Intractable pruritic dermatosis of the perineum in a woman with highly unusual pathologic features

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Key words: doxepin; intractable pruritus; neuroinflammation; neuro-immuno-cutaneous system.

INTRODUCTION

We present a case of an atypical pruritic dermatosis of the perineum in a woman with highly unusual pathologic features. Initially unresponsive to multiple therapies, the patient responded remarkably quickly to doxepin. However, a gradual loss of efficacy was noted after only 1 month of treatment. Although the histopathologic features of the eruption overlapped somewhat with those of pagetoid dyskeratosis and papular acantholytic dyskeratosis, the absence of either epidermal acantholysis or dyskeratosis and a distinct clinical presentation differentiate this case from other described cases of dermatoses. In this report, we briefly discuss possible etiologies, highlighting the rapidly growing recognition of the neuronal regulatory network in cutaneous diseases.

CASE REPORT

A 71-year-old woman presented with generalized pruritus and a rash, which had been worsening over 6 months. She reported experiencing intermittent pruritus and eczema-like rashes for years. Of note, the patient had undergone multiple spinal surgeries since a motor vehicle accident 6 years prior, culminating in an occiput to T11 posterior instrumented fusion, posterior column osteotomies T2-9, and T5 corpectomy 6 months before her initial presentation. She noted that the eruption in her groin was becoming particularly pruritic, with pain and burning, forcing her to use lidocaine gel to experience brief periods of relief. Her medical history included Hashimoto's thyroiditis, autoimmune optic neuritis, asthma, anxiety, and depression. Previous use of prednisone and topical corticosteroids had temporarily alleviated her symptoms everywhere except the groin. Other medications included paroxetine 20 mg daily, omeprazole, levothyroxine 100 mcg daily, alendronate 70 mg daily, hydroxyzine 25 mg nightly. Clinical examination revealed an eczematous eruption on the back and arms and mildly pink patches on the medial proximal thighs and perineum. Over the next 4 months, the patient was treated with methotrexate (15 mg weekly), followed by cyclosporine (100 mg twice a day) and dupixent, which helped the generalized pruritus and the rash, except in the groin. The first skin biopsy from the proximal medial thigh revealed spongiotic and psoriasiform dermatitis with superficial epidermal pallor, papillary dermal edema, and a mild superficial perivascular and interstitial infiltrate composed of lymphocytes, histiocytes, and scattered neutrophils. Gram and Grocott methenamine silver stains were negative, and neither fungal microorganisms nor basement membrane changes were noted. Laboratory test results, including zinc levels, were unremarkable. The patient was also treated with terbinafine 200 mg daily for 2 weeks and gabapentin 300 mg 3 times a day for 1 month, with only a brief reduction in her symptoms. Over the following month, the patient's pruritus in the groin significantly worsened, contributing to her insomnia. Her skin eruption evolved from diffuse erythema with a few pink papules to multiple white papules and erosions

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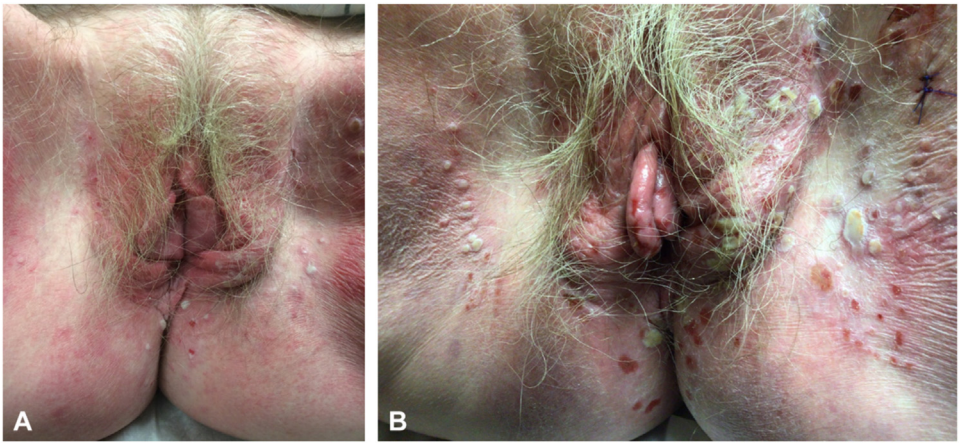

Fig 1. A and **B,** A rapidly worsening skin eruption in the groin, with emergence of white papules and erosions with mild diffuse erythema on the labia, perineum, and proximal medial thighs. Images were taken 2 weeks apart.

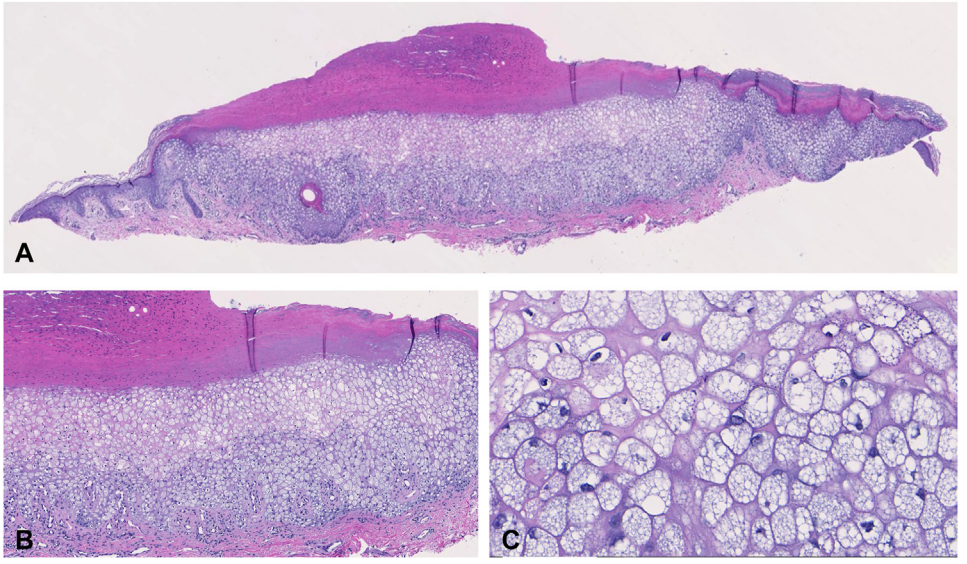

Fig 2. Hematoxylin-eosin staining of the biopsy specimen of a white intact papule demonstrating a well-demarcated lesion, with epidermal hyperplasia with hyperparakeratosis, full epidermal thickness of ballooned keratinocytes laden with numerous vacuoles or vesicles, displaying small to pyknotic nuclei. No acantholysis or dyskeratosis was noted. (**A**) 4×, (**B**) 10×, (**C**) 20× magnification.

on her labia, perineum, and inguinal regions (Fig 1, *A* and *B*). Repeat biopsy revealed epidermal hyperplasia with hyperparakeratosis, with well-demarcated regions of keratinocytes displaying an enlarged and ballooned appearance involving the full epidermal thickness. Cells displayed small to pyknotic nuclei with abundant cytoplasm made up of numerous vacuoles or vesicles (Fig 2, *A-C*). No cytologic atypia or viral cytopathic changes, multinucleation, or koilocytic changes were noted. Mucicarmine, colloidal iron, and glycogen stains were negative. Lesional keratinocytes were negative for cytokeratin 7, epithelial membrane antigen, and auramine-rhodamine stains and a human papillomavirus cocktail (in situ hybridization), human papillomavirus low risk (in situ hybridization), human papillomavirus immunohistochemistry, herpes simplex virus 1/2, Epstein-Barr virus, varicella-zoster virus, pan-polyomavirus, and Treponema stains were negative. The Ki67 stain was limited to the basal epidermal layer, and cytokeratin 7 was negative within the lesion. High molecular weight keratin CK903 and CD5/6 were positive within the lesional and adjacent normal epidermal cells. Viral cultures, polyomavirus

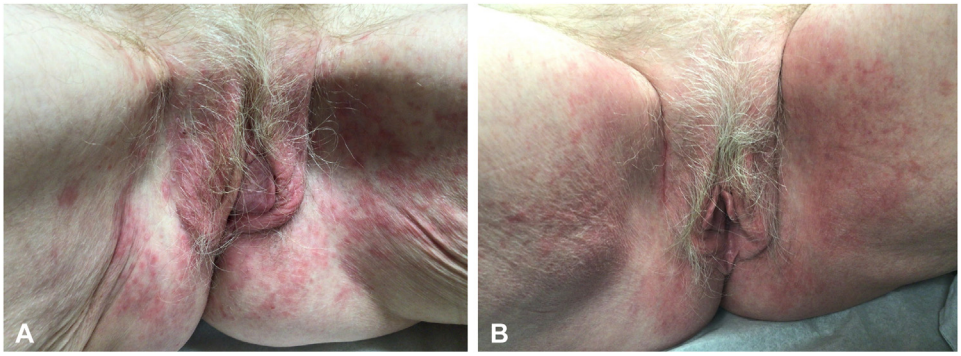

Fig 3. A, Resolution of white papules, erosions, and majority of the erythema, with complete absence of symptoms, 3 weeks after the initiation of doxepin 20 mg daily. Image was obtained 6 weeks after the imaging of Fig 2, *B*. **B,** Re-emergence of severe pruritus and hyperalgesia approximately 4weeks after doxepin initiation. Escalation of doxepin dosage, amitriptyline, and mirtazapine failed to significantly reduce symptoms. However, the patient's skin continued to only demonstrate mild to moderate erythema. This image was obtained 4 months after the imaging of Fig 3, *A*.

polymerase chain reaction, electron microscopy, and immunofluorescence analyses were negative. The patient did not respond to valacyclovir 1 g 3 times a day and acitretin 25 mg daily. She was then treated with doxepin 20 mg daily, which resulted in rapid and complete resolution of her symptoms and clearance of the white papules and erosions within 2 weeks, with minor remaining residual erythema (Fig 3, *A*). However, several weeks later, her symptoms returned, with eruptions of only a few small white papules, and neither an increase of doxepin to 75 mg daily nor carvedilol 6.25 mg daily helped her. Over the next 5 months, the patient was treated with mirtazapine 45 mg daily, amitriptyline 100 mg daily, and doxepin 150 mg daily, all relieving her returned severe symptoms only marginally. However, her skin continued to exhibit very mild erythema without papules or erosions (Fig 3, *B*). The patient did not experience relief from a pudendal nerve block.

DISCUSSION

Intractable pruritus, paresthesia, and hyperalgesia may be caused by multiple factors, including malignancies, medications, surgeries, or other underlying conditions. In the absence of another clear etiology, the gradual emergence of severe localized pruritus, within a year of extensive spinal surgery, in the case presented here suggests that the patient's symptoms are linked to her spinal fusion. Spinal and intracranial surgeries as well as injuries and spinal stenosis have been reported as causes of intractable pruritus.[1-3]

Unless their cause is eliminated, intractable cutaneous neurologic symptoms can present a significant therapeutic challenge. The concept of a neuro-immuno-cutaneous system, where interactions between peripheral neurons, immune cells, and epidermal/dermal cells function in homeostasis or disease states, was advanced years ago.[4] The importance of the neuroimmune axis in skin sensation, immunity, and inflammation is now clearly recognized; however, diagnostic and therapeutic advances in neurogenic inflammation and pruritus are incremental at best.[5,6] The patient presented here did not respond to numerous local and systemic anti-inflammatory agents as well as medications targeting the nervous system, including gabapentin, paroxetine, amitriptyline, mirtazapine, and pudendal nerve block. She only experienced brief periods of relief with topical lidocaine. The dramatic but relatively short-lived reversal of her symptoms and skin findings with low-dose doxepin is puzzling. Doxepin is a highly potent antihistamine (H_1), which is widely used as an antipruritic. It also exhibits strong antiadrenergic (α_1) and anticholinergic activities and moderate antiserotonergic activity and is a selective norepinephrine reuptake inhibitor.[7] The mechanism of the initial response to doxepin is unclear; however, a rapid loss of efficacy suggests a reactive change in the neuro-immuno-cutaneous system, likely at the receptor level on neurons, keratinocytes, and immune or other cells.

Physical examination findings and histopathologic features of the patient's skin eruption were also quite unusual. Specifically, the ballooning of vesicle-laden keratinocytes in a well-demarcated and full epidermal thickness pattern is, to our knowledge, a novel descriptive finding. Alhough the differential diagnosis includes pagetoid dyskeratosis and papular acantholytic dyskeratosis, we did not observe keratinocyte dyskeratosis or acantholysis, arguing that this presentation may be a new pathologic observation. A known viral etiology has

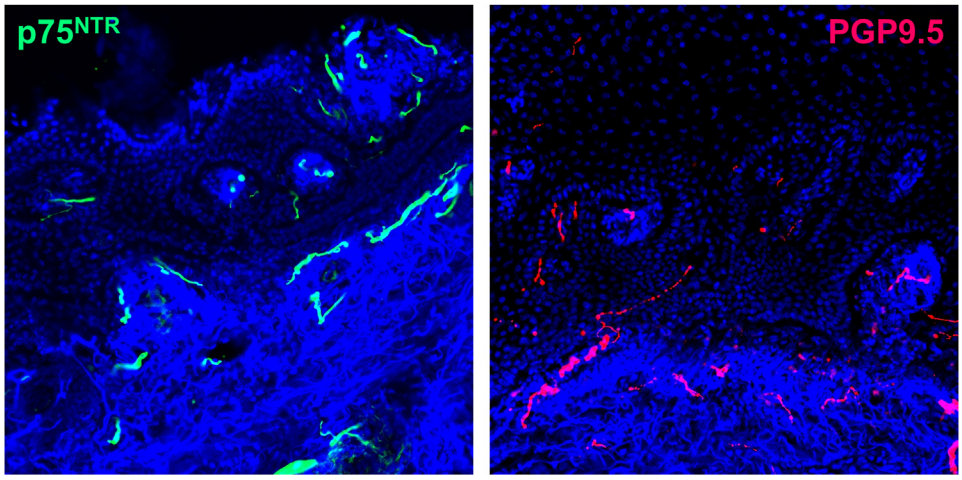

Fig 4. Immunofluorescence imaging of an intact white papule shown in Fig 2, with staining for neuronal markers $p75^{NTR}$ (left) and PGP9.5 (right). The *blue* represents DAPI.

effectively been ruled out, and the cause of such an unusual keratinocyte phenotype and the contents of the intracellular vesicles remain unclear. We confirmed the presence of neurons within these epidermal lesions and at the dermoepidermal junction (Fig 4), suggesting that a causal mechanism of this phenotype may involve the neuroepidermal or neuroimmunoepidermal axis.

Conflicts of interest

None disclosed.

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