Granulomatous drug eruption associated with imipramine

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**INTRODUCTION**

Granulomatous drug eruptions are rare and include interstitial granulomatous drug reaction, drug-induced granuloma annulare, drug-induced accelerated rheumatoid nodulosis, and drug-induced sarcoidosis. The differential diagnosis is broad and includes granuloma annulare, lichen planus, connective tissue disease, sarcoidosis, and mycosis fungoides. Diagnosis is, therefore, best established with tissue examination of a punch biopsy specimen and correlation with clinical history.

Imipramine is a tricyclic antidepressant that is used to treat depression as well as enuresis. It is widely used in medicine but not previously reported to cause a granulomatous drug eruption. Herein we report the first case, to our knowledge, of a granulomatous drug eruption associated with imipramine.

**CASE**

A 75-year-old man with a medical history of hypertension, prostate cancer, and diverticulosis presented to the dermatology clinic for consultation of a rash present on the trunk and proximal extremities for 2 months. Associated symptoms included tenderness of involved skin, but he denied pruritus. He also described chills at night, but was otherwise well. Current medications included lisinopril 30 mg/day, amlodipine 5 mg/day, hydrochlorothiazide 12.5 mg/day, imipramine 25 mg at bedtime, and aspirin 81 mg/day. He denied taking any over-the-counter vitamins or supplements. Before visiting the dermatology clinic, he had received multiple prednisone tapers. He was initially treated with prednisone 20 mg twice a day for 6 days. After the rash recurred, he was treated with 2 prednisone tapers of 80 mg tapered by 20 mg every 3 days. The rash improved with each prednisone course but quickly recurred when the drug was discontinued. He had also been given fluocinonide 0.05% cream and fluocinolone 0.01% oil with only minimal improvement. On examination, he had erythematous edematous papules coalescing into plaques with islands of sparing and fine scaling on the trunk, neck, and extremities (Fig 1, A and B). There was no intertriginous, mucosal, palm, or sole involvement. Laboratory tests were unremarkable, except for a mild elevation of erythrocyte sedimentation rate, C-reactive protein, and platelet levels. A punch biopsy was performed from the flank for further work-up.

Hematoxylin-eosin stained sections showed palisading and interstitial necrobiotic granulomatous dermatitis with neutrophils and eosinophils, without prominent interstitial mucin (Fig 2, A and B). Periodic acid-Schiff and Grocott-Gomori methenamine-silver nitrate stains were negative for pathologic fungal organisms, Gram stain was negative for bacteria, and acid-fast bacteria and Fite stains were negative for atypical mycobacteria. Alcian blue and colloidal iron stains were only patchy positive for interstitial mucin. Due to the increased eosinophils, a granulomatous drug eruption was the favored diagnosis.

Medication history revealed only 1 new medication. Patient had started daily imipramine 25 mg a few weeks before the development of the rash.
All other medications had been unchanged for years. Imipramine was discontinued; within 1 week, the rash improved, and after 2 months, the rash completely resolved. The patient was referred to allergy for possible skin testing, but skin testing was not recommended and was determined to not be needed by allergy, given that the rash resolved and never recurred after discontinuation of imipramine. In addition, he was initially given imipramine for incontinence, which had improved, and the medication was no longer necessary. One year later, the patient continues to do well without recurrence.

**DISCUSSION**

Granulomatous drug eruptions are uncommon. This group of eruptions includes interstitial granulomatous drug reaction, drug-induced granuloma annulare, and other reactions not pertinent to this case. The histologic presentation of interstitial granulomatous drug reaction (IGDR) can vary. The most common findings are a diffuse interstitial infiltrate of lymphocytes and histiocytes with scant mucin deposition. Eosinophils are present in most cases. Atypical lymphocytes have also been found in about half the cases. The histologic findings of drug-induced granuloma annulare (GA) are palisading granulomas, collagen degeneration, mucin, and a lymphohistiocytic infiltrate. Our case had both palisading and interstitial necrobiotic granulomatous dermatitis with only scant mucin, making it histologically an overlap of IGDR and drug-induced GA. However, as it had only scant mucin and many eosinophils, IGDR was favored.

IGDR can have various clinical presentations. It most commonly presents as annular plaques affecting intertriginous areas. Other previously reported presentations include erythroderma, erythema nodosum—like lesions, generalized erythematous macules and papules, and tender papules and plaques on the palms and soles. The patient in this case had tender papules and plaques.
on the trunk and extremities but sparing the palms and soles. He also had a pityriasis rubra pilaris-like presentation with islands of sparing, which has not been previously reported. There are no systemic symptoms in IGDR, although our patient complained of chills.\textsuperscript{1,3}

There is an increasing list of medications causing IGDR, including calcium channel blockers, angiotensin-converting enzyme inhibitors, lipid-lowering agents, histamine h2 receptor antagonists, furosemide, carbamazepine, anti-tumor necrosis factor agents, and tricyclic antidepressants, among others. While imipramine is a tricyclic antidepressant, it has not specifically been previously reported to cause IGDR.\textsuperscript{1}

Interestingly, angiotensin-converting enzyme inhibitors have been reported to inhibit granulomatous reactions. However, this patient developed a granulomatous reaction despite being on lisinopril for many years.\textsuperscript{4}

Diagnosis of IGDR can be challenging in patients on multiple medications, since the lag time between initiation of therapy and appearance of the rash can range from weeks to months. For this patient, the rash appeared just a few weeks after starting imipramine, simplifying our search for the culprit. He also began to develop improvement quickly after cessation of the causative medication. Treatment involves identifying and discontinuing the offending drug.\textsuperscript{1,2}

This case highlights the importance of histologic examination for the appropriate diagnosis and treatment of a diffuse eruption. The patient in this case had a 2-month history of his rash before biopsy evaluation determined the rash to be consistent with a drug eruption, which delayed his treatment. Granulomatous drug eruptions are rare and have various clinical presentations. Our case is the first known reported case of imipramine causing a granulomatous drug eruption. In addition, it was histologically distinct showing findings overlapping with IGDR and drug-induced GA.

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