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Wallengren, Joanna

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An Update on Chronic Prurigo

Joanna Wallengren, MD, PhD
University Hospital, Lund, Sweden

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The term prurigo, originating from the Latin word *pruire* (to itch), was first coined by Ferdinand von Hebra in the mid-19th century to characterize intensely itchy papules and nodules that occur mainly on the arms and legs. At that time, prurigo was one of the most frequent forms of skin disease in Europe, being closely associated with the stings of parasites (such as fleas and mites) that commonly afflicted humans. Today, prurigo strophulus – which is generally provoked by stings of fleas, mosquitos, ticks, or dog parasites – has come to designate an acute form of prurigo.

The genuine chronic form of prurigo is prurigo nodularis (PN) of Hyde, after the man who coined the term in 1909 [1]. This review will deal with this and other forms of chronic prurigo secondary to underlying systemic disease or external provoking factors. In addition, it will focus on the preponderance of prurigo in certain ethnic groups.

The diagnosis of prurigo is a clinical one and histopathology confirms what is seen by the naked eye, including hyperkerathosis, acanthosis, and occasionally epidermal necrosis due to picking.

PN of Hyde

PN can occur at any age, although mainly in those aged 20–60 years, with women being more affected than men. The lesions are hemispherical, often irregular nodes with a horny, rhagadiform, or crateriform depressed surface. They may be as large as several centimeters in diameter and are mainly located on extensor surfaces of the extremities, although the trunk, face, and even the palms can be affected [1]. New nodules can develop over time, and existing nodules can remain pruritic indefinitely, although some regress spontaneously and leave scars. The cardinal symptom is itch.

There has been much confusion in the literature concerning PN. "Prurigo nodularis" is often used erroneously for all forms of chronic prurigo. True PN is an endogenous form of chronic pruigo that is often associated with atopy [2]. The lesions are large nodules (up to 3 cm in diameter) compared with smaller nodules of secondary prurigo.

During the 19th century there was much discussion among dermatologists about whether the PN lesion appears first and produces an urge to scratch or whether its appearance is brought about as a consequence of scratching [1]. According to Hebra, the prurigo papule appears first. In 1899, Johnston wrote in the *Journal of Cutaneous Diseases* that the number of

hypertrophic nerve fibers is increased in prurigo lesions [2]. These nerve fibers show immunoreactivity for sensory neuropeptides, such as calcitonin gene-related peptide, and substance P, which act as transmitters in both the peripheral and in central nervous systems [3]. This finding supports the theory of itch being elicited from the prurigo lesion.

The central neuronal pathways that are involved in itch transmission terminate in the somatosensory cortex and the motor areas that cause scratching [4]. Tissue injury at different signal transmission levels or any alterations in neurotransmitter concentrations (such as in various psychogenic disorders) may contribute to both itch perception and the desire to scratch [4]. Occlusion with elastic bandages for 4 weeks will improve the clinical picture of prurigo, with no enlarged nerve fibers or neurinoma-like structures remaining visible. Such an involution of prurigo nodules would favor the theory that scratching is the triggering factor of prurigo.

As shown in a clinical study of 46 patients with chronic prurigo, 72% of patients felt that psychosocial problems were of relevance to their skin disease and 50% were found to be suffering from depression, anxiety, or another psychological disorder that might require medical intervention [5]. A possible explanation for this association is that mood neurotransmitters such as dopamine, serotonin, or opioid peptides modulate sensor perception.

Secondary prurigo in association with systemic disease

Secondary prurigo is characterized by disseminated, chronic, severely pruritic reddened, flattened, slightly keratotic papules, which are usually 0.4–1.0 cm in diameter. The lesions occur mainly on the extremities and upper back secondary to prolonged and severe scratching in patients with no underlying dermatological condition. Several internal diseases associated with itching may involve the formation of PN-like lesions.

Internal diseases

Itch is a common symptom in patients with chronic renal failure who are receiving maintenance hemodialysis. Perforating folliculitis with superimposed PN in these patients was first described in 1982 [6]. Interestingly, in one patient, who had been completely unresponsive to various treatments, the skin lesions cleared up rapidly 1 week after cessation of hemodialysis and renal allograft transplantation [6]. Acquired reactive perforating collagenosis, a rare disease that is usually associated with diabetes mellitus or renal failure, may involve chronic prurigo [7]. In addition, prurigo-like lesions are associated with various other collagen diseases such as discoid lupus erythematosus, systemic scleroderma, and adult-onset Still's disease [8].

Malabsorption

The association between prurigo and intestinal malabsorption was first observed by Wells in 1962, who described a patient with gluten enteropathy [9]. Since then, seven additional patients with celiac disease and therapy-resistant prurigo have been described in the literature. After several months of treatment involving a gluten-free diet supplemented with vitamins and iron, the intestinal symptoms improved and the typical clinical prurigo nodules disappeared or improved.

Itching and prurigo are also clinical features that are associated with anorexia nervosa [10]. The symptoms disappear with the restoration of weight in these patients.

Malignancy

Prurigo has been associated with T cell lymphoma, leukemia, and visceral neoplasia in the esophagus, ventricles, rectum, liver, and the bile duct [11,12]. Prurigo in lymphoma may precede the symptoms of malignancy. Its occurrence can also be a warning signal for malignant transformation in patients with tumors that were previously diagnosed as benign [12]. Squamous cell carcinoma may occasionally complicate chronic prurigo nodules.

Investigation of an associated disease

Screening is limited to a complete blood cell count as a marker of hematological disease and liver enzymes as markers of hepatic and renal disease. In case of any differing pathologies a specific investigation is recommended. Furthermore, gastrointestinal symptoms are investigated by specific examination.

In reluctant, longstanding cases of chronic prurigo a biopsy is advised to ensure that a squamous cell carcinoma (that may occasionally complicate longstanding chronic prurigo nodules) is not overlooked. Furthermore, biopsy with immunofluorescence may be useful to exclude the diagnosis of pemphigoid nodularis.

Prurigo in association with external factors

Primary forms of prurigo elicited by external factors – including insect stings, parasites, ultraviolet (UV) light, contact allergy, or drugs – are often easy to exclude because of their more acute course.

Infections and parasitoses

In large parts of the world, such as Africa, zoonotic, parasitic, and helminthic infections are widespread and are a major cause of morbidity and mortality [13].

The relationship between prurigo and immunosuppression is illustrated by the fact that prurigo is diagnosed in approximately 6% of patients with HIV infection [14]. In addition, immunosuppressed patients are more susceptible to parasitic and helmetic infections, with skin reactions being persistent, such as in Norwegian scabies [15]. The pruriginous lesions may present with either exaggerated or persistent reactions to insect stings or secondary chronic prurigo [14].

Prurigo has also been found in association with Lyme borreliosis, mycobacteria, *Helicobacter pylori*, and cutaneous toxoplasmosis [16].

Light-induced eruptions

Hutchinson summer prurigo, first described in 1878, occurs in children and young adults. The erythematous papular eruption affects light-exposed areas, most commonly the face [17]. This disease is rarely seen in Europe and appears to be identical to the actinic prurigo found predominantly in native North- and South-American Indians [18].

Actinic prurigo is a chronic photodermatitis characterized by intense pruritus, prurigo-like papules on light-exposed areas, cheilitis, conjunctivitis, scars, and alopecia of the eyebrows [18]. It generally appears at an early age, usually according to a family history and predominantly in females. Furthermore, it is more frequently observed in subjects who live at high altitudes (>2000 m) who have outdoor occupations and a predominance of human leukocyte antigen-DR4.

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 [19]. 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.

Drug reactions

A few orally administered drugs have been reported to provoke prurigo. For example, etanercept has been found to induce acute prurigo [20], carbamazepine to induce subacute prurigo [21], and etretinate to induce nodular prurigo-like reactions [22].

Other forms of prurigo

Prurigo pigmentosa, first reported by Nagashima in 1971, is a distinct clinical entity that is highly prevalent in Japan, where >200 cases have been reported, primarily in women [23]. The disorder is less common in non-Japanese patients, although there have been cases reported in China, Turkey, and Italy. Lesions of this form of prurigo are typically pruritic red papules superseded by reticular hyperpigmented mottling, characteristically on the back, neck, and chest. Histologically, the lesions are lichenoid in character and display a certain pigmentary incontinence; the onset

usually occurs in the spring and summer months. An association between prurigo pigmentosa and both insulin-dependent diabetes and anorexia nervosa has been reported in Japan.

Papular eruption in black men was reported in 1980 by Rosen and Algra [24]. They described seven young black patients with persistant, papular eruptions mainly on the trunk, upper arms, and occasionally the face, buttocks, and thighs. Histologically, a dense perivascular inflammatory infiltrate composed of mononuclear cells and many eosinophils was noted in the upper dermis.

Pemphigoid nodularis

Pemphigoid nodularis is an unusual disorder that has been described in 35 patients since 1981, predominantly in elderly women [25,26]. Initially, patients present with itchy nodules, papules, or plaques. Bullae develop later, sometimes several years after the debut of the noduli. The disorder is considered to be a variant of bullous pemphigoid. Histologically, there is an acanthosis of the epidermis and direct immunofluorescence reveals a linear deposition of immunoglobulin G and C3 in the epidermal basal membrane zone [25].

Management of prurigo

In 1974, Walter B Shelley wrote: "Know this disease for what it is: a terrible, tormenting, relentless itch" [27]. In milder forms of prurigo, topical treatment may suffice but generalized, therapy-resistant cases often require combined sequential treatments that are tailored to the exacerbations.

Topical treatments

High-potency corticosteroids applied topically under an occlusive membrane or intralesionally are generally the first-choice therapy in mild forms of chronic prurigo. In severe, discharging forms of prurigo, potassium permanganate and/or coal tar bath (3%) are used because of their antiseptic, antipruritic, antiparasitic, antifungal, and antibacterial qualities.

Cryotherapy is also recommended for the treatment of prurigo [28]. Freezing will result in blister formation. The purpose is to induce thermal damage to the peripheral sensory nerve fibers at the epidermal/dermal border. After the blisters have healed, topical steroids should be used to prevent relapse.

The question arises as to whether there is an alternative way of affecting peripheral sensory nerve fibers. The intralesional administration of lidocaine has been reported to be effective against itching. Capsaicin, the pungent agent of hot pepper, releases and depletes C-fibers of their neurotransmitters, making them refractory. Since the first report by Cappuggi et al. in 1989 of the treatment of prurigo by capsaicin, the documentation of this has been extended [29]. Capsaicin acts upon heat receptors on the C-fibers, depleting them of their neurotransmitters and making them refractory [29]. There are also cold receptors in the skin – the menthol receptors. This explains why drugs such as menthol, which have been used in dermatology for centuries, actually reduce itch. The mechanism is thought to be related to that of capsaicin. The most commonly used antipruritic ointment contains 1% menthol, 2% camphor, and 3% chloral hydrate.

Topical calcineurin inhibitors have an anti-inflammatory function that has been reported to successfully treat both PN and conjunctival manifestations of actinic prurigo [30]. Calcipotriol ointment has also been reported to be useful in the treatment of PN [30].

Bath PUVA (a psoralen bath followed by UVA-irradiation) is now used instead of the previous combination of tar and UV-light [31]. Bath PUVA can be given daily for 1–4 weeks and then 4 days every other month for 5 months as described in a Finnish study by Väätäinen et al. [31]. Both broadband UVB and narrowband UVB have been found to be of value in the treatment of prurigo [32,33]. Phototherapy can reduce the inflammation and the number of epidermal nerve fibers [33,34].

Systemic treatments

In order to control the itch, sedation as well as non-sedating antihistamines can be

used. Systemic PUVA with use of peroral psoralen is sometimes easier to administer than bath PUVA [31]. In the present author's department, 13 PN patients have been treated with PUVA. Eleven of them improved while two worsened, one of whom developed bullous pemphigoid, most likely pemphigoid nodularis. Seven of the patients received repeated series of treatments, five of whom improved after a second or third series. A fourth series, given to two of the patients, demonstrated no clinical effect. It appears that after some time, PUVA loses its potency.

According to Shelley, an old but very effective treatment of prurigo is erythromycin continued for an extended period of time [27]. Treatment with azathioprine (50 mg twice daily) for PN and actinic prurigo has also been described in the literature [35,36].

In Mexico, chloroquine is considered to be the drug of choice for the treatment of actinic prurigo in young patients [37]. It is generally prescribed at a dosage of 3–5 mg/kg daily for approximately 2–3 months, with the dose being reduced by 50% as the disease improves.

Treatment of prurigo with cyclosporine requires relatively high doses of the drug; 3–4.5 mg/kg daily has been reported to be effective in 18 out of 19 cases studied [38].

Retinoids such as arotinoid acid have also been effective in treating patients with PN, although prurigo-like reactions have been described as a side-effect of etretinate [39,40].

Gabapentin, which is normally prescribed for neuropathic pain, has been successfully used to treat patients with prurigo [41]. Another new promising drug is the neurokinin 1-receptor antagonist, aprepitant [42]. It is a substance P inhibitor and targets the proliferative nerve fibers in the prurigo nodules [4].

Systemic μ-opioid receptor antagonists have been reported to be successful in treating itch [43]. A single oral dose of 50 mg naltrexone, which sometimes needs to be doubled after a few months because of tachyphylaxis, was found to have strong antipruritic effects in patients with PN. However, naltrexone has been demonstrated to have only short-term benefits in treatment of prurigo associated with chronic kidney disease [44].

Dapsone has been regarded as the treatment of choice for prurigo pigmentosa [45]. Currently, in Japan, the routine therapy for prurigo pigmentosa is minocycline with an initial dose of 100–200 mg daily for 1 week followed by 50–100 mg daily for 3–6 weeks [46]. In China, prurigo pigmentosa is treated with doxycycline 200 mg daily for 1–5 weeks [47].

Single cases of prurigo treated with metronidazole or clofazimine (which are also used for the treatment of leprosy, sarcoidosis, and mycobacterial infections) have also been reported [48,49].

Thalidomide has been suggested as an effective treatment of relactant prurigo [50]. A major concern in the use of thalidomide, apart from its teratogenic effects, is its potential for inducing peripheral neuropathy [51]. In treatment of severe prurigo, starting doses of 50–100 mg daily may be used to induce a clinical anti-inflammatory response, but there is a considerable risk of developing a neuropathy. Thalidomide should be regarded as the absolute last line of therapy for chronic prurigo.

Psychopharmacological intervention

Many patients with PN suffer from depression, anxiety, or other psychological disorders that might require medical intervention [2,52]. In these cases, topical or systemic treatment of the skin should be combined with the use of psychopharmacology or psychotherapy.

Neurotransmitters of depression such as dopamine and serotonin are associated with various pruritic conditions, and serotonin is associated with compulsive behaviors such as scratching. Tricyclic antidepressants with anti-histaminic activity such as doxepin or amitriptyline, as well as serotonin reuptake inhibitors such as the selective serotonin reuptake inhibitor anti-depressants, are often helpful in the treatment of chronic prurigo [53]. Opioid pathways are known to be associated with anxiety and with the itch

sensation. Instead of naltrexone, pimozide prescribed at 1–2 mg daily, may be used for its effect on the opioid pathways [54]. A tranquilizer is occasionally beneficial, and chlordiazepoxide or diazepam warrant further investigation [27].

Conclusion

PN of Hyde is an idiopathic disorder that atopic individuals may be predisposed to develop. It results in severe itching and may have an impact on the psychological status of the patient. In patients with chronic, secondary prurigo, underlying diseases such as renal failure, malabsorption, or malignancy should be treated, and external provoking factors, such as contact allergens, should be avoided. As prurigo is a chronic and relapsing disease process, different treatments may be prescribed sequentially or in combination.

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Address for correspondence: Joanna Wallengren, Department of Dermatology, University Hospital, SE-221 85 Lund, Sweden. Email: joanna.wallengren@med.lu.se

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