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Prurigo nodularis of Hyde treated with low-dose thalidomide

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Abstract. – Prurigo nodularis of Hyde is a skin disorder characterized by pruritic excoriated nodules. Improvement in pruritus and decrease in nodules was demonstrated in patients treated with oral thalidomide 200-400 mg daily. We report a case of a 52 year old woman with a history of widespread, persistent, and intensely pruritic lesions on all extremities and a histological diagnosis of "prurigo nodularis". The patient was treated with topical agents without significant improvement. Cyclosporine was administered with partial improvement but it had to be discontinued because of side effects. Treatment with corticosteroids and antibiotics resulted in significant improvement, but at reduction of steroid dosage the skin lesions reappeared. Thalidomide was started at a dose of 100 mg once a day and after one month it was reduced to 50 mg and 100 mg orally on alternate days. Six months after starting thalidomide treatment the patient was in remission with a few residual scars and sporadic asymptomatic lesions. No significant side effects occurred.

In this clinical case, a woman with prurigo nodularis was successfully treated with low-dose of thalidomide. We consider that in the treatment of prurigo nodularis is better to test a low dose of thalidomide before starting higher dosages because low dose of this drug can be efficacy without clinical development of side effects.

Key Words:

Hyde, Prurigo nodularis, Thalidomide, Skin nodules, Pruritic lesions, Low-dose.

Introduction

Prurigo nodularis of Hyde is a skin disorder characterized by pruritic excoriated nodules. The treatment includes topical and oral agents. In the past decades thalidomide was introduced in the treatment and numerous case series demonstrated improvement in pruritus and decrease in nodules after treatment.

We report a case of a woman with prurigo nodularis who was successfully treated with low-dose of thalidomide.

Case Report

A 52 year woman was first seen in July 2007 with a diagnosis of prurigo nodularis of Hyde and a 10 year history of widespread, persistent, and intensely pruritic lesions on all extremities.

In 1997, she presented to her physician with several pruritic excoriated skin lesions on her legs for which she was given topic emollients, but with no significant improvement. In a short time widespread, persistent, and intensely pruritic lesions had appeared on all extremities. Examination revealed numerous, excoriated, erythematosus papules and nodules of variable size, ranging from 1 to 4 cm, accompanied by secondary pigmentary changes and scars. Investigations revealed a normal complete blood count (CBC), BUN, creatinine and liver enzymes. Hepatitis B surface antigen, HCV and HIV antibodies were negative.

In 1999, a histological diagnosis of "superficial perivascular dermatitis" was made such that she was treated with oral corticosteroids (prednisone 25 mg once a day for 2 months) and topical corticosteroids with gradual improvement. However, when the corticosteroids were discontinued the skin lesions reappeared. The patient refused to continue systemic steroid therapy because of side effects and preferred to be treated with topical corticosteroids and emollients with persistence of the skin lesions.

In 2002, a histological diagnosis of "prurigo nodularis" was made and cyclosporine was administered with partial improvement. It had to be

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discontinued after two months because of side effects in the form of hypertension and nausea. During the following years the patient was treated with several modalities including emollients, occlusion with bandaging, menthol, acupuncture, phytotherapy and cryotherapy with no significant improvement. Some bigger skin nodules were surgically removed but after a short time other nodules appeared in adjacent areas.

In July 2007, the patient presented to our outpatient clinic with widespread, pruritic and infected skin nodules on the legs and arms that were also painful (Figure 1). The woman accepted treatment with corticosteroids (prednisone 25 mg once a day) and antibiotics which resulted in a significant improvement.

Assuming that at reduction of steroid dosage the skin lesions would reappear and considering that the patient was a post-menopausal woman, the decision was made to start treatment with thalidomide. In September 2007, thalidomide was started at a dose of 100 mg once a day after a normal baseline work-up, which included CBC, BUN, creatinine, liver function tests, Hepatitis B surface antigen and HCV antibodies, PPD test and chest-X-rays. Topical and oral corticosteroids were discontinued and the patient was only allowed to use an emollient. The pain in the legs improved and the antibiotics were stopped. After one month the pruritus decreased and skin examination revealed that most of the lesions had disappeared and the remaining ones had flattened. The dosage was reduced to 50 mg orally once a day. The blood chemistry remained within the normal range.

In January 2008, there was no pruritus but skin examination revealed a few nodules on the legs. Thalidomide was increased to 100 mg every day and significant decrease in size and number of skin lesions was obtained. After 1 month the dosage was reduced to reach a maintenance of 50 mg and 100 mg orally on alternate days.

Six months after this treatment, the patient was in remission with a few residual scars and sporadic active asymptomatic lesions (Figure 2). Her blood chemistry has remained within the normal range. No significant side effects occurred and the patient did not develop peripheral neuropathy. Her quality of life improved significantly.

Discussion

Prurigo nodularis of Hyde is a chronic skin disorder of unknown aetiology characterized by intensely pruritic excoriated nodules, mainly located on the extremities, the number of which may vary from a few to hundreds. There is a tendency for symmetrical distribution, with predominance on the extensor surface of arms and legs. Prurigo nodularis occurs mainly in adults, especially middle-aged women[1,2].

An association with several other diseases has been observed. An increased incidence of atopy was observed compared to the general population[3]. An increased tendency to develop prurigo nodularis was observed in patients with a deficiency of alfa-1-antitrypsin[4] and in patients with hepatic

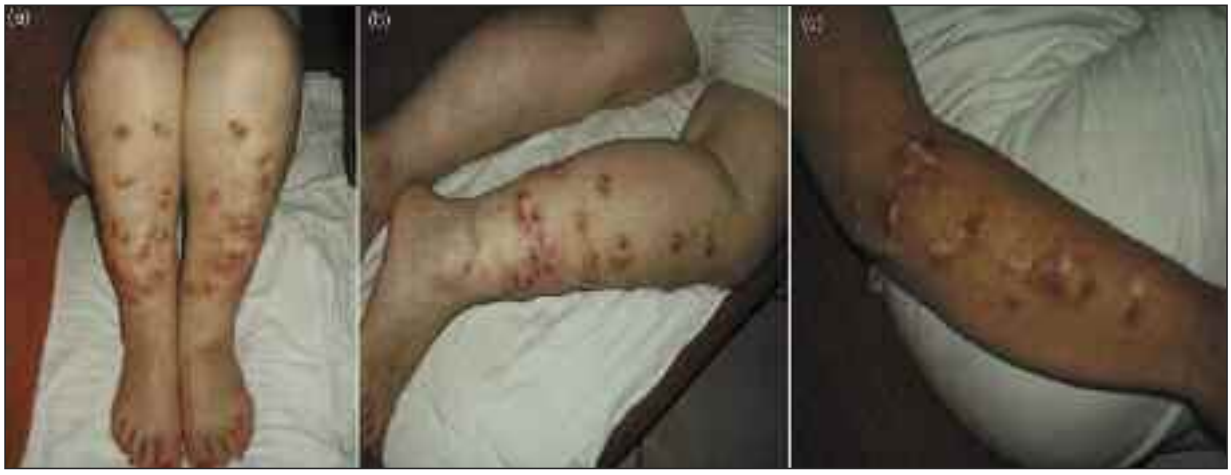

Figure 1. Lesions prior to treatment.

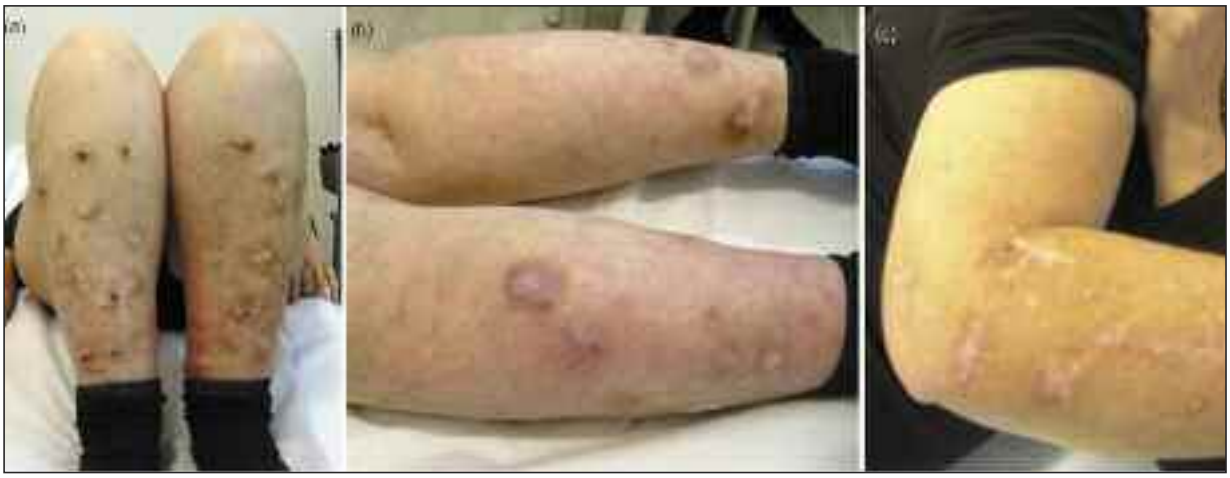

Figure 2. Lesion after 6 months of treatment.

dysfunction[5]. In particular a possible pathogenic link with hepatitis C virus infection was suggested[6]. A relation between prurigo nodularis and gluten enteropathy was described by more than one author[7,8]. Moreover cases of prurigo nodularis as the presenting signs of Hodgkin's disease were reported[9,10].

Histologically prurigo nodularis is characterized by hypertrophy and proliferation of dermal nerves[11], in the epidermis of skin nodules there are increased numbers of Merkel cells[12]. The dermis shows a non-specific inflammatory infiltrate including lymphocytes, mast cells, histiocytes and occasionally eosinophils. There is a proliferation of fibroblasts and it is possible to find a subepidermal deposition of fibrin[13].

The first-line agents used in the treatment are topical antipruritics including emollients, menthol, topical corticosteroids and occlusion with bandaging. Oral antihistamines, sedatives and antideppessants are an alternative treatment. Occasionally a short period of systemic therapy with corticosteroids may be indicated[1,2,14].

Second-line agents include localized phototherapy and photochemotherapy, cryotherapy and topical vitamin D3[15,16,17]. Capsaicin has been shown to be an effective and safe topical treatment[18].

The third-line agents include cyclosporine, of which the use is limited by its side-effects of hypertension and renal damage and relapse of disease after cessation of treatment[1].

In 1965, Sheskin[19] was the first to treat prurigo nodularis with thalidomide. Thalidomide is a tumor necrosis factor-α antagonist. It was first introduced in the 1950s as a sedative drug, but long-term thalidomide use was associated with polyneuritis and other side effects such as rash, constipation, dizziness and thromboembolic complications. In 1961 Thalidomide was withdrawn from the world market on discovery of its teratogenic effect, rare congenital abnormalities such as phocomelia in infants born to women who used thalidomide during pregnancy.

During the past few decades, thalidomide has been reintroduced for use in a variety of refractory dermatologic conditions and other disorders thought to have an autoimmune or inflammatory basis, such as lupus erythematosus, aphthous stomatitis, pyoderma gangrenosum, Behçet's syndrome, actinic prurigo, Kaposi sarcoma, Crohn's disease, multiple myeloma and prurigo nodularis[20,21].

In 1984, Wilkelmann at al.[22] observed that in patients with prurigo nodularis thalidomide administration induced the resolution of the pruritus within weeks and an involution of the nodular lesions in several months. The authors suggest that a long-term benefit may be obtained in about 6 months and state that a 200-mg daily dose is adequate for treatment.

The mechanism of action of thalidomide is through its central sedative effect, causing a reduction in peripheral stimuli perception, such as pruritus. However thalidomide may also have a direct peripheral action on the proliferated neural tissue in the lesions. The rapid improvement of pruritus may possibly be attributed to the immunomodulatory and anti-inflammatory properties of its anti-TNF-α action, or by a decrease in the perception of peripheral stimuli, such as pruritus[20].

The adverse effects such as peripheral neuropathy, dizziness, vomiting and teratogenicity remain a limiting factor in the treatment with thalidomide, particularly in fertile women[20,21].

In 1993 twenty-two patients suffering from prurigo nodularis were treated with thalidomide 50-300 mg daily for an average of 12 months[23]. Twenty patients had an immediate relief from pruritus and a significant decrease in size and number of skin lesions after 1-2 months. The therapy had to be discontinued in 13 patients (59%) due to side-effects, of which neuropathy occurred in five patients.

Bielsa et al[24] reported erythroderma during the use of thalidomide in two patients with chronic renal insufficiency. In both cases rapid resolution occurred after withdrawal of thalidomide.

In 1997 a prospective open trial was conducted[25] to evaluate the efficacy of a sequential combined treatment with thalidomide and ultraviolet B (UVB) therapy in the treatment of prurigo nodularis. Thalidomide administration was followed by UVB irradiation until complete or near-complete remission of the disease occurred. A high rate of response was achieved after an average of 12 weeks of thalidomide therapy and 32 UVB courses.

An Australian case series[26] demonstrated improvement in pruritus and a decrease in nodules in three of five patients treated with oral thalidomide. No remission was achieved in any of the patients. This was thought to be due to the low thalidomide dosages (100-200 mg).

Two years later in California a prospective study[27] was carried out to evaluate safety and efficacy of thalidomide in eight HIV-patients with refractory prurigo nodularis. The dosage of thalidomide ranged from 33 to 200 mg/d. Eight subjects had a greater than 50% response in reduction of itch over 3.4 months; seven subjects had a greater than 50% reduction of skin involvement over 5 months. Three subjects developed a peripheral neuropathy.

In the literature, despite a small number of cases of prurigo nodularis treated with thalidomide, the therapeutic results have been encouraging with dosages of 200 to 400 mg/day and a duration of treatment in the range of 2-3 weeks of starting thalidomide treatment. The flattening of skin lesions requires several months, with an average of 3-5 months[1,2,28].

In a recent study on six patients, Lan et al[29] suggested that low dose thalidomide may be a safe and effective treatment option for patients with prurigo nodularis. Six patients were successfully treated with thalidomide (50-100 mg/day) without clinical development of peripheral neuropathy.

In our patient, thalidomide was started at a dose of 100 mg once a day. After 1 month, thalidomide dosage was reduced to 50 mg once a day for 2 months. Although pruritus was significantly reduced, skin lesions remained and thalidomide was increased to 100 mg every day for 1 month and then again reduced to reach a maintenance dose of 50 mg and 100 mg orally on alternate days. Currently the patient is still being treated with thalidomide.

In the past the regimen for treatment of prurigo nodularis often required thalidomide at 200-300 mg/ day[1,2,28]. Our patient was treated with low-dose thalidomide (50-100 mg) without clinical development of peripheral neuropathy, as reported by Lan et al[29].

In conclusion, in the treatment of prurigo nodularis, is better to test a low dose of thalidomide and wait for 3-6 months before starting higher dosages considering the efficacy of a low dose of this drug without clinical development of side effects.

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