have treated eight patients with prurigo nodularis using broadband UVB; four of them have since improved. In an English study, the prurigo in seven of eight patients also improved with broadband UVB.[47] It is possible that narrowband UVB, or TL01 phototherapy, is better in the treatment of prurigo.[48] Phototherapy can reduce the inflammation and the number of epidermal nerve fibers. An old method worth trying is Bucky irradiation.

High-potency corticosteroids applied topically to a lesion, preferably with an occlusive membrane placed over it, are particularly useful in the treatment of acute or subacute inflammatory lesions. For more chronic lesions, the application of corticosteroids intralesionally is more effective.

Topical cyclosporine has an anti-inflammatory function and has been used successfully for treating conjunctival manifestations of actinic prurigo. We have successfully treated one patient with chronic prurigo caused by a renal failure with tacrolimus. There was a good reduction of itch and the size of the prurigo nodules.

Chronic and scaling keratotic prurigo lesions should be initially treated with some form of keratolytic ointment containing salicylic acid, sometimes covered by an occlusive membrane. Calcipotriol

ointment, originally used for treating psoriasis, has been reported to be useful in treating prurigo nodularis.[49]

Another treatment recommended for prurigo is cryotherapy.[50] Freezing should result in blister formation. The point is to induce thermal damage to the peripheral sensory nerve fibers at the epidermal/dermal border. After the blisters have healed, topical corticosteroids should be used to prevent a relapse.

Is there some other way of affecting peripheral sensory nerve fibers? The intralesional administration of lidocaine (lignocaine) has been reported to be effective against itching.[51] Capsaicin, the pungent agent of hot pepper, releases and depletes C-fibers of their neurotransmitters, making them refractory. Since the first report by Cappugi et al.[52] in 1989 of the treatment of prurigo by capsaicin, the documentation of this has been extended.[53] Capsaicin acts upon heat receptors on the C-fibers. There are also cold receptors in the skin, the menthol receptors. This is an explanation of why such drugs as menthol, used in dermatology for centuries, actually reduce itch. Our favorite antipruritic ointment contains 1% menthol, 2% camphor, and 3% chloral hydrate.

4.2 Systemic Treatments

4.2.1 Systemic Agents

Systemic agents used in the treatment of prurigo and their mode of action are summarized in table III.

The most popular itch-controlling drugs are hydroxyzine, cyproheptadine, and the non-sedating desloratadine.[2]

Systemic PUVA with use of peroral psoralen is sometimes easier to administer than bath PUVA. PUVA therapy has been reported to be successful in the treatment of prurigo.[7] At our department, we have treated 13 prurigo nodularis patients with PUVA. Eleven of them improved and two worsened, one of whom developed bullous pemphigoid, probably pemphigoid nodularis. Seven of the patients received repeated series of treatments, five of them improving after a second or third series. A fourth series, given to two of the patients, was without effect. It appears that after a while PUVA loses its effect.

Table III. Systemic agents used in the treatment of prurigo and their mode of action

Systemic agents	Mode of action
Antihistamines	Antipruritic
Arotinoid acid	Antiproliferative
Azathioprine	Anti-inflammatory
Chloroquine	Anti-inflammatory
Cyclosporine	Anti-inflammatory, antipruritic
Dapsone	Anti-inflammatory
Metronidazole	Anti-inflammatory, antibiotic
Minocycline	Anti-inflammatory, antibiotic
Naltrexone	Antipruritic, opioid pathways
Psoralen + UVA (PUVA)	Anti-inflammatory, antipruritic
Thalidomide	Anti-inflammatory, antipruritic

According to Shelly, a systemic antibacterial such as erythromycin is the single most effective agent in the treatment of prurigo. It may be best to continue therapy of this sort at a maintenance level for a long period of time.[2]

Arotinoid acid has been described as being effective in treating prurigo nodularis. The effects it has on cell proliferation, differentiation, and inflammation are utilized here. One patient was treated with arotinoid acid 35mg daily for a month.[54] Clinically, the pruritus was reduced markedly and the nodules diminished in size. One month after the retinoid therapy was discontinued, the pruritus had disappeared and the condition was in remission for several months, after which the nodules recurred at the same locations. The patient was treated six times with the treatment series lasting for 1–2 months over a period of 2.5 years.[54] Certain caution in the use of retinoids for the treatment of prurigo nodularis is in order, because the treatment of hyperkeratotic eczema of the palms by etretinate has been reported to induce nodular prurigo-like reactions.[45]

Cyclosporine is reported to have been effective in 18 of 19 cases in relieving the clinical symptoms of actinic prurigo.[22] Treatment of prurigo nodularis by cyclosporine requires relatively high dosages, i.e. 3–4.5 mg/kg/day. Two cases involving treatment for 6 and 9 months, respectively, have been described.[55] In both cases, there was a reduction in the severity of pruritus after 2 weeks of treatment. The improvement of pruritus and the resolution of the nodules were almost complete during the period of treatment, although the condition relapsed in both patients a month after the discontinuation of therapy. One patient treated at our department responded well to therapy involving cyclosporine 4 mg/kg/day but relapsed when the dosage was reduced to 2.5 mg/kg/day.

Azathioprine treatment for prurigo nodularis has been described. Two patients were treated with azathioprine 50mg twice daily for 6 and 12 months, respectively.[56] The itch and the number and size of the nodules were reduced after 2–3 months. The first patient relapsed 2 months and the second 3 years after the treatment was stopped. Azathioprine has also been reported to be effective in relieving the clinical symptoms in a patient with actinic prurigo.[57]

In Mexico, chloroquine is considered the drug of choice for the treatment of actinic prurigo in young people.[58] It is used at a dosage of 3–5 mg/kg/day for approximately 2–3 months, the dose being reduced by 50% as the disease improves.

Dapsone has been regarded as the treatment of choice for prurigo pigmentosa.[59] Patients often relapse, however, after treatment has stopped. In Japan today the routine therapy for prurigo pigmentosa is minocycline, which appears to have anti-inflammatory effects similar to those of dapsone.[60] With minocycline 100–200mg daily, the pruritus, papules and erythema rapidly disappear within a few days or up to a week. The dosage of the drug may then be reduced to 50–100 mg/day for the next 3–6 weeks. Thereafter, medication is stopped and long periods of remissions have been reported, although prurigo pigmentosa tends to recur sooner or later and can continue for many years.

Naltrexone, an orally active opioid receptor antagonist, has been reported to be successful in treating itch. A single oral dose of 50mg, which sometimes needs to be doubled after a few months because of tachyphylaxis, was shown to have strong antipruritic effects in 9 of 17 patients with prurigo nodularis and to contribute to the healing of the skin lesions.[61]

A single case report of prurigo treated with metronidazole has been reported.[62]

Since 1973, there have been 53 reports on the treatment of prurigo with thalidomide, suggesting this to be the most successful form of treatment. Some authors recommend it as a treatment of choice.[27] Thalidomide was introduced in the 1950s as an antiemetic, sedative, and hypnotic, but was withdrawn from the world market in 1961 because of its severe teratogenic adverse effects, particularly that of phocomelia, although it remained available for research purposes. In 1965, Sheskin reported skin lesions of erythema nodosum leprosum to be resolved within days after the administration of thalidomide.[63] A major concern with the use of thalidomide, apart from its teratogenic effects, is its potential for inducing peripheral neuropathy. The daily administration of thalidomide is the major risk factor for the development of this adverse effect.[63] For dosages of <25 mg/day, the risk of neuropathy appears to be negligible, regardless of the duration of therapy.[64] However, in the treatment of severe prurigo, higher dosages (typically 100 mg/day but potentially as high as 150–400 mg/day) may be used to induce a clinical anti-inflammatory response. Thereafter, the doses may be gradually reduced to a daily dosage of 25–100mg or even as little as 50mg every fifth day.[65] Thus, at these typical starting doses of thalidomide, there is a dose-related risk of neuropathy, one that may occur rapidly.[64] In a study of 135 dermatologic patients treated with thalidomide, 25% of them presented clinical and electrophysiological evidence of a thalidomide-induced neuropathy. When all potential cases were taken into account, the rate was found to be 56%.[64] The natural history of thalidomide neurotoxicity after its onset shows the neuropathic symptoms to remain unchanged in 50% of cases, to diminish in 25% and to be resolved in 25%, whereas nerve conduction has been found to only rarely improve.[66] These data underline the importance of selecting patients for such therapy very carefully. Other minor adverse effects of thalidomide therapy are drowsiness and dizziness that can be observed in 33–100% of the patients.[66] There are different ways of reducing the treatment time and total dose of thalidomide by using it as an initial therapy for 2–3 months followed by a narrow-band UVB treatment series.[67]

There is a single report on the treatment of five patients with subacute prurigo with interferon-γ.[68] The patients were treated for 1–8 weeks with doses comparable to those used for treating T-cell lymphoma. Although the itch was reduced during treatment, it recurred upon cessation of therapy and worsened in three cases, making it difficult to recommend this drug for the treatment of prurigo.

4.2.2 Psychopharmacologic Intervention

Psychopharmalogic agents used in the treatment of prurigo and their targets are summarized in table IV.

Many patients with prurigo nodularis experience depression, anxiety, or other psychological disorders requiring medical intervention.[8] In such cases, topical or systemic treatment of the skin should be combined with the use of psychopharmacology or with psychotherapy.

Neurotransmitters of depression such as dopamine and serotonin are associated with various pruritic conditions. In addition, serotonin is associated with compulsive behaviors such as scratching. Treatment with a selective serotonin reuptake inhibitor may be indicated under such conditions.[69] Opioid pathways are associated with anxiety and the itch sensation. Instead of naltrexone, pimozide (1–2mg daily) may be used for its effect on the opioid pathways.[69] A tranquillizer is occasionally of benefit, and chlordiazepoxide or diazepam can be worth a try.[2]

5. Conclusion

Prurigo is a skin reaction associated with a marked proliferation of sensory nerve fibers and with severe itch. Although some acute

Table IV. Psychopharmacologic agents used in the treatment of prurigo and their targets

Psychopharmacologic agents	Targets
Non-selective antidepressants, MAOIs	Serotonin and noradrenalin receptors
Selective antidepressants, SSRIs	Serotonin receptors
Pimozide	Opioid receptors
Tranquillizers	Opioid receptors

MAOIs = monoamine oxidase inhibitors; **SSRIs** = selective serotonin reuptake inhibitors.

forms may be induced by insect stings, most of the subacute and chronic forms appear to be idiopathic. Several metabolic, infectious and malignant disorders may be associated with pruritus and occasionally with prurigo. The principal cutaneous signs of pruritus are excoriations rather then nodules, suggesting prurigo to be a specific cutaneous reaction provoked in susceptible individuals. Atopy may predispose a person to such a reaction pattern. Emotional aspects are important, in both primary and secondary prurigo. Any possible underlying diseases should be treated and any external provoking factors should be avoided. The course of chronic prurigo is prolonged and the long-term results of any treatment tend to be disappointing. There are, however, many different combinations of treatments that can be tried to keep the intractable itch at bay.

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