Dermatologic Therapy, Vol. 21, 2008, 42–46
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DERMATOLOGIC THERAPY
ISSN 1396-0296

Prurigo nodularis and lichen simplex chronicus

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ABSTRACT: Emotional tensions in predisposed subjects may play a key role in inducing a pruritic sensation, leading to a scratching that, becoming a self-perpetuating pathomechanism, may represent the main feature of two distinct cutaneous clinical entities: prurigo nodularis and lichen simplex chronicus. Psychogenic factors play a relevant role in both conditions, and they are often associated with depression and dissociative experiences. Hence, the importance of the evaluation of these patients from the point of view of psychodermatology, which may analyze the relationship between skin disease and psychological factors. Patients with real or perceived imperfections in particular areas of the body (face, scalp, hands, and genital area) are more prone to psychologic distress, whereas cutaneous diseases may lead to experience a heightened level of distress. As psychosomatic factors have been estimated to be present in at least one-third of dermatologic patients, effective management of skin conditions involves consideration of the associated emotional factors.

KEYWORDS: lichen simplex chronicus, management, prurigo nodularis, psychodermatology

Introduction

According to a psychosomatic perspective usually agreed upon in the scientific community, emotional tensions in predisposed subjects may play a key role in inducing itch, thus provoking scratch. This phenomenon can become a self-perpetuating pathomechanism bringing to distinct cutaneous clinical entities that include prurigo nodularis (PN) and lichen simplex chronicus (LSC).

Prurigo nodularis is a dermatologic condition characterized by the presence of papules and nodules with primary intense pruritus. PN (chronic circumscribed nodular lichenification, Picker's nodules) can occur at all ages and equally in both sexes. It presents with hard nodule(s) 1–5 cm in diameter, with a warty, excoriated, pigmented dark red surface with central crusts, usually surrounded by an irregular hyperpigmented ring (FIG. 1). The extensor area of the limbs, face, and trunk are usually affected by the lesions, which may leave scars when spontaneously regress (FIG. 2). Itch is intense, and severe crises can be triggered by emotional stress.

Lichen simplex chronicus (LSC) is a skin disorder characterized by lichenification of the skin as a result of primary excessive scratching (FIG. 3). LSC (circumscribed neurodermatitis) is characterized by a central lichenificated plaque thickened and often hyperpigmented, usually surrounded by lichenoid papules and, along the borders with surrounding normal skin, by an indefinite zone of slight thickening. The most common sites are the neck (sides), ankles, scalp, vulva, pubis, scrotum, and extensor forearms. The peak of incidence is between 35 and 50 years of age, and women are more affected than men (F:M = 2:1).

Lichen simplex chronicus is in the nomenclature differentiated by other forms of secondary lichenification, which usually complicate persistent itching skin lesions of different types, but the borderline is sometimes tenuous. Variants (i.e., the giant lichenification of Pautrier, of the genitocrural region, and the so-called pebbly lichenification of atopic subjects) have been described. Itch is the predominant symptom. It is characterized by paroxystical attacks, which are intensely scratched with great satisfaction, followed by a refractory

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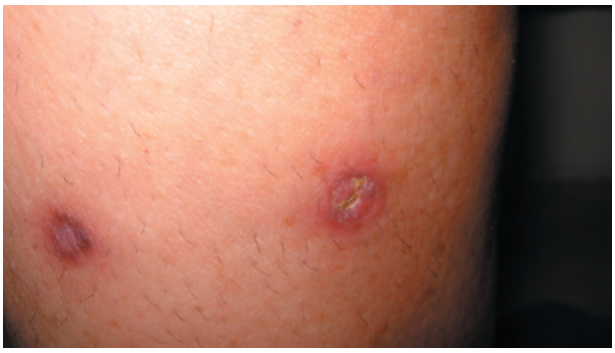

FIG. 1. Prurigo nodularis. Two hyperpigmented nodules with clear-cut margins; the one on the right with a central crust.

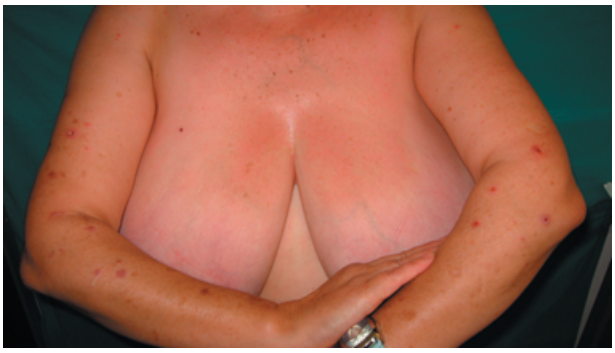

FIG. 2. Prurigo nodularis. Many nodules of different color and size, mainly localized on extensor surface of forearms and residual scarring lesions.

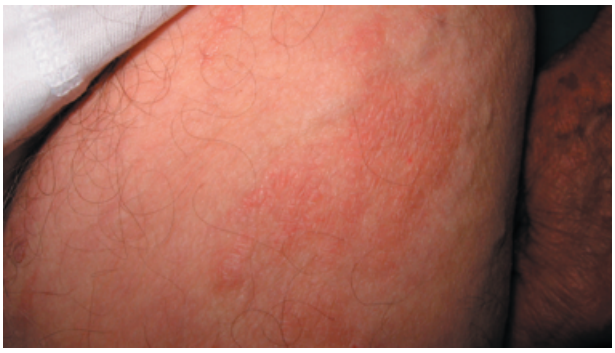

FIG. 3. Lichen simplex chronicus. Area of lichenification due to chronic scratching of the upper side of the thigh.

period of 1–5 hours and then by another attack of pruritus. Usually, scratching is continued also in the refractory period, provoking clear skin sores, especially when severe psychologic stress is experienced.

In both PN and LSC, pruritus is the main symptom, and the persistence and the progression of skin lesions are strictly correlated to scratching and rubbing. It is widely known that the definition of pruritus is at least unsatisfactory and we still accept to describe it as a "sensation that, if sufficiently strong, will provoke scratching or the desire to scratch" (1,2). In most of the dermatologic diseases the symptom "pruritus" is associated and is therefore strictly linked to the main dermatosis. In other cases, pruritus becomes a consequence of the primary cutaneous disease as a sign of progression or chronicization of the dermatosis. In both PN and LSC the underlying stimulus (and the only apparent cause) and the most important symptom is pruritus.

The first definition of LSC was introduced by Vidal and then further described by Brocq; Hardway reported a skin condition characterized by multiple nodular lesions and pruritus. Hyde later on defined this condition as PN (3).

Some authors (3) use the definition of PN as synonymous of LSC but according to others, they are two distinct clinical entities characterized by having both pruritus as stimulus. Hypotheses trying to explain pruritus related to PN and LSC focus on internal medical disorders, associated dermatoses, and above all psychologic aspects. The most frequent general related disorders reported in the literature are renal failure or chronic obstructive biliary disease, Hodgkin's lymphoma, hyperthyroidism, polycythemia rubra vera, gluten-sensitive enteropathy; triggering dermatoses are atopic dermatitis, allergic contact dermatitis, stasis dermatitis, and insect bites.

Psychogenic factors may play a relevant role in both PN and LSC; the evaluation of the psychiatric profile has evidenced that they are often associated with depression and dissociative experiences (4,5). The field of psychodermatology has developed because of an increased interest in understanding the relationship between skin disease and various psychologic factors (6). Patients with real and perceived imperfections in important image areas (face, scalp, hands, and genital area) are more prone to psychologic distress. Moreover, people with cutaneous diseases experience a heightened level of distress, as measured by the General Health Questionnaire and structured diagnostic interviews (7,8). As psychosomatic factors in dermatologic diseases have been estimated to be present in at least one-third of dermatologic patients, effective management of the skin condition involves consideration of the associated emotional factors (8,9).

Histopathology and pathogenesis

The histopathological features of PN are epidermal hyperplasia with orthokeratosis, focal parakeratosis and irregular acanthosis, mild to severe hypergranulosis and proliferation of Swann cells, and neural hyperplasia. An increased number of Merkel cells in the epidermis has been shown (10). The inflammatory infiltrate in the dermis is constituted mainly by lymphocytes, mast cells, histiocytes, and occasionally eosinophils (11,12). Mast cells in PN are characterized by a more dendritic shape as compared to normal skin, where they are normally roundish or elongated, are more numerous, and are closely linked to nerve endings. The morphology of these cells and the neighborhood to nerve endings correlates with an increase in nerve growth factor (NGF) release (12,13) and to all mediators of itch produced by mast cells as: histamine, tryptase, leukotrienes, prostaglandins, interleukins 2,4,6 (14–17). In addition, eosinophils, which are increased in the dermis, contain high levels of eosinophil cationic protein and eosinophil-derived neurotoxin/eosinophil protein x. Both proteins are able to degranulate mast cells (16).

The histopathological features in lichen simplex are epidermal hyperplasia, orthokeratosis, and hypergranulosis with a regular elongation of the rete ridges. There is a perivascular infiltrate of lymphocytes and occasionally of macrophages. The macrophages are not clearly dendritic as in PN and much less numerous. Moreover, in LSC there is no neural hyperplasia and abundancy of NGF and lack of positive immunostaining for NGF receptor mediators of pruritus as in PN (3,14). These recent investigations not only further contribute to differentiate PN from LSC, but provide interesting data for speculating on the pathogenesis of the two disorders.

Diagnosis and differential diagnosis

In PN and in LSC, the clinical features are usually sufficient for diagnosing the disorders. The first step is to exclude any underlying disease and then to address causes of general pruritus, which can be monitored by the laboratory (Table 1). Instrumental evaluation as CT scan and chest X-rays are performed in case of suspicion of lymphoma. Once general causes have been excluded, the most common dermatologic differential diagnoses for PN are: hypertrophic lichen planus, multiple keratoacanthomas, and pemphigoid nodularis. If there are few lesions also nodular scabies can be considered.

Table 1. Suggested investigations in prurigo nodularis

Blood count
Renal functionality (urea, creatinine, and electrolytes)
Liver function tests and serology for hepatitis
Thyroid and parathyroid hormones
Total serum IgE levels
Patch test
HIV test and Mantoux test (if indicated)
Skin biopsy

Lichen simplex chronicus has to be differentiated from psoriasis, mycosis fungoides, lichen planus, and lichen amyloidosis. All these dermatoses can be easily excluded or not according to the histopathology.

PN and LSC – A model for cutaneous psychoneuroimmunology?

Links between mental and affective disorders and the cutaneous related neuro-immune-endocrine status are well described (18), thus supporting the hypothesis that psychologic and social factors influence diseases processes in the skin. The skin, in particular, can be interpreted as the juncture of the simultaneous and connected activity of brain, immune system, and the skin itself. In this context neuropeptides, interleukins, and immune system messengers not only are the messengers, but also the actors of the specific clinical entities. Surprisingly, in front of many papers dealing with general interactive models in the area of stress and psychoneuroimmunologic factors in dermatology, very few clinical and experimental studies have investigated the association of data and well-defined clinical entities. Nevertheless, psychotropic agents and nonpharmacologic psychotherapeutic interventions may have a strong positive impact on some dermatoses, including PN and LSC, according to others' experience and that of the present authors (19–21).

Well-defined clinical entities like PN and LSC probably represent the optimal area of investigation to understand the psycho-neuro-immune events in the human skin.

Management and treatment

Both lichen simplex and PN are frustrating conditions (for both patient and dermatologist) to treat,

in the absence of any clear underlying association, because of their high resistance to therapy. There is an "itch-scratch" cycle, which is extremely difficult to stop, but moreover, there is a "particular" psychologic state of the patients affected by both dermatoses (14,15). Therefore the therapeutic strategies (21) other than pharmacologic are extremely important.

Topical aspecific antipruritic agents as 1% menthol and phenol in base creams, recommended in the past, are not very helpful. Potent topical glucocorticoid creams or ointments as betamethasone dipropionate (under occlusion) or intralesional glucocorticoids such as triamcinolone acetonide are often successfully employed. Topical application of capsaicin (0.025–0.1%), which is able to prevent the accumulation of neuropeptides in unmyelinated polymodal C-type and small myelinated A-delta type cutaneous nerves (22), can be effective in the very early manifestations. Topical tacrolimus has proved to be effective in LSC (23).

In diffuse and/or resistant forms of PN, ultraviolet-based therapy utilizes UVB (both broadband and narrowband) and UVA; narrowband UVB seems to be more effective and less dangerous then PUVA which is slowly loosing the therapeutic prevalence of the past. In resistant forms of PN, cyclosporine reduces the severity of pruritus by inhibiting lymphokine transcription and lymphocytes activation and proliferation. The dosages should not be lower than 4 mg/kg/day for periods not shorter than 6 months. Thalidomide and naltrexone can also be effective in recalcitrant, diffuse forms of PN. Thalidomide reduces polymorphonuclear leukocyte chemotaxis and selectively inhibits TNF-alpha production by enhancing degradation of TNF-alpha mRNA (24) thus interacting with the described patho-mechanisms. The antipruritic effects of naltrexone are apparently the result of its antagonizing activity on central and peripheral opiate receptors. There are reports (25) on the efficacy of etretinate (50–75 mg/day) in reducing pruritus even if the specific mechanisms of action are not well documented.

Next to the pharmacologic treatment, psychosomatic interventions can be suggested. One of the best documented strategy is the biofeedback. As reported by Shenefelt (26) in cutaneous disorders with documented autonomic nervous system component, biofeedback with or without associated hypnosis can be helpful. With trainings, individuals can consciously experience how to alter the autonomic response and with enough repetition they may establish new habit patterns, possibly avoiding, e.g., scratching and rubbing.

The supportive counseling comprises many different psychologic interventions that the physician can apply to pay attention to the disturbances reported by the patient. Approaches range from reassurance to clarification regarding the exact nature of the disease, to the point of triggering called "flash" (18). In such a case, the physician can succeed in transmitting "a flash of comprehension" to the patient. Early rational clarification of the symptoms can prevent the development of an obsessive vicious circle regarding illness and the consequent chronicity of the clinical pattern. Also, the cognitive-behavioral therapies have given good results in LSC and PN (27). These methods have the aim to modify behaviors that are considered nonadaptive to the individual. Moreover, they draw in part on the cognitive therapies of identifying dysfunctional negative self-talk or reframing the thought picture by offering a new positive perspective.

Conclusions

Patients affected by dermatologic diseases as LSC and PN are challenging patients for the dermatologist, because they usually need not only dermatologic problem-solving skills to manage the physical care demands, but also emotion-regulating skills to handle their "emotional disease." Moreover, in this view, the collaboration with an expert psychodermatologist or, at least, with a psychotherapist keen in the field of managing dermatologic patients, may result in the optimal management of the patient.

References

1. Bernhard JD. Pruritus. Lancet 1995: **345**: 1584.
2. Bernhard JD. Itch and pruritus: what are they and how should itches be classified? Dermatol Ther 2005: **18**: 288–291.
3. Soter NA. Nummular eczema and Lichen simplex chronicus/prurigo nodularis. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. Fitzpatrick's dermatology in general medicine, Vol. 1, 6th edn. New York: McGraw-Hill USA, 2003: 1194–1198.
4. Konuk N, Koca R, Atik L, et al. Psychopathology, depression and dissociative experiences in patients with lichen simplex chronicus. Gen Hosp Psychiatry 2007: **29**: 232–235.
5. Krishnan A, Koo J. Psyche, opioids, and itch: therapeutic consequences. Dermatol Ther 2005: **18**: 314–322.
6. Koo J, Do JH, Lee CS. Psychodermatology. J Am Acad Dermatol 2000: **43**: 848–853.
7. Hughes J, Barraclough B, Hamblin L, et al. Psychiatric symptoms in dermatology patients. Br J Psychiatry 1983: **143**: 51–54.

8. Panconesi E. Psychosomatic dermatology. Clin Dermatol 1984: **2**: 8–14.
9. Gupta MA, Gupta AK. Psychodermatology: an update. J Am Acad Dermatol 1996: **34**: 1030–1046.
10. Nahass G, Penneys NS. Merkel cells and prurigo nodularis. J Am Acad Dermatol 1994: **31**: 86–88.
11. Weedon D. Tumors of the epidermis. In: Skin pathology, 2nd edn. London: Churchill Livingstone, 2002: 753–802.
12. Liang Y, Jacobi JA, Marcusson M, Haak-Frendscho M, Johansson O. Dendritic mast cells in prurigo nodularis skin. Eur J Dermatol 1999: **9**: 297–299.
13. Liang Y, Marcusson JA, Johansson O. Leight and electron microscopic observations of p75 nerve growth factor receptor-immunoreactive dermal nerves in prurigo nodularis. Arch Dermatol Res 1999: **291**: 14–21.
14. Lee MR, Shumack S. Prurigo nodularis: a review. Australas J Dermatol 2005: **46**: 211–220.
15. Stante M, Hanna D, Lotti T. Itch, pain and metaesthetic sensation. Dermatol Ther 2005: **18**: 308–313.
16. Schmelz M. Itch mediators and mechanisms. J Dermatol Sci 2002: **28**: 91–96.
17. Lotti T, Hautmann G, Panconesi E. Neuropeptides and skin. J Am Acad Dermatol 1995: **33**: 482–496.
18. Urpe M, Pallanti S, Lotti T. Psychosomatic factors in dermatology. Dermatol Clin 2005: **23**: 609–617.
19. Panconesi E. Psychosomatic factors in dermatology: special perspectives for application in clinical practice. Dermatol Clin 2005: **23**: 629–634.
20. Pallanti S, Lotti T, Urpe M. Psychoneuroimmunodermatology: from empiric data to the evolutionary hypothesis. Dermatol Clin 2005: **23**: 695–703.
21. Urpe M, Buggiani G, Lotti T. Stress and psychoneuroimmunologic factors in dermatology. Dermatol Clin 2005: **23**: 609–618.
22. Lotti T, Teofoli P, Tsampau D. Treatment of aquagenic pruritus with capsaicin cream. J Am Acad Dermatol 1994e: **30**: 232–235.
23. Ashoff R, Wozel G. Topical tacrolimus for the treatment of lichen simlex chronicus. J Dermatolog Treat 2007: **18**: 115–117.
24. Wines NY, Cooper AJ, Wines MP. Thalidomide in dermatology. Australas J Dermatol 2002: **43**: 229–240.
25. Gip L. Prurigo nodularis (Hyde) trated with Tigason (Abstract). Dermatologica 1984: **169**: 260.
26. Shenefelt PD. Biofeedback, cognitive-behavioral methods, and hypnosis in dermatology: is it all in your mind? Dermatol Ther 2003: **16**: 114–122.
27. Phillips KA. Body dysmorphic disorder: diagnosis and treatment of imagined ugliness. J Clin Psychiatry 1996: **57**: 61–65.