

Topiramate-induced reactive granulomatous dermatitis



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INTRODUCTION

The clinicopathologic spectrum of reactive granulomatous dermatitis (RGD) includes 4 subtypes: palisaded neutrophilic and granulomatous, interstitial granulomatous, polycyclic (granuloma annulare-like), and drug-induced reactive granulomatous dermatitis (diRGD).¹ Granulomatous drug eruptions encompass the latter in addition to drug-induced variants of accelerated rheumatoid nodulosis, granuloma annulare (GA), sarcoidosis, and interstitial granulomatous drug reaction.¹⁻³ Topiramate is an anticonvulsant drug used for migraine prophylaxis. We report a case of topiramate-induced RGD with clinical and histologic features that differentiate it from the recently reported topiramate-induced granuloma annulare.⁴⁻⁶

REPORT OF A CASE

A white woman in her 60s with a history of prediabetes and migraines presented for a 5-year history of presumed GA refractory to topical steroids, minocycline, and hydroxychloroquine. Her medications included apixaban, aspirin, atorvastatin, and topiramate, 100 mg/d, which she had taken regularly over 8 years for migraine prophylaxis. Physical examination found firm, smooth, erythematous papules coalescing into interlacing and expansile annular plaques on the upper back, arms, and chest (Fig 1). Punch biopsy of the right shoulder found interstitial and palisaded granulomata composed of lymphocytes, histiocytes, and multinucleated giant cells, with a minimal increase in dermal mucin (Figs 2 and 3). Elastophagocytosis was not present.

Abbreviations used:

diRGD:	drug-induced reactive granulomatous dermatitis
GA:	granuloma annulare
RGD:	reactive granulomatous dermatitis

Clinicopathologically, her presentation was most consistent with RGD. GA, in contrast, would be distinguished histologically by more prominent mucin deposition. Laboratory workup found no evidence of underlying autoimmune, connective tissue, infectious, or lymphoproliferative disease. Her glycosylated hemoglobin level remained within prediabetic range. Chest radiography and recent mammography found no evidence of occult malignancy.

Based on isolated reports describing topiramate-induced GA,⁴⁻⁶ the patient was advised to taper topiramate over 4 weeks followed by complete discontinuation and replacement with acetaminophen as needed. Four months after topiramate discontinuation, the patient exhibited near complete resolution of her dermatitis without concurrent systemic or topical treatment (Fig 4). Clinical remission was maintained at 1-year follow-up, and a final diagnosis of topiramate-induced RGD was made.

DISCUSSION

DiRGD can present as either palisaded neutrophilic granulomatous, interstitial granulomatous, or polycyclic (granuloma annulare-like) cutaneous eruptions. Our case has many features typical of

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Fig 1. Clinical findings at presentation. Pink papules coalescing into linear serpiginous cords and expansile annular plaques with central clearing.

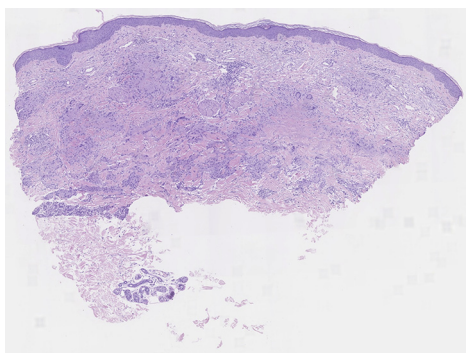


Fig 2. Histologic findings (low power). Scanning magnification shows a palisaded and interstitial lymphohistiocytic infiltrate in the dermis. (Original magnification: $\times 5$.)

RGD, including the appearance of GA-like annular plaques and histology showing an interstitial granulomatous infiltrate with scant mucin deposition, distinguishing it from classic GA. The lack of intertriginous skin involvement or the distinctive vacuolar interface change, eosinophilia, and atypical lymphocytes on histology distinguished this case from interstitial granulomatous drug reaction.¹ Moreover, the lack of a systemic disease association, unresponsiveness to standard topical and systemic therapies, and complete resolution after discontinuation of topiramate further support the diagnosis of diRGD.

The precise etiopathogenesis of RGD is unknown, but aberrant reactive immune complex deposition or medication reaction has been proposed.¹ Indeed, RGD is often linked to underlying autoimmune connective tissue disease, rheumatoid arthritis, anti-neutrophil cytoplasmic antibody-associated vasculitides, lymphoproliferative disorders, inflammatory bowel disease, and Behçet disease, among others.¹ Reported causes of diRGD continue to expand, including calcium channel blockers, β -blockers,

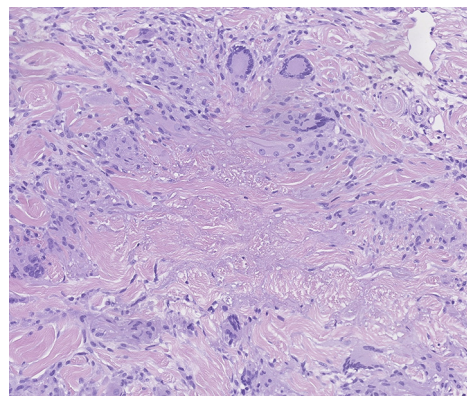


Fig 3. Histologic findings (high power). Higher power highlights a palisade of histiocytes and multinucleated giant cells surrounding a focus of necrobiosis. (Original magnification: $\times 40$.)



Fig 4. Clinical findings after discontinuation of topiramate. Four months after discontinuation of topiramate, the patient experienced near-complete resolution of dermatologic findings.

angiotensin-converting enzyme inhibitors, statins, tumor necrosis factor- α inhibitors, furosemide, and sorafenib.¹ Topiramate is an antiepileptic drug used for migraine prophylaxis and to treat bipolar disorder, eating disorders, and alcoholism. Pharmacologically, this sulfamate-modified D-fructose molecule inhibits neuronal voltage-gated sodium and calcium channels and is found to downregulate splenic monocytopoiesis.⁷ Mechanistically, we hypothesize that topiramate immunomodulation may lead to a paradoxical increase in granuloma formation as seen in our case of diRGD, akin to what is observed in paradoxical psoriasis due to tumor necrosis factor- α inhibitors.⁸

Cases of topiramate-induced GA have been reported that clinically presented with scattered papules on the lower legs,⁴ an isolated plaque of the ankle,⁵ and coin-sized annular plaques of the dorsal hands.⁶ Each case showed prominent mucin deposition histologically.⁴⁻⁶ In contrast, this case

displayed distinctive clinical and histologic features, including the lack of dermal mucin, most consistent with diRGD.

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