Diffuse Prurigo Nodularis Masquerading as Dermatitis Herpetiformis Treated With Cyclosporine

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Prurigo is a group of severely pruritic skin disorders that often is debilitating for the patient and difficult to treat. Lesions may present with grouped excoriated papules and nodules that can mimic other skin disorders, such as dermatitis herpetiformis (DH). We report a case of a 46-year-old man who presented with multiple prurigo nodules and intense intractable pruritis with positive response to cyclosporine therapy.

Prurigo nodularis is an intense pruritic eruption that often is persistent and emotionally distressing for the patient. Chronic itching elicits an irresistible urge to scratch and thus disrupts regular sleep patterns, affects work performance, and negatively affects self-esteem.[1] Although the etiology remains unknown at this time predisposing factors have been elucidated. Among these are psychosocial disorders, including anxiety, stress, and depression.[2,3] It remains unclear whether psychosocial disorders have a primary association with prurigo nodularis or are a secondary association caused by itch. Prurigo also has been associated with atopy, pregnancy, metabolic disorder, malabsorption due to gluten enteropathy, and malignancy.[2-7] This case report and review of the literature examines the clinical presentation, differential diagnosis, and subsequent use of cyclosporine in the treatment of diffuse prurigo nodularis refractory to multiple treatment regimens.

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CASE REPORT

A 46-year-old man presented to the dermatology clinic for evaluation of a severely pruritic eruption that began 7 months earlier. Following the intital month of symptoms the patient stated that the lesions quickly spread to involve his entire body, including the scalp. The unrelenting pruritus disrupted his regular sleep pattern and interfered with activities of daily living. The patient's past medical history was remarkable for occasional heartburn and hay fever. The patient stated that he was otherwise in good health with no known drug allergies and his family medical history was noncontributory. Previous topical treatments included betamethasone dipropionate, triamcinolone acetonide, clobetasol propionate, mometasone furoate, and capsaicin. Prior oral therapy included hydroxyzine hydrochloride 25 mg, levocetirizine dihydrochloride 5 mg, and doxycycline 100 mg, without relief.

Physical examination revealed a well-nourished, well-developed, healthy man with Fitzpatrick skin type IV.

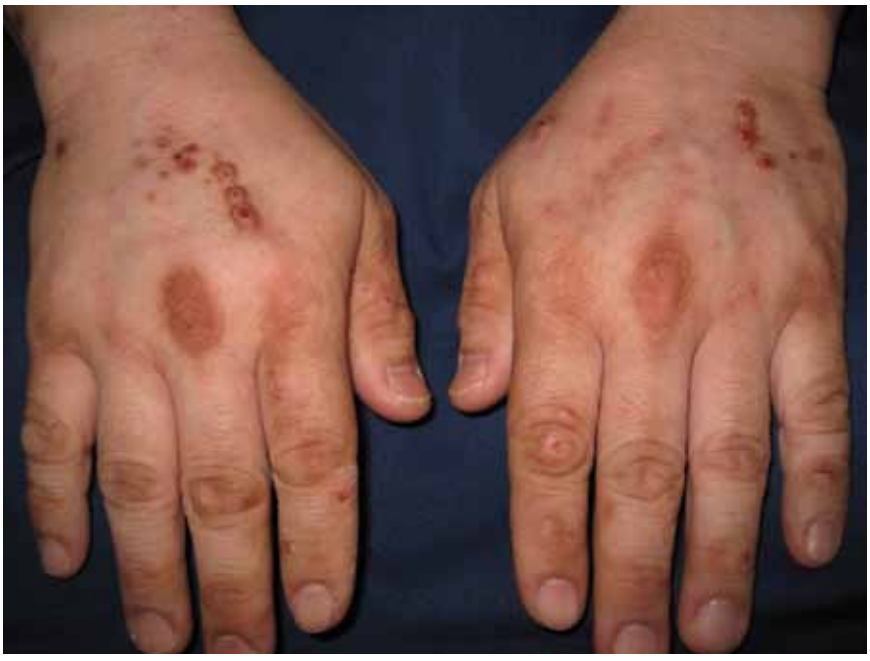

Figure 1. Firm hyperpigmented prurigo nodularis on the dorsal surfaces of the hands bilaterally.

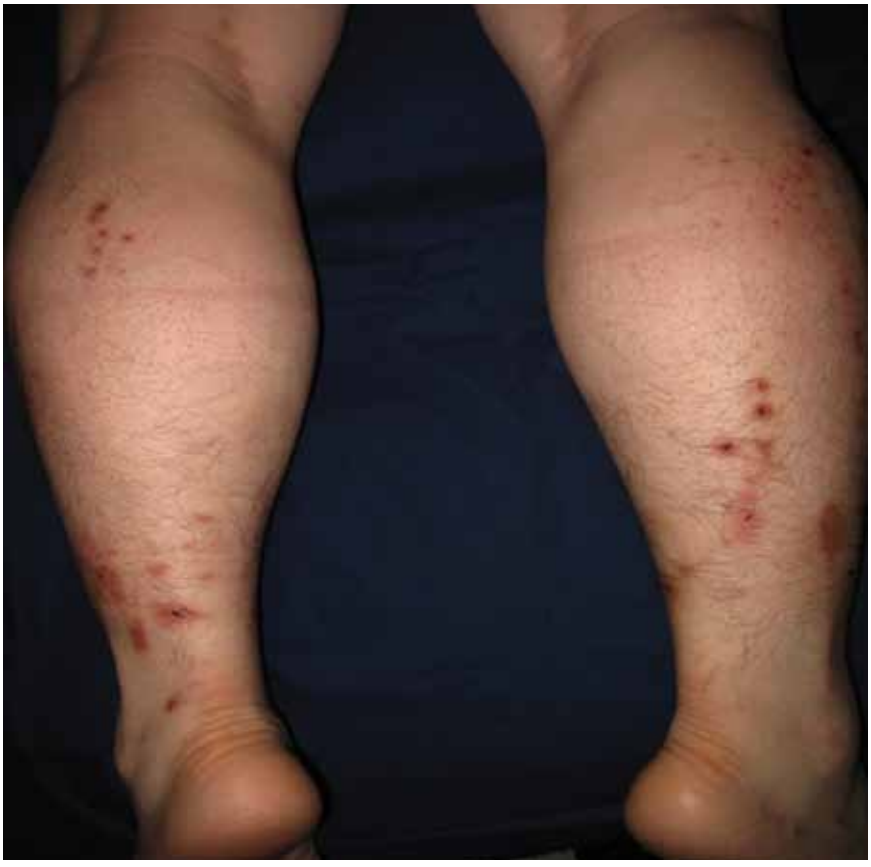

Figure 2. Grouped, excoriated, erythematous papules on the bilateral lower extremities.

Numerous excoriated and crusted papules and nodules appeared on the scalp region. There were multiple 3- to 6-mm lichenified firm nodules grouped mainly on the bilateral upper and lower extremities with scattered areas of involvment on the trunk and buttocks (Figures 1–4). Diffuse areas of excoriation also were evident on the face and ears. The palms of the hands, soles of the feet, and mucous membranes were spared.

Laboratory test results revealed normal hepatic and renal functions and the patient's fasting blood glucose

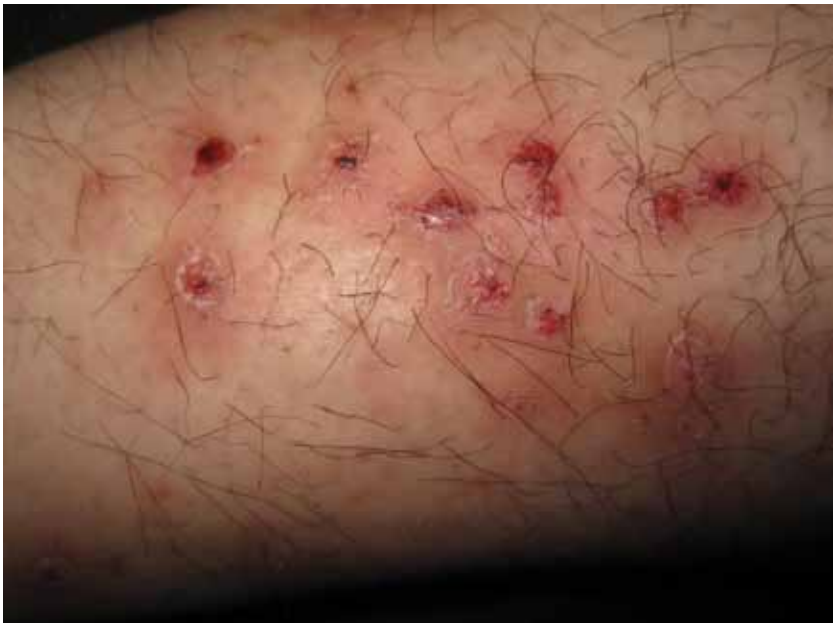

Figure 3. A grouping of 3- to 6-mm lichenified firm lesions of prurigo nodularis on the lower extremity.

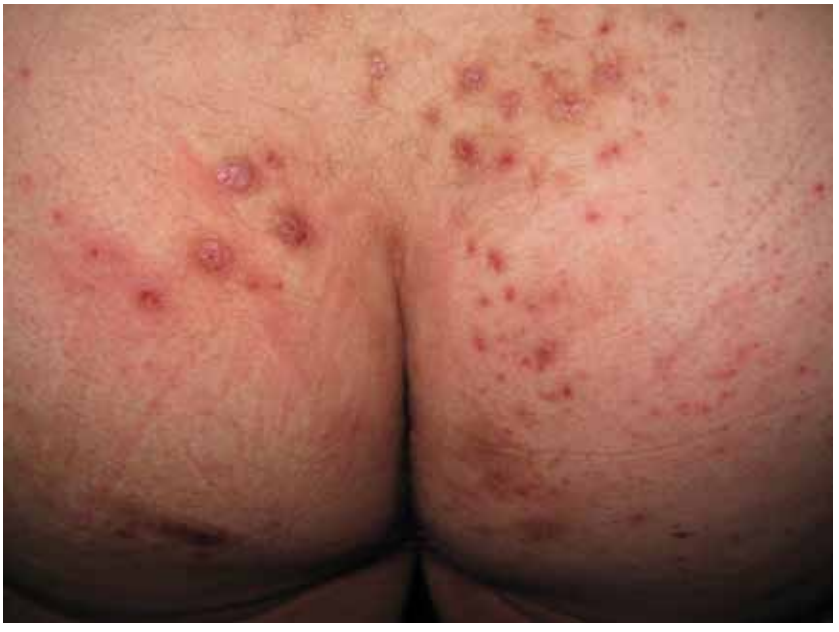

Figure 4. Scattered areas of prurigo nodularis involvement on the buttocks.

level was 90 mg/dL (reference range, 70–110 mg/dL). A complete blood cell count (CBC) with differential was within reference range. In addition, an enzyme-linked immunosorbant assay was negative for tissue transglutaminase as well as antigliadin antibodies. Punch biopsy specimens were obtained from the right elbow and thigh for histopathologic examination of lesions. Direct immunofluorecence (DIF) staining was negative for IgG, IgM, C3, C5-9, and fibrinogen deposition. Histologic evaluation of biopsy specimens with hematoxylin and eosin staining displayed irregular acanthosis with hypergranulosis and overlying compact orthokeratosis with parakeratosis and crust. Dermal fibrosis and lymphocytic perivascular infiltrate also were evident (Figure 5). Thus, a diagnosis of diffuse prurigo nodularis was rendered.

A trial of cyclosporine was initiated at approximately 5 mg/kg with a calculated dose of 500 mg daily (divided into 2 doses, 300 mg in the morning and 200 mg in the evening). Monthly hemogram, CBC, and urinalysis were ordered. Topical glucocorticosteroids were used as adjuvant therapy for individual lesions. The patient was instructed to apply clobetasol propionate ointment to affected areas twice a day and continue using clobetasol

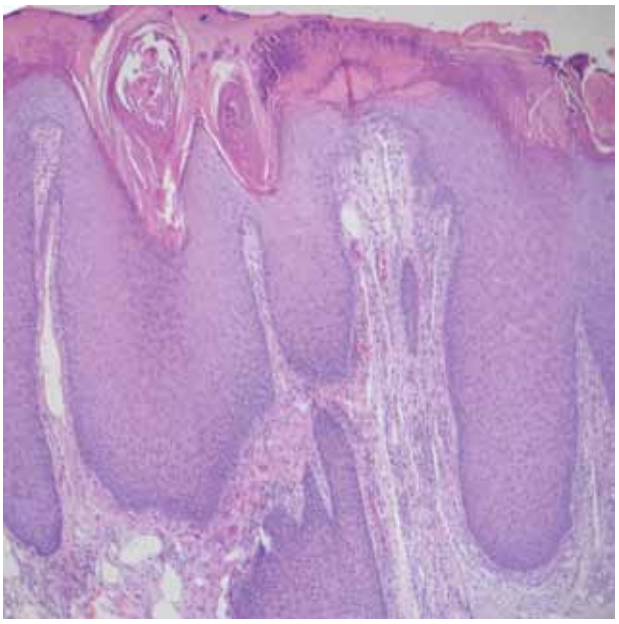

Figure 5. Irregular acanthosis with hypergranulosis and overlying compact orthokeratosis with parakeratosis and crust. Dermal fibrosis and lymphocytic perivascular infiltrate also are seen (H&E, original magnification ×10).

propionate shampoo for scalp lesions. In addition, the patient continued taking levocetirizine dihydrochloride 5 mg each morning and doxepin 25 mg at night. The patient showed marked improvement with substantial reduction of pruritus following the initial week of cyclosporine treatment. He continued to improve after 1 month of treatment, and subsequently the dosage of cyclosporine was reduced to 200 mg twice daily. After 3 months, cyclosporine therapy was well tolerated with a maintenance dose of 200 mg twice daily and there was a remarkable decrease in the number of prurigo nodules. Residual hyperpigmentation was seen with isolated areas of excoriated papules on the occipital scalp, which was treated with intralesional triamcinolone acetonide injectable suspension.

DISCUSSION

The term *prurigo* originates from the Latin term *pruire* meaning to itch.[3] In fact, it is characterized by an intense itch of unknown etiology with 3 main types of prurigo described in the literature, including acute, subacute, and chronic forms.[3,8] The acute type of prurigo is more common in patients with a medical history of atopy or reactions to insect stings and bites. Clinically, lesions can be papular, vesicular, or urticarial in form and last for approximately 1 week.[3] The subacute type of prurigo commonly is associated with emotional distress and tends to occur more frequently in middle-aged women.[9] Although subacute in nature, lesions may persist for months. Lastly, the chronic and often unrelenting type of prurigo can be associated with a multitude of triggering factors, including atopy, internal diseases, malabsorption, malignancy, collagen diseases, stress, infections, or parasitosis.[3] Prurigo nodularis falls under this category and can be characterized by firm papules and lichenified nodules with secondary excoriations intermixed with postinflammatory hypopigmented or hyperpigmented macules.[10] Prurigo nodules can be single, grouped, or disseminated all over the body.[3]

Histological examination reveals marked hyperkeratosis and irregular acanthosis, such as in our patient. Focal areas of hypergranulosis and parakeratosis with compact orthokeratosis also can be observed. The papillary dermis may show a predominantly lymphocytic infiltrate with vertically oriented collagen bundles.[11]

When intense pruritus is the predominant symptom, an exhaustive list of differential diagnoses is considered. In this case, clinical suspicion led to evaluation of the patient for dermatitis herpetiformis (DH). Prurigo and DH share a number of overlapping clinical features. Both entities can display an intensely pruritic papulovesicular eruption distributed symmetrically on the extensor surfaces of the extremities.[12] Prurigo nodularis can be grouped similarly to DH, which was the case with our patient who had a distinctly firm nodular appearance to his hands but also had grouped excoriated lesions and erosions on the upper and lower extremities. There are reports in the literature of patients with gluten sensitivity associated with both DH and prurigo nodularis.[2,4,5] In fact, one report describes a patient with celiac disease associated with DH and prurigo nodularis.[13] Although the connection between gluten sensitivity in DH as well as prurigo nodularis remains unknown, histopathologic examination clearly delineates the two disease entities. Dermatitis herpetiformis shows characteristic dermal papillary neutrophilic microabscesses, a feature absent in prurigo. In addition, perilesional biopsy specimens of DH are positive for granular deposits of IgA at the dermoepidermal junction on DIF staining, whereas DIF staining for IgA is negative in prurigo nodularis.[11,12] To further confirm the diagnosis of prurigo nodularis and rule out DH in our patient, tissue transglutaminase and antigliadin antibody tests were ordered and results were negative.

The course and treatment of prurigo is a prolonged one. Systemic therapy should be considered in severe disseminated prurigo or prurigo that has been refractory to conventional topical regimens. Cyclosporine, originally approved in the United States for prophylaxis of organ transplant rejection, currently is approved by the US Food and Drug Administration for the treatment of

psoriasis.[14] There are, however, a large number of other dermatoses for which this drug has been helpful. Cyclosporine was first shown to be effective in the treatment of prurigo nodularis in a published report in 1995.[15] Since that time there have been additional case reports of similar success in the treatment of prurigo nodularis, reduction of lesions, and decrease in pruritus with cyclosporine.[16,17] Cyclosporine is thought to inhibit lymphokine transcription and lymphocyte activation and proliferation.[15] Although this form of systemic therapy is not cytotoxic or teratogenic and is not a bone marrow suppressor, it can be associated with substantial adverse drug reactions and patients must be monitored carefully. Side effects include renal and hepatic dysfunction, hypertension, and neurologic symptoms (tremors, paresthesia, hyperesthesia, and headaches).[14] Other reversible side effects include hyperlipidemia, hypertrichosis, and gingival hyperplasia.[18] Nevertheless, cyclosporine is well tolerated by most patients and has been shown to have good efficacy overall.[14] Prior to placing patients on cyclosporine therapy, a thorough medical history should be taken and examination for existing infection or tumor should be performed along with blood pressure measurements on 2 different occasions.[14] Baseline laboratory evaluations for serum creatinine levels, blood urea nitrogen levels, urinalysis, CBC, liver-function tests, and fasting lipid profiles also should be performed. These laboratory tests, along with monitoring of blood pressure at each visit, should be repeated every 2 weeks for the first 1 to 2 months, then monthly thereafter while on cyclosporine therapy.[14]

SUMMARY

Prurigo is a chronic disorder characterized by intense pruritus that often is frustrating for both the patient and physician alike. Prurigo often is refractory to multiple treatment regimens and negatively affects work and activities of daily life. Once the itch-scratch cycle is initiated, it often is very difficult to stop. When approached with a general symptom of intractable pruritus along with a clinical suspicion of prurigo or DH, a diagnosis can be rendered with lesional and perilesional biopsies as well as DIF studies of the specimen. At times, the severity of the condition may warrant the initiation of systemic therapy. Treatment with cyclosporine seems to have good efficacy with reduction of pruritus and decrease in prurigo nodules. Patients undergoing cyclosporine treatment need to be monitored carefully and frequent laboratory evaluations and blood pressure measurements during each visit.

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