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Combined carvedilol and gabapentin treatment induces a rapid response in red scrotum syndrome

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Abstract

Red scrotum syndrome (RSS) is a rare dermatologic condition characterized by persistent erythema and analgesia of the male genitalia that cannot be attributed to contact or atopic dermatitis or acute or chronic infections. Treatment of RSS is challenging since it often fails to respond to corticosteroids, antifungals, antivirals, and antibiotics. Several reports described RSS patients who responded to gabapentin, pregabalin, and β-adrenergic receptor blockers, suggesting a neuropathic etiology. Here we present a refractory RSS case with rapid clinical improvement on a combined carvedilol plus gabapentin therapy. We suggest that RSS manifestations are driven by neurogenic inflammation and that the efficacy of gabapentin/carvedilol relates to the suppression of the neuro-immuno-epidermal axis.

Keywords: carvedilol, gabapentin, neurogenic inflammation, neuropathic pain, red scrotum syndrome

Introduction

Red scrotum syndrome (RSS) is a rare cause of chronic treatment-resistant dysesthetic erythema of the scrotum. The differential diagnosis of RSS includes contact dermatitis, atopic dermatitis (AD), tinea cruris, cellulitis, syphilis, mycotic infections, and histiocytosis. Red scrotum syndrome typically affects men over the age of 60 and is ultimately a diagnosis of exclusion, characterized by persistent scrotal erythema, pain, and burning. Topical and systemic corticosteroids, as well as other anti-inflammatory agents, are often ineffective in the treatment of RSS. Novel therapies, such as gabapentin, timolol, and carvedilol, have recently been successfully utilized in few cases of refractory RSS [1-3]. We report a case of multi-treatment-resistant RSS that responded remarkably quickly and completely to dual therapy of carvedilol and gabapentin. We discuss the important emerging strategy of targeting the nervous system to treat certain cutaneous conditions characterized by neurogenic inflammation and dysesthesia.

Case Synopsis

A 64-year-old man presented with worsening hyperalgesia, erythema, and desquamation of the scrotum for approximately two months (**Figure 1**). Prior to his initial presentation, and several weeks after the onset of the symptoms, the patient was treated with doxycycline, clobetasol ointment, clindamycin lotion, lidocaine cream, and ketoconazole creams without improvement. The patient's past medical history included hepatitis C in remission, nonalcoholic liver cirrhosis, esophageal varices, chronic bronchitis, and osteoarthritis. The patient had no history of cardiac disease or congestive heart failure. To rule out contact dermatitis, the patient was asked to discontinue all topical agents and was prescribed a three-week prednisone taper with a starting dose of 40mg. In one week, the patient presented to the ED with worsening pain and skin erosions of the scrotum and

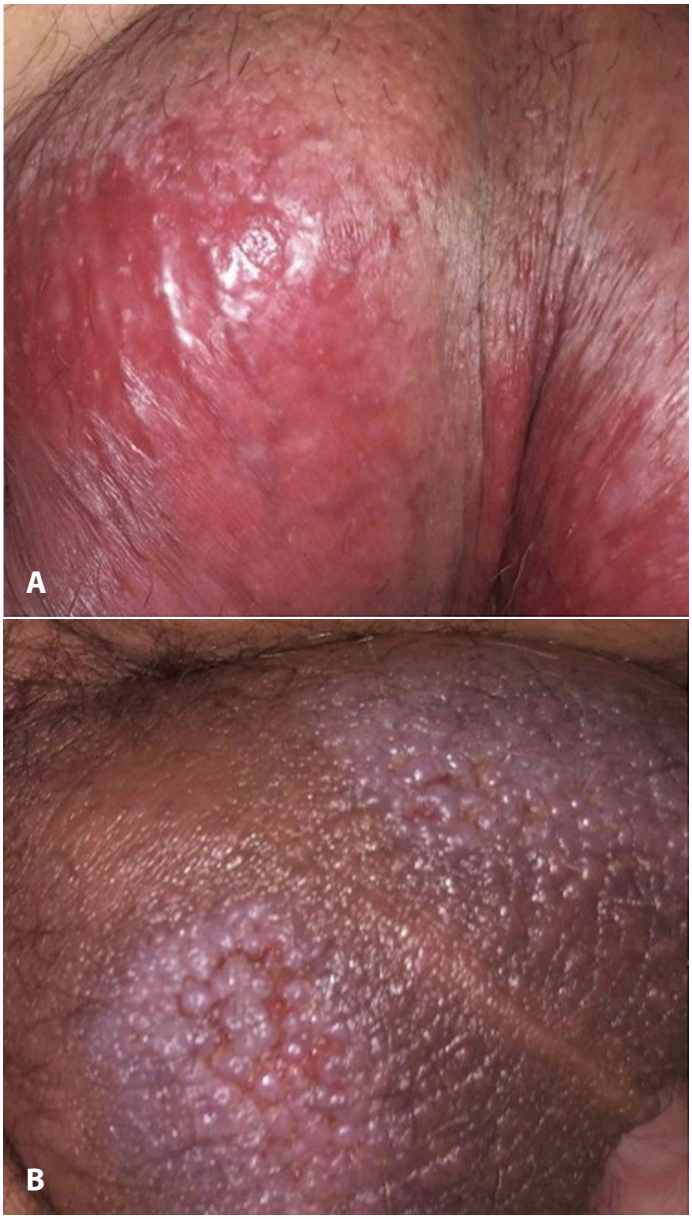

Figure 1. ***A)*** *Initial presentation showing erythema without scaling of the scrotum.* ***B)*** *Worsening erythema and edema of the scrotum after three weeks of failed response to multiple topical and systemic agents.*

was empirically treated with valacyclovir. Tests for herpes, chlamydia, and gonorrhea were negative. The patient returned in a few days to the dermatology clinic with severe scrotal pain causing significant difficulty in laying or sitting. Patient was diagnosed with RSS and was started on carvedilol 6.25mg daily and gabapentin 300mg daily. Within two days, the patient reported significantly decreased scrotal swelling and 80% reduction in pain (**Figure 2A)**. In two weeks, the patient had complete resolution of all symptoms with no residual erythema (**Figure 2B)**. He completed an 8-week course of carvedilol and gabapentin with no recurrence. Six months later, our patient remained symptom free with no additional treatment.

Case Discussion

Red scrotum syndrome is often a diagnosis of exclusion and is challenging to treat, with anti-inflammatory agents such as corticosteroids and doxycycline being largely ineffective. The RSS diagnosis in the above case was only made after excluding other etiologies. Although an allergic contact dermatitis cannot be definitively excluded without negative patch testing, in this case irritant/allergic contact dermatitis was not favored because of the following: 1) sudden onset of symptoms without the history of being in contact with a possible allergen or an irritant, 2) severe pain without pruritus, 3) worsening symptoms despite the discontinuation of all topical medications, 4) failure to respond to topical and systemic corticosteroids.

The above case demonstrates high RSS treatment efficacy of carvedilol and gabapentin when used together. Carvedilol is a nonselective β-adrenergic receptor (AR) and a weak α1-AR inhibitor. Gabapentin is a GABA analog that binds to voltage-gated calcium channels and reduces neuronal excitability and allodynia. Our report suggests that RSS is driven by the cutaneous neuro-immuno-epidermal axis, which is increasingly implicated in the pathogenesis of various skin diseases [4,5].

Several reports described the use of carvedilol and gabapentin to treat cutaneous disorders associated with neuropathic pain, pruritus, and inflammation. Carvedilol is used at a low dose (6.25mg daily or twice daily) compared to standard dose of 50mg/day for patients with heart failure. Two cases of RSS were successfully treated with carvedilol over four weeks [3]. The authors suggested that the clinical response was related to the vasoconstriction of cutaneous arteries by carvedilol [3]. Carvedilol also induced remission within three weeks in two patients with red vulva syndrome, a condition analogous to RSS

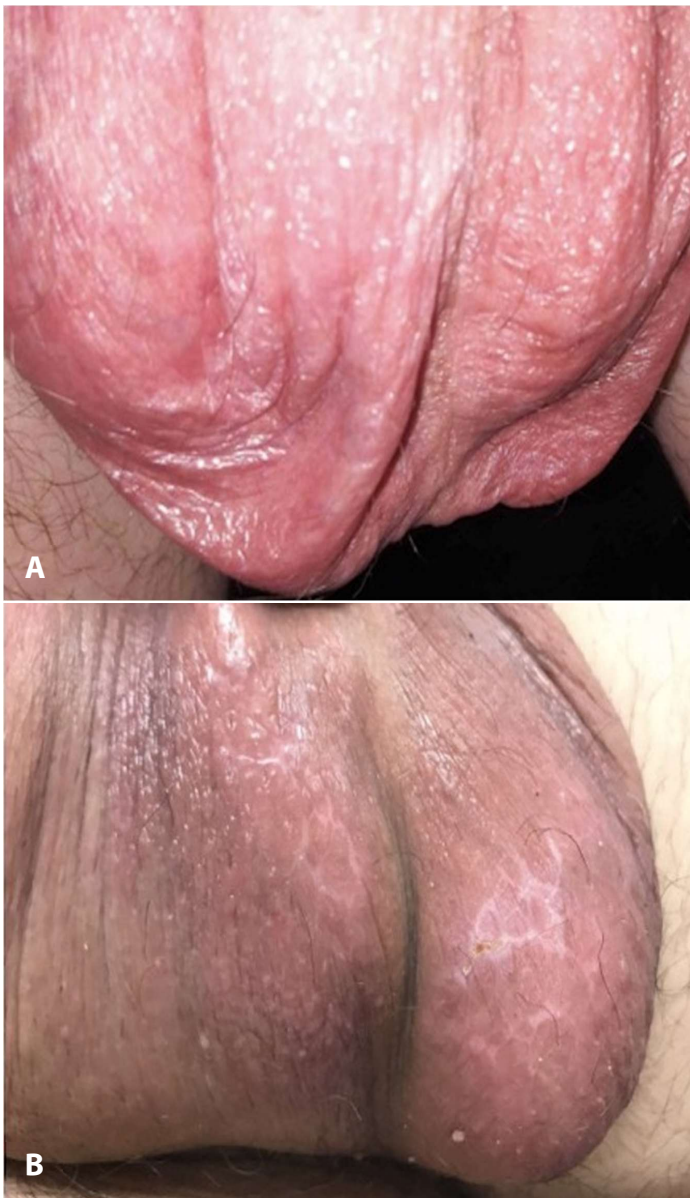

Figure 2. ***A)*** *A significant clinical and symptomatic improvement after two-day treatment with carvedilol and gabapentin.* ***B)*** *Complete and persistent improvement two weeks after the initiation of carvedilol and gabapentin.*

[6]. More generally, beta blockers have been utilized to treat refractory rosacea, adrenergic urticaria, aquagenic pruritis, erythromelalgia, and other skin disorders with dysesthesia and inflammation [7].

Gabapentin (titrated up to 300mg three times daily) has also been successfully utilized to treat RSS, with a partial response in two weeks and complete remission in four to 8 weeks in two patients [1]. Pregabalin 50mg three times daily was also effectively used to treat RSS in two patients that failed gabapentin therapy, resulting in resolution of symptoms over one to three weeks [2]. In addition, gabapentin has been used to treat pruritis, chronic urticaria, postherpetic neuralgia, diabetic neuropathy, and other chronic conditions with neuropathic pain [8].

A rapid clinical response to carvedilol and gabapentin in only two days in the case described here suggests that both medications may act synergistically through reducing neurogenic inflammation and neuropathic pain. The mechanism behind the efficacy of carvedilol and gabapentin in treating RSS is not known. However, modes of action of both medications suggest a central role of postganglionic sympathetic and sensory cutaneous neurons. Skin is densely populated by sensory afferent and efferent autonomic fibers [5]. These peripheral cutaneous neurons control pain, itch, and vascular tone among other sensory and autonomic functions. Importantly, they also mediate inflammatory responses through the production of neuropeptides and catecholamines [9]. For example, substance P chemoattracts and activates the immune cells and promotes the release of cytokines from the epidermal keratinocytes. [9]. Norepinephrine activates keratinocytes via ARs and promotes cytokine-driven sensitization of cutaneous nerves and allodynia [10]. Both keratinocytes and immune cells express α-AR and β-AR. Therefore, the benefit of carvedilol may relate to its action on these cells in addition to its effect on smooth muscle vasculature.

The role of the peripheral neurons in initiating or sustaining cutaneous inflammation has received increased attention recently from the research community [4,5]. It is now clear that some skin disorders are, at least partially, driven by the interaction of the peripheral nerves with the immune system and the keratinocytes. Clinical dermatology and basic research of skin diseases are perfectly positioned to complementarily improve our understanding of the peripheral nerve involvement in skin pathophysiology. Targeting peripheral neurons is an attractive approach to skin disorders that are resistant to conventional treatment. Given the large number of pharmaceuticals which target neurons through a broad range of mechanisms, we

should expect to see more cases involving the repurposing of these agents to treat select skin disorders, such as discussed in the above case of RSS.

Conclusion

This is the first case, to our knowledge, of refractory RSS successfully treated with the dual therapy of carvedilol and gabapentin. Our report suggests that neurogenic inflammation may drive RSS and thus targeting the cutaneous nerves and inflammatory process can improve clinical symptoms. We hope to encourage further investigation of the role the neuro-immune-epidermal axis plays in RSS and other skin disorders.

Potential conflicts of interest

The authors declare no conflicts of interests.

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