Prurigo

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Key Points

- Establishment of prurigo nomenclature and its differential diagnoses.
- Presentation of the probable etiologies of chronic prurigo by showing the importance of the patient's clinical assessment.
- Update of the therapeutic options for prurigo management.

Concepts

The word *prurigo* has been used to designate a heterogeneous group of dermatoses that have papular eruption and pruritus as common aspects. Prurigo can be seen as a reactive clinical pattern, and 20% of the cases are still regarded as idiopathic. This term has been used whether the cause is known or unknown.

The clinical aspect of the lesions may vary and includes papules and nodules with excoriation, erosion, lichenification, crust-covered papules, and seropapules. Scars and residual hyperchromia can be found.

Clinical Presentation

The different types of prurigo had been described and designated by eponyms, with a confusing terminology. Greither [1] and Jorizzo et al. [2] classified the previously reported groups into acute, subacute, and chronic, as shown in Table 68.1. In addition to this division, we may include other varieties of prurigo in the classification, such as the prurigo of pregnancy, prurigo pigmentosa, and actinic prurigo [3, 4].

Adapted from Wallengren [3] and González et al. [4]

Table 68.1 Classification of prurigo and synonyms

Acute prurigo	Strophulus, prurigo mitis, papular urticaria, prurigo Hebra (prurigo "ferox"), prurigo simplex acuta Brocq, prurigo temporanea Tommasoli
Subacute prurigo	Prurigo subacuta Kogoj, prurigo vulgaris Darier, prurigo multiforme Lutz, lichen urticatus Vidal, prurigo simplex subacuta, urticaria papulosa chronica perstans, neurotic excoriation
Chronic prurigo	Prurigo nodularis Hyde, keratosis verrucosa, lichen obtusus corneus, urticaria perstans verrucosa, eczema verrucocallosum
Other	Besnier's prurigo
	Prurigo of pregnancy
	Dermographic prurigo
	Prurigo pigmentosa
	Actinic prurigo
	Hutchinson prurigo

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R. Rangel Bonamigo (ed.), *Dermatology in Public Health Environments*,
https://doi.org/10.1007/978-3-031-13505-7_68

Acute Prurigo

Most often found in childhood, 86% of cases occur during the first 3 years of life. It is common among the economically lower classes, especially during summer [4].

Acute Prurigo: Simplex

Also known as strophulus, prurigo mitis, lichen urticatus, and papular urticaria, acute prurigo (simplex) is characterized by papules, vesicles, and/or urticaria during the early years of life, lasting for about a week. Hypersensitivity to arthropod bites, such as mosquitoes, ants, and fleas, is the main cause. Association with food allergies and psychological and infectious factors have also been described [5, 6]. Patients with acute prurigo show greater sensitivity to insect antigens during skin tests. Patient improvement in adulthood may correspond to desensitization resulting from repetitive bites [4]. On superficial blood vessels, granular deposits of C1q, C3, and immunoglobulin M were found suggesting that dissemination is mediated by the immune complex [7].

It has sudden onset, with a small pruriginous vesicle/papule, which breaks up if scratched, being covered by a crust. It is believed that the early lesions primarily result from insect bites and that the subsequent symmetric and disseminated lesions are probably due to hematogenic dissemination of the bite-inoculated antigen [4].

Erosions, lichenification, and secondary infection may also be noticed. Lesions may show themselves as erythematous-edematous plaques, vesicles, and blisters, with blisters more often seen on the limbs. The papules persist over a week, with the development of new, nonconfluent lesions; lesions of varying stages may coexist, sometimes leaving scars, hyperchromia, or residual hypochromia as seen in Fig. 68.1. The trunk and the limbs are the main locations; lesions are seldom seen on the face. The genital, perineal, and axillary regions are usually spared [4]. It is more frequently seen in children of 2–7 years of age, also being associated with the presence of atopy [3, 8].

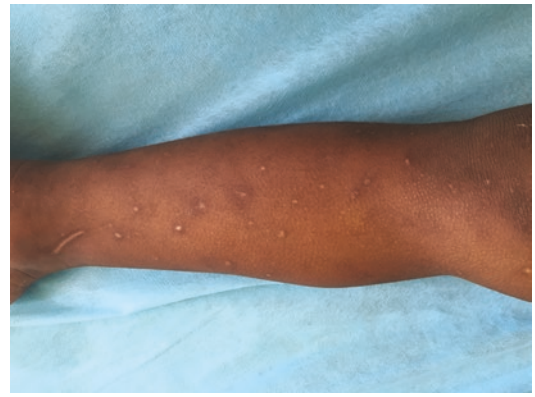

Fig. 68.1 Residual hypochromia surrounded by hyperpigmentation on a lower limb of a patient with strophulus

The histopathologic examination is unspecific and shows the presence of perivascular inflammatory infiltrate, with lymphocytes and eosinophils, acanthosis, spongiosis with intraepidermal vesicle, and parakeratosis [3].

The diagnosis is clinical, based on lesion and pruritus history, location, and aspect. Epicutaneous tests can be helpful. The differential diagnoses may include scabies, body pediculosis, herpetiform dermatitis, varicella, and urticaria [3].

Acute Prurigo Simplex: Adulthood

Prurigo simplex temporanea Tommasoli has a presentation similar to that of strophulus, except that it occurs in young adults. The clinical presentation is characterized by papules on the extensor surfaces of the upper limbs and the anterolateral surfaces of the lower limbs. It has an insect bite hypersensitivity, but may be related to hormonal factors, and infectious and parasite foci. In persistent lesions, systemic causes, such as diabetes, hepatopathies, nephropathies, and neoplasms, must be assessed. The diagnosis is clinical, and the differential diagnosis includes herpetiform dermatitis and scabies [1, 2].

Prurigo Hebra

Known as prurigo "ferox," it displays prurigi-nous, eczematous, impetiginous, and lichenified papules, with lymphadenopathy mainly in atopic children. It occurs mainly in geographic areas lacking sanitation and good nutritional conditions [3]. The histopathology is the same as described for prurigo simplex.

Subacute Prurigo

Prurigo subacuta Kogoj, prurigo vulgaris Darier, prurigo multiforme Lutz, lichen urticatus Vidal, urticaria papulosa chronica perstans, and neurotic excoriations are multiple entities that share the same clinical and histologic presentation. It mainly affects middle-aged women, being related to emotional and psychogenic factors. Atopy, dermographism, and seborrheic dermatitis are also associated [9].

Subacute prurigo shows papules, excoriations, and symmetric urticariform plaques on the trunk, extensor surfaces of the limbs, face, and scalp, but not on the palms and the foot plantar region, as seen in Fig. 68.2. The pruritus develops in successive flares and may be precipitated by exercise, heat, or emotional status [4].

The differential diagnosis includes herpetiform dermatitis, transient and persistent acantholytic dermatitis, and scabies.

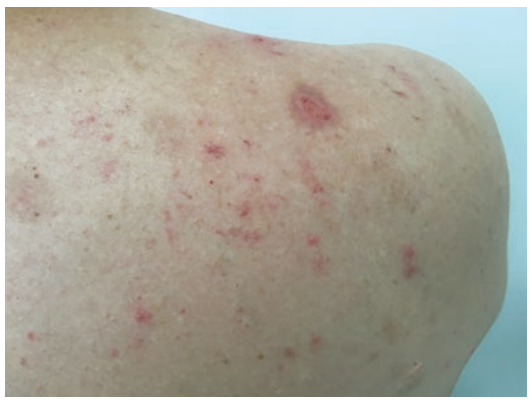

Fig. 68.2 Subacute prurigo: papules, excoriation on the back of a male patient

The histologic examination shows acanthosis, hyperkeratosis, proliferation of nervous fibers, focal spongiosis, and perivascular and perifollicular inflammatory infiltrate [3].

Chronic Prurigo

The term Prurigo nodularis is the most characteristic representative of chronic prurigo in the terminology, described in 1909 by Hyde as nodules on the extensor surface of a woman's arms and legs, relatively rare and difficult to treat. Similar cases were reported by Hardaway in 1880 [10] and Brocq in 1900 [11]. In 1934, Pautrier showed the presence of dermal neural hyperplasia, known as Pautrier's neuroma [12].

Lichen simplex chronicus and lichen amyloidosis may correspond to the same disease spectrum given their similar clinical presentation and histopathologic findings, according to Weyers in 1995 [13]. Many authors regard prurigo nodularis as an atypical form of circumscribed dermatitis [14]; nevertheless, the indirect immunofluorescence of nerve bundles in prurigo nodularis showed increased immunoreactivity for substance P and the calcitonin gene-related peptide (CGRP) [15]. In 2017, European experts of the EADV Task Force Pruritus (TFP) aimed to achieve a consensus on the definition, classification, and terminology of chronic prurigo. Chronic prurigo (CPG) is a distinct disease defined by the presence of chronic pruritus and multiple localized or generalized pruriginous lesions [16].

CPG shows symmetric, hardened, hyperkeratosis, very pruriginous nodules and papules mainly on the extensor surfaces of the limbs, more often found in middle-aged women (Fig. 68.3). The lesions may show variation in quantity and may affect the sacral region in 50% of patients and the abdominal region in 44%; palms, soles, and face are rarely affected [17]. Lesion onset is insidious, with chronic evolution. The pruritus is intense and intermittent, relieved by scratching to the point of skin mutilation and bleeding. In chronic lesions verrucous papules, lichenoid plaques, and excoriation may

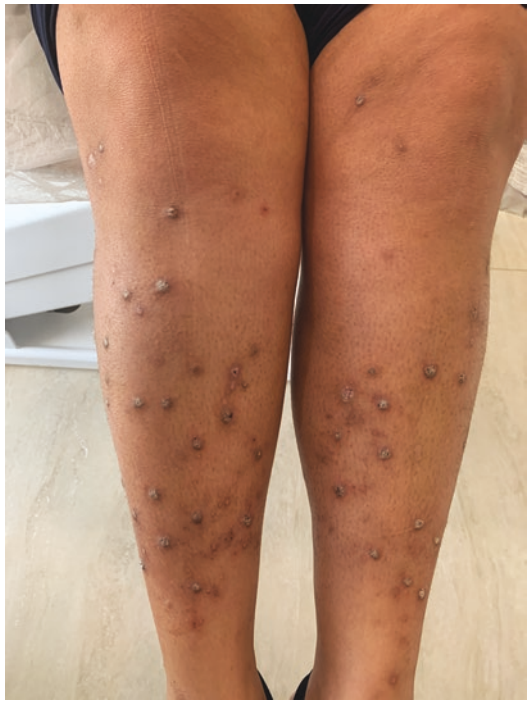

Fig. 68.3 Prurigo nodularis: pruriginous nodules and excoriations on the lower limbs of a female patient

be noticed, as well as postinflammatory hyperchromia and scars. The papular distribution mainly follows the cleavage lines but not Blaschko lines [18].

The cause is unknown, CPG occurs due to a neuronal sensitization to itch and the development of an itch-scratch cycle. CPG can be of dermatological, systemic, neurologic, psychiatric/psychosomatic, multifactorial, or undetermined origin [16].

Sixty five to eighty percent of the patients are atopic [17]. Metabolic changes (such as anemia, hepatopathies, uremia, and myxedema), trauma, and neuronal etiology were suggested as related to prurigo nodularis [2, 17]. Focal causes of pruritus, such as insect bites, venous stasis, folliculitis, and nummular eczema are also related to this condition. Gluten-driven enteropathy with prurigo nodularis was already described by some authors, with improvement of both presentations when food is restricted [19–23].

However, it can be deduced from the comprehensive clinical experience of the involved experts that independently of the etiology of the underlying pruritus, predisposed patients with chronic pruritus and prolonged scratching develop specific and easily to diagnose pruriginous lesions which have a similar appearance across patients. Once established, CPG necessitates an own therapeutic approach and does not resolve if the underlying etiology is cured or treated [16].

Histopathology shows acanthosis, hyperkeratosis with proliferation of small vessels, and unspecific inflammatory infiltrate on the dermis (histiocytes, lymphocytes, mastocytes, and eosinophils). Fibroblast proliferation occurs, possible findings including a subepidermal fibrin deposit [2, 24, 25], papillomatosis, and irregular epidermal proliferation. The histologic findings may be similar to those of chronic eczema or persistent reaction to insect bite [17, 24]. Some authors believe that the detected neural and vascular hyperplasia may result from mechanical trauma [26].

The diagnosis is clinical, according to the lesion history, location, and clinical aspect.

The EADV experts suggest that three major criteria must be present: 6 or more weeks of chronic pruritus, history and/or signs of repeated scratching (e.g., excoriations, scars), and localized or generalized presence of multiple pruriginous lesions.

Histologic examination may complement the diagnosis [16].

The differential diagnosis includes lichen simplex chronicus, hypertrophic lichen planus, pemphigoid nodularis, pruriginous epidermolysis bullosa, multiple keratoacanthoma, epidermal cysts, disseminated cutaneous cytomegalovirus in HIV-positive patients, and botryomycosis [27].

Endogenous and Exogenous Factors Related to Prurigo

Table 68.2 shows the main factors related to prurigo onset [3].

Table 68.2 Endogenous and exogenous factors related to prurigo

Endogenous	Exogenous
Atopy	Infections and parasitoses
Internal diseases	Contact allergy and drug reactions
Malabsorption	Light eruption
Malignancy	–
Emotional factors	–
Pregnancy	–
Ethnic predisposition	–

Adapted from Wallengren [3]

Atopy

The term Besnier's prurigo is used to designate the chronic papular and lichenified form of atopic dermatitis as seen in Fig. 68.4. Many cases of Hebra prurigo have possibly involved patients living under poor social conditions. This prurigi-nous form of atopic dermatitis is less frequent and found in 9% of young adults who have had the disease during childhood [28].

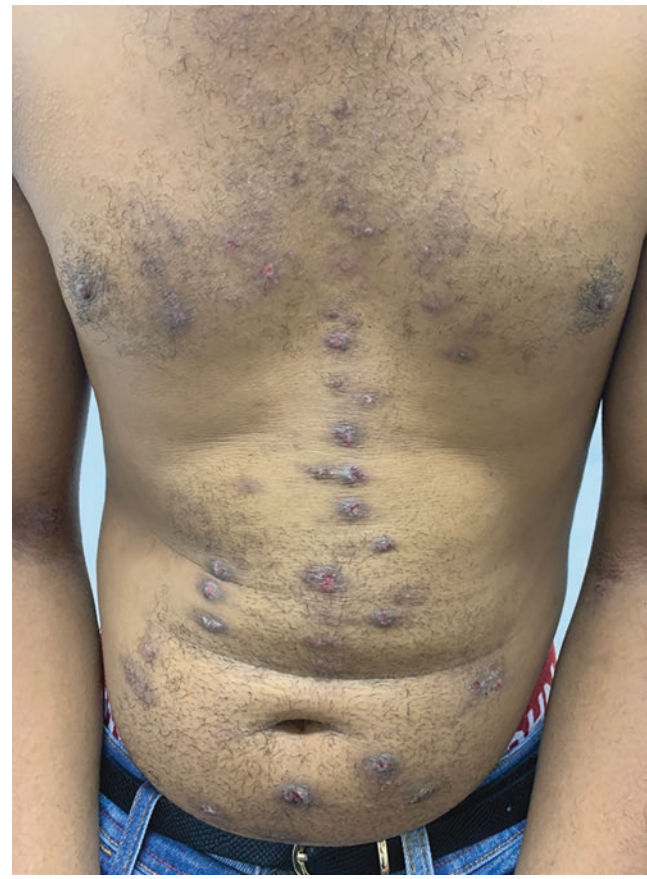

Fig. 68.4 Lichenified papules on the anterior trunk of an atopic dermatitis patient

Internal Diseases

Many internal diseases associated with pruritus may yield skin lesions that simulate prurigo nodularis resulting from scratching. Pruritus is a very common symptom in patients suffering from chronic renal failure who undergo hemodialysis. Perforating folliculitis with overlaying nodular prurigo has been described [29].

Diabetes mellitus, disseminated lupus erythematosus, systemic scleroderma, and deficiency of α1-antitrypsin may be associated with prurigo nodularis or prurigo-like lesions [30, 31].

Malabsorption

The association of prurigo nodularis with malabsorption was described in 1962 in a patient with celiac disease. Some other cases have been described since then in association with therapy-resistant enteropathies and prurigo nodularis. After some months of gluten-free diet, complemented with vitamins and iron, the intestinal symptoms improved and the skin lesions reduced or disappeared [32]. Anorexia nervosa and prurigo were associated because pruritus is one of the characteristics resulting from low weight. Once the weight is normalized, the prurigo lesions improve [33].

Malignancy

Pruritus and excoriations may be a nonspecific marker of internal malignant disease. Prurigo has been associated with T cell lymphoma and esophageal visceral, ventricular, rectal, hepatic, and biliary duct neoplasia. In a patient with lymphoma, the prurigo may appear before the symptoms of malignancy [34]. Prurigo may also be a warning sign for malignant change in patients with early tumors diagnosed as benign. In malignant cases, prurigo nodules possibly result from scratching [35].

Emotional Factors

In clinical studies of patients with nodular prurigo, 50% of the subjects showed depression, anxiety, or some other psychological disease, and 72% of the patients reported that psychological problems were relevant to the skin disease [17].

Prurigo of Pregnancy

Prurigo of pregnancy, prurigo gestationis Besnier, is a pregnancy-specific, benign, self-limited dermatosis that affects 1 out of 300 pregnant women [36–44]. Earlier classified as pregnancy dermatosis of exclusion, it has now been reclassified as a subtype of atopic gestational eruption [44]. There are no risks for either the baby or the mother. Box 68.1 reports a related case.

Box 68.1: Case Report: Prurigo of Pregnancy
In 2010, Fan Wen-Ge and Qu Yun reported a case of a pregnant woman with a clinical presentation compatible with prurigo of pregnancy which, in 1995, resulted in fetal death. At that time, the woman and baby underwent investigation whereby both showed no laboratory or chromosomal alterations, anomalies, or illnesses. In 2005, the same woman presented with gestational prurigo, underwent follow-up, and was treated with topical and intravenous corticosteroids to aid the baby's lung maturation; the gestational process was interrupted in the 34th week, with both being healthy [37].

It is considered the second most common gestational-specific dermatosis, although its etiology is unknown [42]. It is one of the presentations of the atopic rash of pregnancy that is considered the most common pruritic disorder in this population [45].

The trigger could involve some immunity-related change resulting from the pregnant condition: a decrease in cellular immunity and T-helper 1 (Th1) cytokine production compared with an increase in Th2 cytokine production through humoral immunity [37]. There seems to be a correlation with atopy, and some authors believe that it is the severe gestational pruritus in atopic patients [41–43]. In 20% of cases, it is an exacerbation of a pre-existing atopic dermatitis, but in 80% of patients it is the first time that it appears or appears after a long time of remission of an eczema [45]. It can occur in all trimesters of pregnancy, but most commonly it starts between 25 and 30 weeks [46]. Small 0.5- to 1-cm papules, extremely pruriginous, erythematous, and even hyperchromic, which evolve into nodules on the extensor surface of the limbs may be noticed. Eventually they may spread; they usually appear as excoriated lesions more often occurring between the 25th and the 30th gestational weeks, although they are not limited to the period between those 2 weeks. The condition subsides some weeks postpartum or may last for up to 3 months [43]. No vesicles or bullae are noticed [42]. Recurrence is variable in subsequent pregnancies [46]. It does not increase the maternal-fetal risk [45].

Considered an exclusion diagnosis, it is based on clinical and normal laboratory tests, except for a possible increased IgE [37, 40–42]. The anatomopathologic examination is unspecific; it may present a perivascular lymphocytic infiltrate on the upper dermis, possibly affecting the epidermis. Direct and indirect immunofluorescence is negative.

Differential diagnoses are other gestational dermatoses, such as cholestasis and pruritic urticarial papules and plaques of pregnancy (PUPP), besides atopic dermatitis, arthropod bites, scabies, and drug reactions.

Ethnic Predisposition

Prurigo pigmentosa, or Nagashima's disease, is a rare condition in the Western world, more common in young Japanese women aged 23–27 years [47], although male cases and other ethnic background cases have been reported [48]. The etiopathogenesis remains uncertain. There are hypotheses of an association with ketosis, type 1 diabetes mellitus, anorexia nervosa, *Helicobacter pylori* infection, and atopy. Several cases have been reported associated with intermittent fasting, bariatric surgery, and extremely restricted diets. Such relation is corroborated by the fact that the lesion improves with simple dietary changes, since it corrects ketosis [49–51]. It is not clear whether the highest incidence on Japanese women results from environmental factors or genetic predisposition [48]. It is severely manifested as intense pruriginous erythematous papules and papules/vesicles [48]. The lesions usually concentrate on the back, chest, and cervical region [52]. With evolution, the lesions heal and scars are seen as hyperchromic macules with a reticular pattern [48]. The clinical course oscillates, with both exacerbations and remissions [53].

The diagnosis is based on clinical and histopathologic manifestations. There is variation in the anatomopathology according to the stage of lesion evolution. The most recent lesions show a superficial perivascular neutrophilic infiltrate while the well-established lesions show spongiosis and many necrotic keratinocytes. Eventually, the late lesions display a predominantly lymphocytic infiltrate, with melanophages in the papillary dermis [48].

The differential diagnoses in the severe phase are herpetiform dermatitis, acute erythematous lupus, and linear IgA dermatosis in regard to the remission phase, ashy dermatosis, macular amyloidosis, and confluent and reticulated papillomatosis (Gougerot–Carteaud syndrome) must be excluded [48].

Infections and Parasitic Infections

The organ most affected by HIV is the skin [54]. An average 90% of HIV-positive patients will present some form of dermatosis during their lives [54–56]. Dry skin, atopic dermatitis, nodular prurigo, pruritic papular rash, and idiopathic pruritus have a prevalence of 37.5% of this popu-

lation [57]. The HIV pruritic papular eruptions result in high morbidity and are difficult to treat [58]. It is a noninfectious chronic dermatosis, more often seen in highly immunologically affected patients [54, 59–61]. Evidence suggests that the degree of xerosis and pruritus reflect the general degree of immunosuppression, with lower CD4 T lymphocyte counts [57].

It is a chronic, recurrent condition with papular lesions, papulopustules, and/or nodules mainly affecting the distal region. There is intense pruritus and high recurrence. Eventually it disseminates [54]. Multiple lesions (more than 100) represent the usual pattern, although one or two lesions have been reported [56]. A linear disposition is common, usually evolving with dyschromias [56]. Both men and women are affected [56]. The etiopathogenesis is not well known, and in HIV patients, the treatment is challenging [60, 61]. Some authors believe that there may be some hypersensitivity to arthropod bites [61, 62]. By virtue of the HIV, there would be greater stimulus of B lymphocytes, inversion of the CD4/CD8 relationship, decrease in number and function of Langerhans cells, alteration of macrophage function, d IgE increase, possibly leading to a hypersensitivity reaction, more common in higher phototypes and CD4 cell count <50 [54, 56, 63]. Some research studies show lower levels of interleukin-2 and interferon-γ [61]. The skin of these patients has a lower content of epidermal lipids and is partially responsible for a defective skin barrier [57]. It is less often seen in Europe and North America [61, 62]. Firstly, we must exclude causes leading to pruritus and, therefore, prurigo lesions. Also, infectious and neoplastic diseases such as lymphoma and hepatic, renal, and neurologic diseases must be excluded. Eosinophilia and increased serum IgE may be found in laboratory tests [61, 64]. HIV testing is recommended for patients with intractable itch or newly diagnosed nodular prurigo [57]. The anatomopathologic examination is usually unspecific; there is perivascular inflammatory infiltrate mainly comprising lymphocytes, with or without eosinophils. There must be hyperkeratosis, acanthosis, and papillomatosis with dermal fibrosis [56].

Differential diagnosis includes syphilis, drug eruption, scabies, folliculitis, demodicidosis, and tuberculids [61].

Strophulus prurigo may be caused by flea, mosquito, and tick bites. Lyme disease, mycobacteriosis, skin toxoplasmosis, and *H. pylori* infection have also showed an association with prurigo [3].

Perspectives:

With a multifactorial etiology that is not so well known, better control of this dermatosis was achieved in 1997 after the introduction of antiretroviral therapy. The emergence of a new drug, raltegravir, which is an integrase inhibitor, is a hope in the treatment of this condition [65].

Contact Allergy and Drug Reactions

Contact allergy is usually related to intense itch and can occur together with prurigo secondary to scratching. Patients with already established prurigo may develop a contact allergy to the drugs used to manage the condition. In a study at the Mayo Clinic, 29 out of 199 patients with prurigo who underwent contact tests were positive to neomycin, fragrance, and nickel. Many patients reported improvement after removal of the allergen [66].

Some drugs, such as etanercept, may induce acute prurigo; carbamazepine may induce subacute prurigo, and etretinate may induce nodular prurigo-like reactions [3].

Light Eruption

Actinic prurigo, also known as Hutchinson summer prurigo, is a photoinduced dermatosis, with the collaboration of hereditary and geographic components. It is more common among Native Americans and is seldom seen in Europe, Asia, and Oceania [67]. A possible relationship with the presence of HLA-DR4 has been investigated, and it is more frequent in higher-altitude inhabitants (1000 m above sea level) [68]. Women are more affected than men [68], and actinic prurigo usually starts during childhood [69]. It may be

induced by solar exposition, with higher incidence in the summer and spring, with possible remission in fall and winter [70]. Some authors have suggested that actinic prurigo may be a specter of polymorphous light eruption [71, 72].

Exposure to solar radiation has been suggested as the main trigger, which would lead to yield the production of self-antigens and a consequent immune reaction in genetically predisposed individuals [67]. Recent studies suggest that this immune reaction is a type IV hypersensitivity reaction driven by both Th1 and Th2 inflammatory pathways, the latter of which leads to secretion of IL-4, IL-5, IL-13, and production of B cells, IgE, and IgG4 [73–75].

It manifests as flat papules, which may coalesce to create plaques and nodules in photoexposed areas, mainly the face, cervical region, upper torso, extensor aspect of the forearms, and dorsum of the hands. On the face, the lesions tend to concentrate on areas of more direct incidence of light, such as the forehead, nasal dorsum, and malar regions. The lesions are heavily pruriginous, leading to the development of excoriations and possible scars. They are usually associated with cheilitis (mainly on the lower lip), conjunctivitis, and eyebrow alopecia [67, 70, 76].

The diagnosis is based on the clinical and histopathologic manifestations. Regarding the anatomopathology, the recent lesions usually show spongiosis while the older lesions are similar to prurigo nodularis [77]. The finding of HLA-DR4 favors the diagnosis. A photoprovocation test may be carried out [70]. Differential diagnoses include polymorphous light eruption, prurigo nodularis, cutaneous lupus erythematosus, and porphyria [69, 70].

Diagnosis

The diagnosis of prurigo is usually clinical. Additional investigation is important to define the related factors [78]. Box 68.2 synthesizes the basic assessment for prurigo when its cause cannot be established by early clinical assessment.

Box 68.2: Additional Examinations in Prurigo Investigation

- Complete blood count.
- Urea, creatinine, and electrolytes.
- Liver function.
- Blood sugar.
- Hepatitis serology.
- HIV serology.
- Total serum IgE.
- Protein electrophoresis.
- Thyroid/parathyroid function.
- Chest X-ray or computed tomography/magnetic resonance imaging.
- Skin biopsy.
- Patch test.

Therapeutic Approach

When assessing a patient with a prurigo nodularis, it is important to search for the underlying cause. Acute prurigo also has inflammation and heavy pruritus that can be treated with topical corticosteroids and antihistamines. Subacute prurigo is a relapsing disease which demands treatment during its exacerbation periods. The courses of nodular and secondary prurigo are long. The chronic and persistent forms are treatment resistant, which force patients to go through many kinds of therapeutic experiences. Encouraging the patient to avoid scratching the lesions is important, since lesion manipulation worsens the symptoms [79].

Topical Treatments

The use of moisturizer must be encouraged because xerosis may exacerbate the pruritus [78].

Topical corticosteroids, preferably with occlusive membrane on the lesions, are very useful in acute and subacute injuries. In the case of more chronic lesions, the application of an intralesional corticosteroid is more effective. Coal tar with antipruritic and antibacterial properties is used

during the severe phases in patients showing many excoriations. Calcipotriol is also effective for prurigo nodularis [80].

Cryotherapy has been recommended, since it induces thermal damage to peripheral sensory nerves. The application time varies from 10 to 30 s for 2 to 4 cycles. If postprocedural improvement of the lesion occurs, a topical corticosteroid must be applied. Intralesional lidocaine and capsaicin cream are also effective. Menthol cream at 1% and camphor at 2% are good antipruritic applications [81–83].

Calcineurin inhibitors, such as pimecrolimus and tacrolimus, have been successful in decreasing pruritus in the investigated patients [84].

Systemic Treatments

Hydroxyzine (or similar sedative antihistamine of first generation) is very important for pruritus control, at 10–50 mg/day (or 0.5–1 mg/kg/day), every 6 or 12 h [3].

Systemic psoralen combined with ultraviolet A in research studies was effective, although it may lose efficacy after some time [85]. Narrowband ultraviolet B has also been proposed as an effective option [3, 86].

Azathioprine 50 mg, twice a day, over 6–12 months, decreased pruritus and nodules in patients with prurigo nodularis. Relapses can occur between 2 months and 3 years after treatment interruption. Its efficacy in decreasing actinic prurigo symptoms has also been shown [87, 88].

Cyclosporine must be used at high doses (3–4.5 mg/kg/day) over 6–9 months, resulting in pruritus decrease after 2 weeks. Pruritus and nodules may decrease and disappear during the period of treatment, although the condition relapses only 1 month after interruption [89].

Dapsone use to be the drug of choice to treat prurigo pigmentosa. However, minocycline and doxycycline have been preferred and used efficiently in the acute phase and also in preventions of relapses, with a better side effect profile. Relapse tends to occurs after treatment interruption. Hyperchromia usually persists, being difficult to treat [47, 48, 52, 90].

Oral corticosteroids can be used in recalcitrant cases of prurigo in pregnancy, giving preference to prednisone and not exceeding 20 mg/day, replacing vitamin D and calcium [45]. If necessary, prolonged use keep around 7.5 mg/day [46]. Guide and reassure the pregnant woman that there is no fetal risk.

Naltrexone was successfully used to treat pruritus at a daily dose of 50 mg, with the possibility of doubling the dose in a few weeks. Naltrexone has a considerable antipruritic effect, thus playing a role in improving prurigo nodularis lesions [91].

Gabapentin and pregabalin inhibited neurotransmitters that provoke pruritus in prurigo nodularis patients [92, 93]. In a study with pregabalin, 23 out of 30 patients (77%) showed complete remission of pruritus and prurigo lesions at a dose of 25 mg, three times a day, over 3 months. The maintenance dose is 50 mg/day for up to 2 years [93].

In 1973, the successful treatment of prurigo nodularis with thalidomide was described, since when it has been implemented [94]. Pruritus decreased in a few weeks while lesion involution took a few months. When there was drug interruption, the pruritus took 2 months to reoccur and became severe in 4 months. The authors suggested a long-term treatment at a dose of 200 mg/day, possibly higher [95]. In patients with HIV prurigo, thalidomide has been signaled to have a promising role considering that it is not an immunosuppressive drug. However, one-third of the investigated patients developed peripheral neuropathy [58]. Thalidomide should not be used in women within fertility range if they do not use a satisfactory contraceptive method because of the drug's teratogenicity.

Lenalidomide is an analogue of thalidomide that is more powerful and associated with less neurotoxicity. Kanavy et al. (2012) and Liu et al. (2013) described the first two cases of prurigo nodularis that were treated with lenalidomide because the patients developed neuropathy due to thalidomide. Doses were 5 mg/day and 10 mg/day, respectively with complete response [96].

Dupilumab, a monoclonal antibody to the IL-4 receptor that blocks the biologic effect of cytokines IL-4 and IL-13, may be useful and effective therapy for generalized prurigo nodu-

laris [97–102]. The mechanism is unknown. It is possible that dupilumab was effective because prurigo nodularis was the clinical manifestation of underlying atopy. Other possibility is that dupilumab interrupts aberrant neuroimmune interactions in the skin, driving the chronic itch-scratch cycle in prurigo nodularis [103].

Glossary

Erosion Erosion is caused by loss of the surface of a skin lesion; it is a shallow moist or crusted lesion.

Excoriation A scratch mark. It may be linear or a picked scratch (prurigo). Excoriations may occur in the absence of a primary dermatosis.

Lichenification Lichenification is caused by chronic rubbing, which results in palpably thickened skin with increased skin markings and lichenoid scale. It occurs in chronic atopic eczema and lichen simplex.

Nodule An enlargement of a papule in three dimensions (height, width, length). It is a solid lesion.

Papules Small palpable lesions. The usual definition is that they are less than 0.5 cm diameter, although some authors allow up to 1.5 cm. They are raised above the skin surface and may be solitary or multiple.

Plaques A palpable flat lesion greater than 0.5 cm in diameter. Most plaques are elevated, but a plaque can also be a thickened area without being visibly raised above the skin surface. They may have well-defined or ill-defined borders.

Vesicles Small fluid-filled blisters less than 0.5 cm in diameter. They may be single or multiple.

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