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Thalidomide in 42 Patients with Prurigo Nodularis Hyde

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Key Words
Prurigo nodularis Hyde · Thalidomide · Peripheral neuropathy

Abstract
The aim of this study was to describe the use of thalidomide in the treatment of prurigo nodularis Hyde (PNH) refractory to other treatments or in cases where other treatments cannot be used due to side effects. 77 medical records were retrospectively reviewed for the following data: sex, age, age at the beginning of thalidomide treatment, dermatological diagnosis, duration of the skin disease, previous treatments, indications for treatment with thalidomide, effect of treatment, duration of treatment with thalidomide, reasons for cessation of thalidomide treatment, and side effects. 54 patients had PNH. All patients were refractory to standard therapy or had side effects to treatment. 42 patients were treated with thalidomide and the majority of patients experienced clinical improvement. The most common reason for discontinuation of therapy was side effects, the most frequent being peripheral neuropathy and sedation. Thalidomide effectively treats PNH refractory to standard medications. However, physicians must be aware of possible side effects, especially peripheral neuropathy.

Introduction

Thalidomide is a glutamic acid derivative (alpha-phthalimidoglutarimide). It is marketed as a white crystalline powder which is poorly soluble in water and is therefore only available for oral use. The exact mechanisms of action are still not completely elucidated. It appears to act through several different targets which eventuate both hypnotic, immunomodulatory, anti-inflammatory and anti-angiogenic properties [1, 2]. Thalidomide is approved by the US FDA in the treatment of chronic recurrent/severe erythema nodosum leprosum and in Europe by EMEA in the treatment of multiple myeloma in combination with melphalan and prednisone in patients who have not been treated for multiple myeloma before. Thalidomide is also used for a large variety of both dermatologic and nondermatologic conditions [1, 3]. Besides the notorious teratogenicity, thalidomide has numerous well-known side effects. Peripheral neuropathy is important because there is a risk of irreversibility, and in Denmark this is monitored by performing neuronography prior to treatment. Among the more frequent side effects are sedation, constipation, rash and dizziness. Less frequent adverse effects include edema, dryness, pruritus, neutropenia, bradycardia, tachycardia, hypotension, headache, mood changes, nausea, increased appetite, weight gain, male sexual dysfunction, amenorrhea, ovarian failure and thrombosis [1, 3–5]. In addition, thalidomide can result in hypothyroidism [6]. The purpose of this study was to describe thalidomide treatment of prurigo nodularis Hyde (PNH) at the Department of Dermatology, Aarhus University Hospital, including types of treatments given prior to thalidomide treatment, indications for thalidomide treatment, effects and side effects.

Patients and Methods

In this retrospective study 77 medical records were available for analysis. 54 patients were diagnosed with PNH; 42 of these patients were treated with thalidomide and were therefore included in our study. The diagnosis of PNH was based on thorough clinical examination demonstrating dome-shaped nodules with crusts and central depression located predominantly on the extensor aspect of the extremities; only patients with these clinical changes were included (fig. 1). Patients with prurigo simplex and patients with other causes of prurigo were excluded. A clear clinical distinction was made between PNH patients presenting dome-shaped nodules with crusts located predominantly on the extensor aspect of the

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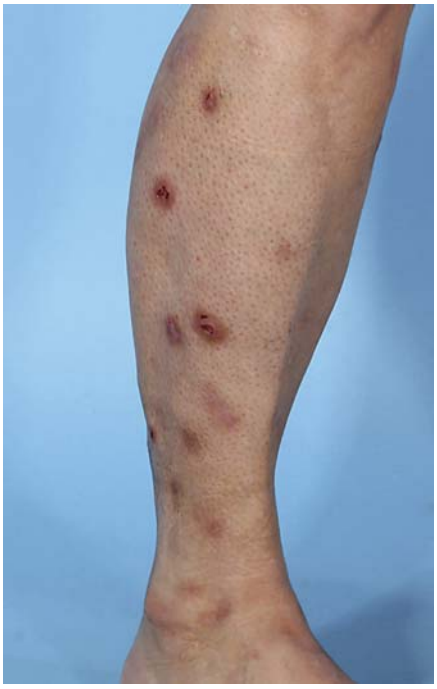

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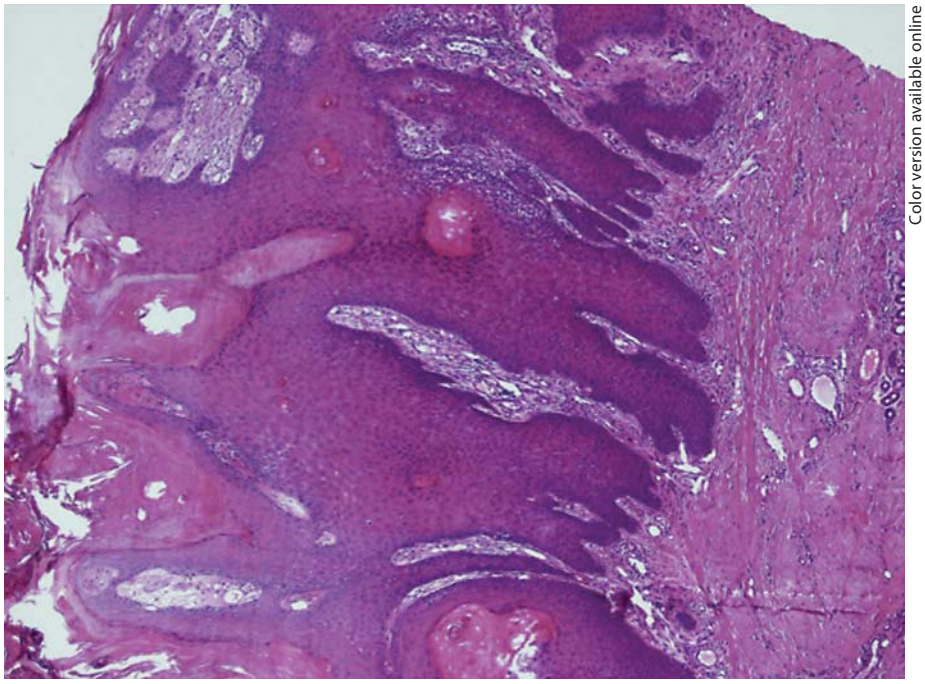

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Fig. 1. Typical clinical image of a patient with PNH.

Fig. 2. Histological examination of a typical skin biopsy specimen stained with hematoxylin and eosin showing epidermal hyperplasia and pronounced hyperkeratosis and a chronic inflammatory infiltrate together with fibrosis (magnification ×40).

extremities and patients with other clinical presentations resulting from scratching due to underlying pruritic conditions.

34 of the PNH patients had their diagnosis verified with histological examination showing changes consistent with PNH (i.e. epidermal hyperplasia and hyperkeratosis together with a dermal inflammatory infiltrate and neural hyperplasia). Histological examination from a typical skin biopsy specimen stained with hematoxylin and eosin is shown in figure 2. 4 patients had no biopsy performed and 4 patients had nonspecific histopathology in their skin biopsy specimens, but these 8 patients presented with skin changes clearly consistent with PNH. Patients were amenable to treatment with thalidomide when the hospital on behalf of the patient had permission from the National Health Service of Denmark to use thalidomide in the treatment of PNH. 21 patients were considered for treatment, but never started treatment.

The patients were included regardless of whether or not the treatment was initiated. This resulted in 2 groups: patients who had been treated with thalidomide (from 1983 to 2008) and patients who had not been treated with thalidomide. Each of the medical records from the group of thalidomide-treated patients was reviewed for obtaining the following data: sex, age, age at the beginning of thalidomide treatment, dermatological diagnosis, duration of the skin disease (this was calculated from onset of disease until our collection of data, May 2008, unless the patient had been completely cured), previous treatments, indications for treatment with thalidomide, effect of treatment (graded as no effect, slight improvement, moderate improvement, marked improvement and clearing), duration of treatment with thalidomide, reasons for cessation of thalidomide treatment and suspected side effects. All patients had neuronography performed prior to treatment at the Department of Neurophysiology.

Results

Medical records from 77 patients were reviewed retrospectively. All patients were considered for thalidomide treatment because of inadequate effect or side effects of previous treatments of their skin disease. All patients had neuronography performed prior to treatment and all neurograms were normal. 42 patients diagnosed with PNH were treated with thalidomide (17 males, 25 females). Figure 3 shows previous treatments for all patients treated with thalidomide. Topical and systemic steroids were used in most patients, UV radiation and immunosuppressants were less frequently used, whereas hydroxicin was used in about half of the patients. All patients had been treated with other medications (topicals, phototherapy and systemics) before being considered for thalidomide treatment. All patients had either insufficient effect of these treatments or showed side effects to treatment leading to cessation of therapy. Therefore, these patients were considered for thalidomide treatment.

Table 1 shows the effect of thalidomide treatment on patients with PNH. Patients with PNH were on average treated with thalidomide for 105 weeks and the average dose of thalidomide was 100 mg daily. However, a few patients were treated with 50 mg daily due to gastrointestinal side effects on 100 mg daily. Duration of treatment and clinical data are shown in ta-

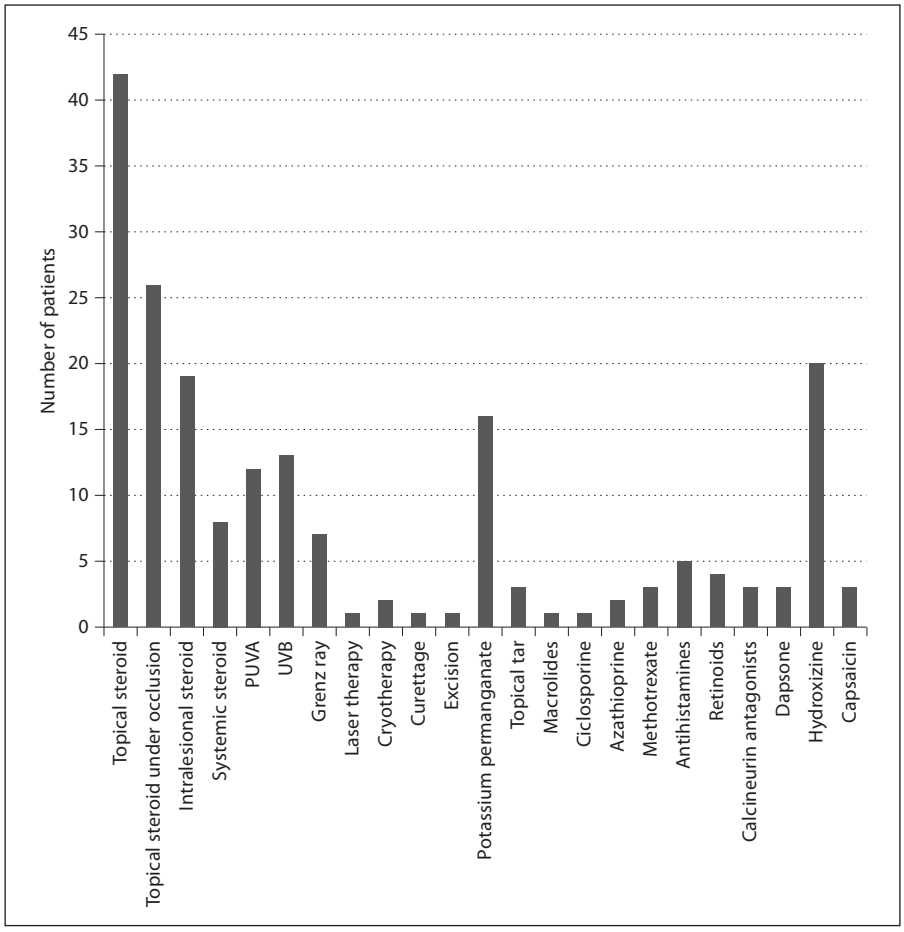

Fig. 3. Overview of treatments prior to thalidomide (PNH patients).

Table 1. Demographics and effect of treatment with thalidomide

Diagnosis	n	Mean age at treatment start	Mean disease duration	Mean duration of treatment	Effect of thalidomide	
Prurigo nodularis Hyde	42	46 years	16 years	105 weeks	no effect	6
					slight improvement	6
					moderate improvement	20
					marked improvement	5
					clearing	1
					unknown	4

ble 1. From the patient records the effect of thalidomide could not be determined in 4 patients, no effect was observed in 6 patients, whereas improvement was observed in 31 patients and clearing in 1 patient. The most frequent reasons for stopping thalidomide treatment for all of the PNH patients were neuropathy (59.5%), sedation (12%), no effect of the treatment (10%) and clearing of the skin disease (10%). A large variety of other less frequent side effects were reported (table 2). The occurrence of neuropathy was based on clinical evaluation and treatment was stopped as soon as this side effect was observed and in our case series, the neuropathy was reversible in all patients. No correlation was made between the cumulative dose and the onset of neuropathy. Neuropathy is the most frequent side effect caused by thalidomide and therefore it is of interest to determine the time needed to develop this side effect. The average time before thalidomide treatment of the PNH patients was stopped because of neuropathy was 89 weeks (ranging from 1 week to 7.5 years). In comparison the mean duration of treatment was 105 weeks for PNH patients.

Table 2. Side effects of thalidomide in PNH patients and reason for stopping treatment

Parameter	Reason for stopping thalidomide	Side effects
Peripheral neuropathy	25	25
Sedation	5	9
Lack of treatment effect	4	
Dizziness	3	7
Rash	4	5
Clearing of disease	4	
Unknown	2	
Depression	1	3
Nausea	2	3
Undefined symptoms	2	
Weight gain		1
Diarrhea	1	1
Tremor		2
Male impotence	1	1
Nervousness	1	2
Restless legs		1
Facial edema	1	1
Flickering (eyes)		1
Paresis of facial nerve	1	1
Malaise	1	1
Headache		1
Thrombocythemia		1
Polyuria		1
Polydipsia		1
Raynaud symptoms		1

Discussion

The results of this study including 42 patients with PNH indicate that thalidomide can be used as a safe drug in the treatment of PNH in cases where all other treatments have either failed or cannot be used due to side effects. In our study we treated 42 patients with PNH with thalidomide and the majority of these patients had improvement of their skin condition and only 10 patients had either no or an unknown effect on disease activity. From these results it can be concluded that thalidomide had an effect on PNH. As can be concluded from table 2, the main reason for stopping thalidomide treatment was peripheral neuropathy, which was the reason for stopping thalidomide in 25 patients (59.5%). Other reasons for stopping treatment included sedation, no effect of treatment and clearing of skin disease. Peripheral neuropathy is a well-known side effect and unfortunately this side effect is irreversible. However, our patients had neuronography done prior to treatment and all those neurograms were normal. None of the patients in our study who stopped treatment due to peripheral neuropathy had ongoing neuropathy on follow-up. As our study is a retrospective one, the patient records did not provide detailed information on the correlation between the dose of thalidomide and the occurrence of neuropathy. Sedation was reported as the reason for stopping treatment in 12% of patients, which is not surprising as thalidomide is a drug that was initially used as a sedative.

PNH is a rare skin disease characterized by widespread nodules associated with severe itch. Patients present inflamed nodules mainly on the extensor aspect of the extremities and due to the intense itch, PNH has a negative impact on quality of life. Therefore, there is a need for effective treatment and as a consequence patients are treated with a variety of different treatment modalities (summarized in fig. 3). Other treatments such as thalidomide are therefore considered in order to treat these patients. However, side effects occur and treatment is stopped after a certain treatment period. The majority of the previous treatments had either a lack of efficacy or were stopped due to side effects. Therefore, the use of thalidomide in PNH is a treatment option that should be considered in cases as those described in the study. However, the use of thalidomide is limited due to its potential side effects; peripheral neuropathy is the most predominant one [5] that is well known and has the potential to become chronic if patients are not monitored carefully in terms of measurements of nerve function. The risk of neuropathy seems to be associated with increasing dose of thalidomide [7]. However, in our study we saw no persistent neuropathy and this may be explained by the relatively low dose of thalidomide given (50–100 mg daily). Thalidomide exerts its effect through its immune-suppressant, anti-inflammatory and anti-angiogenic properties [1, 2]. However, in addition to its capability of inducing peripheral neuropathy, it is well known that thalidomide is highly teratogenic [4]. Therefore, female patients should not get pregnant during treatment with thalidomide. Recent studies have focused on the treatment of different skin diseases with thalidomide [8] and in these studies the conditions treated were mainly PNH, but also lupus erythematosus and lichenoid eruptions. The conclusion was similar to our conclusion that thalidomide is effective in the treatment of PNH refractory to standard medications.

Treatment with thalidomide has been covered intensely in the existing literature as review articles and in a number of single case presentations and case series. In this article, we therefore mainly cite these reviews and in tables 3 and 4 we have summarized the dermatological and nondermatological indications and summarized contraindications, monitoring and precautions. Rosenbach and Werth [1] have reviewed the use of thalidomide in dermatological conditions. In another extensive review [9], Faver et al. add more dermatological conditions to the list (table 3). Their conclusions are similar to those of our study and in addition, Rosenbach and Werth outline guidelines for the use of thalidomide [1]. When planning treatment with thalidomide, it is of importance to follow national guidelines as these may vary from country to country. As thalidomide is not a drug of first choice, it is useful

Table 3. Conditions treated with thalidomide (general indications for thalidomide are conditions refractory to conventional therapy or side effects to conventional therapy)

Dermatological	Nondermatological
Erythema nodosum leprosum (FDA-approved)	AIDS
Aphthous stomatitis	Severe perianal ulceration in AIDS
Behçet's syndrome	Post herpetic neuralgia
Kaposi sarcoma	Colitis
Prurigo nodularis	Cold hemagglutinin disease
Langerhans cell histiocytosis	Rheumatoid arthritis
Uremic pruritus	Multiple myeloma (EMEA-approved)
Lichen planus	Waldenström's macroglobulinemia
Jessner's lymphocytic infiltrate	Myelodysplastic syndromes
Sarcoidosis	Acute myeloid leukemia
Erythema multiforme	Myelofibrosis with myeloid metaplasia
Graft-versus-host disease	Renal cell carcinoma
Melanoma (metastatic)	Malignant gliomas
Cutaneous lupus erythematosus	Prostate cancer
Actinic prurigo	Colorectal cancer
Pyoderma gangrenosum	Ovarian cancer
Scleroderma	Breast cancer
Scleromyxedema	Squamous cell carcinoma of the head and neck
Polymorphous light eruption	Hodgkin's disease (after autotransplantation relapse)
Pemphigoid disorders	Congestive heart failure
Palmoplantar pustulosis	Epithelioid leiomyosarcoma
Pustular vasculitis	Small-cell lung cancer
Cutaneous lymphoid hyperplasia	Hepatocellular carcinoma
Leishmaniasis	Crohn's disease
Immune complex vasculitis	Cachexia
Porphyria cutanea tarda	Tuberculosis
Photodermatosis	Reflex sympathetic dystrophy
	Systemic-onset juvenile rheumatoid arthritis
	Adult-onset Still's disease
	Seronegative spondylarthropathy

Adapted from references 1 and 8.

Table 4. Contraindications and monitoring of treatment with thalidomide

Contraindications	Monitoring	Precautions
Toxic epidermal necrolysis	Pretreatment neuronography	Safe contraception (male and female) 4 weeks prior to treatment, during and 4 weeks after cessation of treatment
Pregnancy	Neuronography every 6 months	
Neuropathy	Pretreatment pregnancy test, pregnancy test every 4 weeks, routine blood test and screening for risk factors for thrombosis	
Patients not able to comply with treatment guidelines	In HIV patients white blood cell count should be monitored closely	

National guidelines must be followed in order to use this drug safely as guidelines may vary from country to country.

to consult such guidelines in planning the treatment strategy for these difficult-to-treat dermatological conditions. The use of thalidomide in dermatology is generally based on single case presentations and case series such as described recently by Doherty and Hsu [8] based on 48 patients and as described by Rosenbach and Werth [1], and the overall conclusions are similar in all studies.

The use of thalidomide has been extensively reviewed during more than a decade [1, 4, 10–16], focusing on indications for use and focusing on limitations due to thalidomide's teratogenicity and on its ability to induce neuropathy. However, thalidomide has been used in a comparative study in patients with toxic epidermal necrolysis [17] and it was found that it increased mortality and is therefore contraindicated in this severe dermatological condition. The results from this study together with the scientific evidence indicate that thalidomide can be used as a treatment option in PNH where other treatment modalities cannot be used either due to lack of efficacy or due to side effects. However, treatment with thalidomide should be used with special attention to side effects such as peripheral neuropathy and the risk of teratogenicity. Finally, when considering the use of thalidomide, national guidelines must be followed in order to use this drug safely.

Disclosure Statement

The authors have no financial interest.

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