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# Perforating disorder secondary to leflunomide and review of the literature of medications associated with perforating disorder

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## Abstract

The perforating dermatoses are a group of disorders characterized by transepidermal elimination of a material from the upper dermis. The most widely accepted classification consists of four primary perforating disorders that are defined by the type of material eliminated and the type of epidermal disruption. Pathogenesis of the perforating dermatoses is poorly understood, but some appear to have a genetic component. There are also acquired forms, which have been associated with underlying systemic diseases and the use of certain drugs. In this report, we describe a perforating disorder that occurred secondary to leflunomide therapy. To our knowledge, this is the first case in which this has been reported. We also review the recent literature on medications associated with perforating disorders.

*Keywords: perforating disorder, leflunomide, acquired perforating dermatosis*

## Introduction

The perforating dermatoses are a group of disorders characterized by transepidermal elimination. The most common clinical presentation is small, erythematous keratotic papules in multiple stages of development and regression. The four major perforating disorders, which have been defined by their histological and clinical features, include elastosis perforans serpiginosa (ESP), reactive perforating collagenosis (RPC), perforating folliculitis

(PF), and acquired perforating dermatosis (APD). As the names imply, abnormal elastin fibers are the material eliminated from the epidermis in ESP and altered collagen fibers are eliminated in RPC. PF is characterized by perforation of the infundibular portion of the hair follicle. APD is a term used to describe a perforating dermatosis (PD) that occurs in adulthood and is usually associated with a systemic disease. Chronic renal failure and diabetes mellitus are the two diseases most frequently associated with APD. One study showed that up to 11% of patients with chronic renal disease on hemodialysis developed APD [1] so that this disorder could possibly be renamed as “keratinizing disorder associated with renal failure.” However APD has also been reported to be associated with other diseases including, but not limited to, malignancy, HIV, thyroid dysfunction, primary sclerosing cholangitis, autoimmune disease, and scabies [2-4].



**Figure 1:** Clinical Image - Patient's left arm with multiple well demarcated 4-6mm erythematous papules with central crusting.

## Case Synopsis

A woman in her 40s with a 20-year history of severe, refractory cutaneous small cell vasculitis (CSSV) was previously reported to have responded successfully to leflunomide 10mg/d, after trying and failing multiple other drugs [5]. Her other medications included duloxetine, acetaminophen-hydrocodone, atenolol, and zolpidem, all of which she had been taking for many years. Unfortunately, after six months of leflunomide treatment, the patient developed an acute eruption with erythematous, pruritic papules on her upper and lower extremities (**Figure 1**). The initial differential diagnosis included breakthrough disease of her CSVV and drug eruption. A biopsy was consistent with PD (**Figure 2**). She did not have any other medical conditions reported to be associated with PD. Leflunomide was discontinued immediately and the rash resolved over several weeks without requiring systemic corticosteroids. There were no other changes to her medications during this time. She remains free of perforating lesions nine months after discontinuing leflunomide.

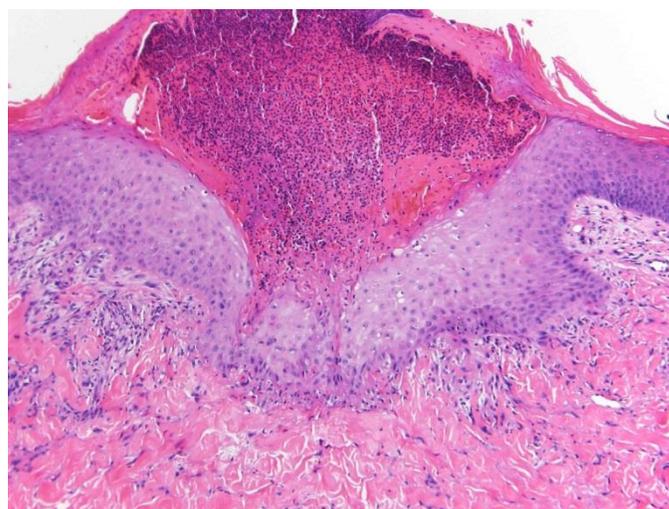
## Case Discussion

Leflunomide, a pyrimidine synthesis inhibitor approved for the treatment of rheumatoid and psoriatic arthritis, has also been reported to be effective in treating several vasculitides [6-8]. The most common side effects associated with leflunomide are diarrhea, elevated liver enzymes, and alopecia [9]. Owing to the timing of onset and resolution with discontinuation of the drug, absence of post-discontinuation relapse, and lack of associated risk factors, we hypothesize that the patient's PD was most likely secondary to leflunomide. Drug induced PD is rare, and to our knowledge it has not been reported with any pyrimidine synthesis inhibitors.

PD has been reported with the use of many drugs (**Table 1**). The majority of patients reported were male (83.3%). The time of onset of PD after starting the inciting drug varied from 2 weeks to 5.5 years (mean: 37.7 weeks, median: 8 weeks). Pruritus (88.2%) and pain (11.8%) were the most common symptoms associated with the eruption. However, 11.8% were asymptomatic. It is unclear based on the

cases reported whether the symptoms preceded the onset of the rash. Areas of involvement varied by case, but the upper and lower extremities were commonly involved. Only 2 of 18 patients (11.1%) had diabetes mellitus or renal failure. The treatments that have been used with reported success in drug induced PD include oral isotretinoin, topical corticosteroids, low dose oral corticosteroids, and topical tretinoin 0.05%. In most cases, however, the only effective treatment was to discontinue the drug. The time from discontinuation of the drug to resolution of lesions varied from as little as a few days to 9 months (mean: 9.9 weeks; median: 4 weeks). A summary of the drugs, patient demographics, time to onset of rash, areas of involvement, symptoms, risk factors, and treatments is presented in **Table 1**.

Although the pathogenesis of the perforating dermatoses is not fully understood, it is possible that the presence of endothelial damage leading to decreased blood flow and an environment of relative hypoxia in the dermis may predispose patients to developing this disorder. Vano-Galvan et al. proposed that the anti-angiogenic effect of drugs that inhibit vascular endothelial growth factor (VEGF) may cause a hypoxic environment that facilitates the transepidermal elimination of dermal collagen [17]. Of the 13 drugs that have been reported to cause PD, 8 (61.5%) have been shown to directly or indirectly inhibit VEGF [24-29]. Although epidermal keratinocytes do not express VEGF, the abnormal



**Figure 2:** Histopathology from a lesional punch biopsy specimen. This biopsy shows slight cup-shaped invagination of the epidermis with areas of collagen intercalating and between the keratinocytes with areas of necrotic inflammatory debris. H&E, 10x.

materials that are being eliminated through the epidermis originate in the dermis, where VEGF inhibitors could cause a hypoxic environment. Indinavir has been shown to inhibit angiogenesis through a different mechanism involving matrix metalloproteinase [27]. Diabetes mellitus and chronic renal disease, the two diseases that have been most strongly associated with PD, are both known to cause endothelial dysfunction [30, 31]. The damage to the endothelium causes vasculopathy and hypoxia in the dermis, which results in an environment similar to that induced by VEGF inhibitors. Our patient experienced intense pruritus prior to onset of the lesions that she developed while on leflunomide. The self-trauma from scratching along with the dermal hypoxia may have had a synergistic effect in the development of PD in our patient [29]. Another hypothesis for the development of PD, which needs to be confirmed with larger studies, is the possibility of a vitamin A

metabolism defect or vitamin A deficiency, owing to its clinical presentation resembling phrynoderma and response to topical retinoids [32, 33].

## Conclusion

Drug induced PD is rare, but has been reported most often in association with diseases or drugs that cause endothelial damage, decreased blood flow, and an environment of hypoxia within the dermis. Owing to the timing of onset and resolution with discontinuation of the drug, we hypothesize that our patient's PD was most likely secondary to leflunomide. This is the first case reported of perforating disorder associated with a pyrimidine synthesis inhibitor. Despite the experience of our patient developing PD on leflunomide, we would still encourage clinicians to consider leflunomide as a treatment option for refractory CSSV.

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**Table 1.** Review of medications reported to be associated with perforating disorder.

Drug	Age/sex	Class	Time to onset of PD after	Comorbid Conditions	Symptoms	Drug	Age/sex	Class	
Gefetinib [10]	46/M	Biologic	2 mo	Squamous cell carcinoma of the lung	Pruritis	Lateral thighs		Topical emollients; no improvement	Complete resolution at 9 mo
Sorafenib [11]	77/M	Biologic	7 wk	Renal cell carcinoma	None	Lower extremities ,buttocks, lumbar area		Topical corticosteroids; no improvement	Complete resolution at 8 mo (continued to take drug)
Sorafenib [11]	66/M	Biologic	5 mo	Diabetes mellitus; clear cell renal carcinoma	None reported	Legs, buttocks, flank		Tretinoin, mometasone furoate, calcipotriol, and minocycline; no improvement after 8 wk Isotretinoin 3mg/kg BW; improvement after 5 mo	Residual skin lesions resolved completely with discontinuation of drug
Sorafenib [13]	52/M	Biologic	5.5 yr	Renal cell carcinoma	None	Trunk and extremities		None	NR
Sorafenib [14]	49/M	Biologic	2 mo	Renal cell carcinoma	Pruritis	Lumbar and inguinal regions		None	Complete resolution at 1 mo
Sorafenib [14]	75/M	Biologic	38 mo	Hepatocellular carcinoma	Pruritis	Diffuse		None	50% improvement 1 mo after discontinuing drug
Sorafenib [14]	51/M	Biologic	2 mo	Hepatocellular carcinoma	Pruritis	Buttocks and thighs		None	Continued to take drug
Erlotinib [15]	68/M	Biologic	2 wk	Diabetes mellitus; small cell lung cancer	Pruritis	Back and shoulders		Topical betamethasone and dose decrease of drug; complete resolution at 3 mo	Continued to take drug
Infliximab [16]	61/M	Biologic	NR	Rheumatoid arthritis, pulmonary fibrosis	Pruritis	Elbows and scalp		Topical corticosteroids and tazarotene; no improvement	Complete resolution at 1 mo
Etanercept [16]	61/M	Biologic	2 mo	Rheumatoid arthritis, pulmonary fibrosis	None reported	Elbows and scalp		Allopurinol; no improvement	Complete resolution at 1 mo

**Table 1 (continued).** Review of medications reported to be associated with perforating disorder.

Drug	Age/sex	Class	Time to onset of PD after	Comorbid Conditions	Symptoms	Drug	Age/sex	Class	
Bevacizumab [17]	51/M	Biologic	2 mo	Colorectal cancer	Pruritis	Neck		Topical corticosteroids; improved pruritis only	Continued to take drug and develop new lesions
Natalizumab [18]	43/F	Biologic	6 mo	Multiple sclerosis	Pruritis	Extremities and ears		Topical corticosteroids and emollients; no improvement Low dose oral corticosteroids; minimized appearance of new lesions	Resolved 15 days after each infusion
Nilotinib [19]	48/M	Biologic	NR	Chronic myeloid leukemia	Pruritis	Trunk and proximal extremities		Emollients; showed slight improvement	Continued to take drug
Indinavir [20]	40/M	Protease inhibitor	3 wk	HIV	Pruritis	Diffuse		Topical corticosteroids and UVB-NB; no improvement	Complete resolution at 3 mo
Indinavir [20]	29/M	Protease inhibitor	5 wk	HIV	Pruritis & pain	Extremities		None	Complete resolution at 4 mo
Telaprevir [21]	50s/M	Protease inhibitor	3 wk	Hepatitis C Virus	Pruritis	Lower legs		Betamethasone and petroleum jelly; improvement after 2 wk	Complete resolution at 2 mo
Azathioprine [22]	26/F	Purine analog	3 wk	Ulcerative Colitis	Pruritis	Dorsum of hands and lateral neck		Tacrolimus 0.1%; improved pruritis only	Improvement within days of stopping drug
Lenalidomide [23]	59/M	Thalidomide analog	16 mo	Myelofibrosis	Pruritis & pain	Axilla, chest, back		Tetracycline 250mg 4x daily; no improvement Intralesional triamcinolone (TAC) 10 mg/ml for painful nodules, doxycycline 100mg, TAC 0.1% in sodium fusidate ointment; no improvement Topical tretinoin 0.05%	Improvement within 3 weeks of stopping drug