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Interstitial granulomatous drug reaction related to hydrochlorothiazide

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Abstract

Interstitial granulomatous drug reaction is a rare condition presenting as erythematous-to-violaceous plaques on the lateral trunk, axillae, buttocks, and thighs. Calcium-channel blockers, angiotensin converting enzyme inhibitors, beta-blockers, and statins have been described as drugs that can trigger interstitial granulomatous drug reaction. We present a case of interstitial granulomatous drug reaction related to hydrochlorothiazide and our approach to management of this condition. The diagnosis was confirmed with a skin biopsy and a rechallenge of hydrochlorothiazide, which exacerbated the patient's symptoms. The patient improved significantly with rigorous photoprotection, combination dapsone-alitretinoin therapy, and discontinuation of hydrochlorothiazide.

Keywords: interstitial granulomatous drug reaction, hydrochlorothiazide

Introduction

Interstitial granulomatous drug reaction (IGDR) is a distinct inflammatory reaction of the skin characterized by erythematous-to-violaceous plaques on the lateral trunk, axillae, buttocks, and thighs [1]. We present the first case of IGDR related to hydrochlorothiazide (HCTZ), to our knowledge, and our approach to management of this condition. Hydrochlorothiazide is a thiazide diuretic commonly used as a first line treatment for hypertension. Hydrochlorothiazide is also used to treat water

retention in patients with congestive heart failure, liver cirrhosis, or kidney disease. Commonly reported adverse effects include electrolyte abnormalities, orthostatic hypotension, hyperglycemia, and photosensitivity [2].

Case Synopsis

A 70-year-old man presented with a one-month history of an itchy rash distributed over his central chest, abdomen, back, arms, face, scalp, and thighs that started after returning from Florida. On examination, he had symmetrically distributed salmon pink-to-reddish indurated polygonal papules, some with central umbilication, coalescing into plaques with psoriasiform scales on his torso and limbs (**Figure 1**). His past medical history was significant for well-controlled hypertension, hyperlipidemia, GERD, and COPD. His medications included citalopram, HCTZ, atorvastatin, amiloride, and rabeprazole. He had no history of skin disease, rheumatoid arthritis, systemic vasculitis, or other autoimmune conditions. Complete blood count and urinalysis were normal and he tested negative for ANA, ENA, ANCA, HIV, and Hepatitis B/C. A trial of prednisone was initiated by his primary care physician with no effect.

Histopathology of punch biopsies taken from multiple areas on the chest and limbs, showed intense granulomatous inflammation in the upper dermis characterized by palisaded granulomas centered around a core of necrobiotic collagen

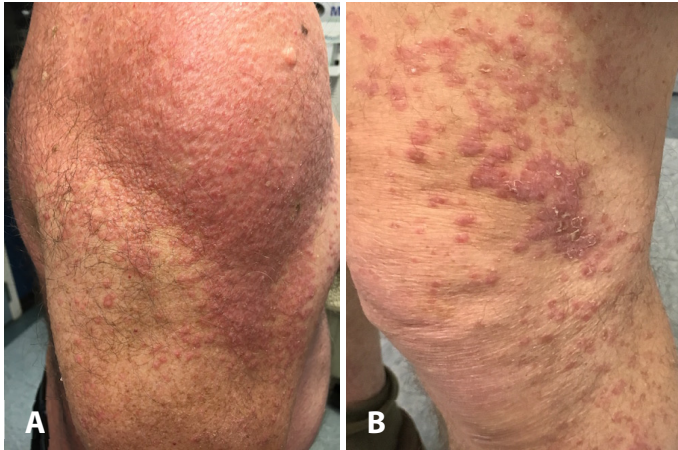


Figure 1: Initial patient presentation. **A)** Clinical photograph depicting red psoriasiform scales on the right shoulder. **B)** Clinical photograph showing violaceous plaques over the left anterior thigh.

mixed with neutrophils and basophilic necrotic debris (**Figure 2**). Special stains for bacteria, fungus, and acid-fast mycobacteria were negative. The

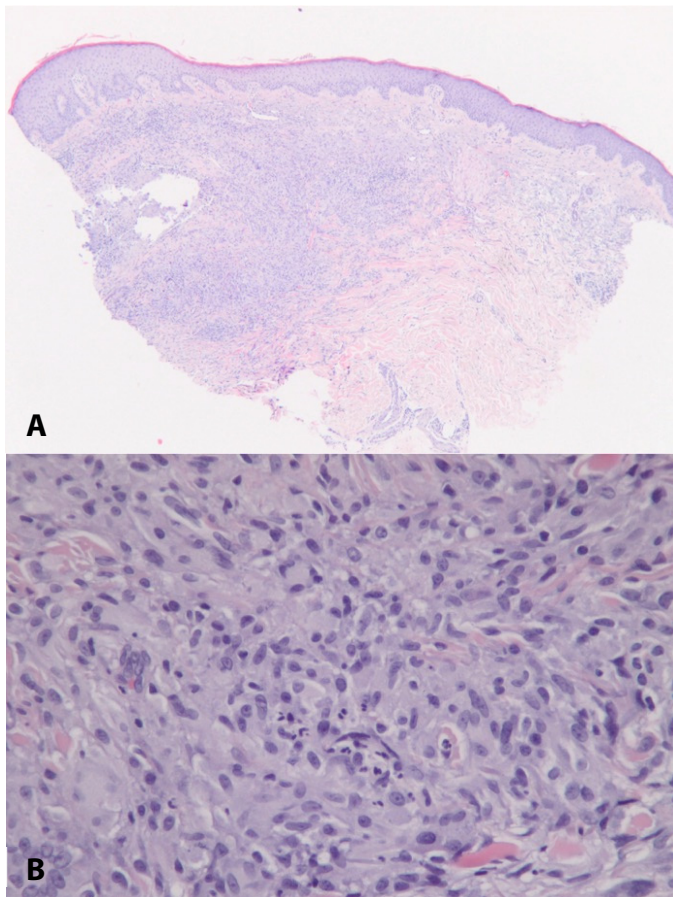


Figure 2: Skin biopsy results. **A)** Low power micrograph demonstrating the presence of dense infiltrate spanning the dermis. H&E, 40x. **B)** High power micrograph demonstrating the presence of histiocytic inflammation and foci of neutrophilic degeneration. H&E, 400x.

pathology was suggestive of palisaded and neutrophilic granulomatous dermatitis but with more mucin than usual. Owing to the preponderance of neutrophils on pathology, dapsone was initiated with modest improvement. Over time, he also developed quite significant hand dermatitis, and alitretinoin was added. He was noted to be extremely photosensitive, with flares occurring with each trip to sunny southern climates. His skin improved significantly with rigorous photoprotection and a combination of dapsone 100mg daily and alitretinoin 30mg daily but flared with tapering of these medications. In consultation with his family doctor, HCTZ, rabeprazole, and atorvastatin were gradually stopped or replaced. After stopping HCTZ, he developed severe peripheral edema and thus restarted it, leading to a dramatic reappearance of his cutaneous disease (**Figure 3**). Substitution of HCTZ for spironolactone allowed clearing of his skin condition without subsequent exacerbations. A timeline of our patient's clinical course is shown in **Figure 4**.

Case Discussion

Reactive granulomatous dermatitis is a term which encompasses palisaded neutrophilic and



Figure 3: Patient presentation after restarting HCTZ. Clinical photograph showing pink indurated papules with some central umbilication coalescing into plaques.

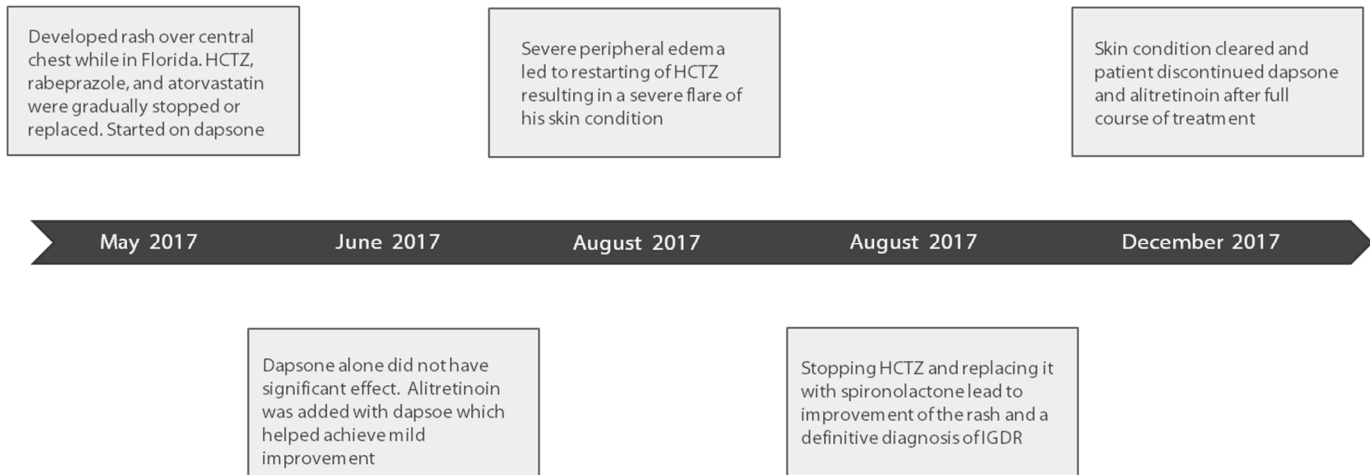


Figure 4: Timeline of clinical course.

granulomatous dermatitis (PNGD), interstitial granulomatous dermatitis (IGD), and interstitial granulomatous drug reaction (IGDR). The etiopathogenesis is not well understood but it is believed to result from immune complex deposition, resulting in altered vascular dynamics and subsequent collagen degeneration, which triggers granulomatous inflammation [3]. Clinical and histological features can help differentiate between these conditions (**Table 1**).

PNGD presents with skin-colored to erythematous papules on extensor surfaces with central

umbilication. However, IGD and IGDR both present with a range of cutaneous manifestations including erythematous papules, plaques, and ropelike cords usually found on the lateral trunk, axillae, thighs, and buttocks [1]. IGDR can mimic PNGD and IGD both clinically and histologically. IGDR may occur after a long delay ranging from 4 weeks to 25 years (mean 5 years) after starting the culprit medication and resolves in 1-40 weeks (mean 8 weeks) after drug discontinuation [4]. Common offending medications include calcium channel blockers, statins, furosemide, beta-blockers, antihistamines, angiotensin-converting enzyme inhibitors, TNF

Table 1. Comparison of the three types of reactive granulomatous dermatitides.

	Palisaded neutrophilic and granulomatous dermatitis (PNGD)	Interstitial granulomatous dermatitis (IGD)	Interstitial granulomatous drug reaction (IGDR).
Clinical Presentation	Skin-colored to erythematous papules on extensor surfaces with central umbilication [8]	Various manifestations including erythematous papules, plaques, and ropelike cords usually found on the lateral trunk, axillae, thighs, and buttocks [1,9]	Presents similar to IGD
Pathology	Intense neutrophilic and interstitial histiocytic infiltrate along with potential evidence of vasculitis [8]	Diffuse dermal infiltrate of lymphocytes, eosinophils, histiocytes and necrobiotic collagen [9]	Vacuolar interface dermatitis, atypical lymphocytes, prominent eosinophils, a lack of neutrophils and minimal collagen degeneration [11]
Associations	Connective tissue diseases including rheumatoid arthritis (RA), systemic lupus erythematosus, and systemic vasculitis [8]	RA, seronegative arthritis/ polyarthralgia, autoimmune thyroiditis, as well as paraneoplastic presentations associated with a range of solid hematopoietic tumors [1]	Beta blockers, calcium channel blockers, statins, antihistamines, NSAIDs, TNF-alpha inhibitors, and diuretics [10]

inhibitors, and anakinra. Rare causes include carbamazepine, diazepam, bupropion, darifenacin, sennoside, and ganciclovir [5].

Histologically, IGD is characterized by diffuse dermal infiltrate of lymphocytes, eosinophils, histiocytes, and necrobiotic collagen [6]. In contrast, PNGD has an intense neutrophilic and interstitial histiocytic infiltrate along with potential evidence of vasculitis. Histological features that favor IGDR include vacuolar interface dermatitis, a variable amount of mucin deposition, atypical lymphocytes, prominent eosinophils, a lack of neutrophils, and minimal collagen degeneration [7].

The diagnosis of reactive granulomatous dermatitis necessitates investigations for associated connective tissue conditions. PNGD is reported to be associated with connective tissue diseases including rheumatoid arthritis, systemic lupus erythematosus, and systemic vasculitis (particularly granulomatosis with polyangiitis). The most common associations with IGD are rheumatoid arthritis, seronegative arthritis/polyarthralgias, and autoimmune thyroiditis; there are also paraneoplastic presentations associated with a range of solid and hematopoietic tumors [7].

Our patient presented with characteristic symmetrical erythematous papules and plaques over his central chest, abdomen, back, arms, face, scalp, and thighs. Extensive testing for connective tissue diseases was negative. Our patient's eruption was exquisitely photosensitive and he experienced significant exacerbation with sun exposure, which

has not been previously reported in IGDR. A possible explanation is that the causative medication in his case was HCTZ, which is a known photosensitizer. However, HCTZ has not been previously reported to cause a granulomatous reaction. Definitive diagnosis of a drug eruption requires rechallenge. Our patient's self-directed reinitiation of HCTZ to treat worsening peripheral edema satisfies the rechallenge requirement and identified HCTZ as the culprit drug causing IGDR. To further support this, discontinuing HCTZ led to clearing of his skin condition.

The most important treatment for IGDR is withdrawal of the offending medication. Adjunctive therapies with reported efficacy include topical or intralesional corticosteroids, dapsone, and hydroxychloroquine [3]. For our patient, the combination of dapsone, alitretinoin, and rigorous photoprotection was effective.

Conclusion

Our presentation highlights an unusual case of IGDR related to HCTZ and associated with significant photosensitivity. Treatment with dapsone and alitretinoin fully cleared the eruption before we were able to identify the causative medication. Full resolution occurred with discontinuation of the offending medication, HCTZ.

Potential conflicts of interest

The authors declare no conflicts of interests.

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