

# Interstitial Granulomatous Dermatitis as an Adverse Reaction to Vedolizumab

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## PRACTICE POINTS

- Reactive granulomatous dermatitis, interstitial granulomatous dermatitis (IGD) type, can occur as an adverse reaction to vedolizumab despite the minimal adverse effect profile of the medication.
- Evidence of IGD type reactions to monoclonal antibodies is accumulating; this disorder can be considered in the differential diagnosis for patients who develop a new rash when treated with an agent of this therapeutic class.

A 61-year-old woman with a medical history of ulcerative colitis (UC) developed an erythematous, mildly pruritic, maculopapular rash that was histologically consistent with reactive granulomatous dermatitis (RGD) with interstitial granulomatous dermatitis (IGD)-type features 1 week after vedolizumab infusion. Awareness of this complication is key to enhanced recognition and appropriate management as use of this medication becomes more prevalent.

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The number of monoclonal antibodies developed for therapeutic use has rapidly expanded over the last decade due to their generally favorable adverse effect (AE) profiles and efficacy.<sup>1</sup> Tumor necrosis factor  $\alpha$  inhibitors and general integrin antagonists are well-known examples of such monoclonal antibodies. Common conditions utilizing immunotherapy include

inflammatory bowel diseases (IBDs), such as Crohn disease and ulcerative colitis (UC).<sup>2</sup>

The monoclonal antibody vedolizumab, approved in 2014 for moderate to severe UC and Crohn disease, selectively antagonizes  $\alpha 4\beta 7$  integrin to target a specific population of gastrointestinal T lymphocytes, preventing their mobilization to areas of inflammation.<sup>3</sup> Adverse effects in patients treated with vedolizumab occur at a rate comparable to placebo and largely are considered nonserious<sup>4,5</sup>; the most commonly reported AE is disease exacerbation (13%–17% of patients).<sup>5,6</sup> Published reports of cutaneous AEs at administration of vedolizumab include urticaria during infusion, appearance of cutaneous manifestations characteristic of IBD, psoriasis, Henoch-Schönlein purpura, and Sweet syndrome.<sup>7-10</sup>

We present the case of a 61-year-old woman with UC who developed reactive granulomatous dermatitis (RGD), interstitial granulomatous dermatitis (IGD) type secondary to vedolizumab. This adverse reaction has not, to our knowledge, been previously reported.

## Case Report

A 61-year-old woman with a medical history of UC treated with vedolizumab and myelodysplastic syndrome treated with intravenous immunoglobulin (due to hypogammaglobulinemia following allogeneic stem cell transplantation 14 months prior) presented with a concern of a rash. The patient had been in a baseline state of health until 1 week after receiving her second dose of vedolizumab, at which time she developed a mildly pruritic maculopapular rash on the back and chest.

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Triamcinolone ointment and hydroxyzine were recommended during an initial telehealth consultation with an oncologist with minimal improvement. The rash continued to spread distally with worsening pruritus.

The patient returned to her oncologist for a routine follow-up appointment 5 days after initial teleconsultation. She reported poor oral intake due to oropharyngeal pain and a worsening rash; her husband added a report of recent onset of somnolence. She was admitted to the hospital, and intravenous fluids were administered.

At admission, the patient was hypotensive; vital signs were otherwise normal. Physical examination revealed the oropharynx was erythematous. Pink lichenoid papules coalescing into plaques were present diffusely across the trunk, arms, and legs; the hands, feet, and face were spared (Figure 1).



**FIGURE 1.** Well-defined papules coalescing into plaques on the anterior aspects of the thighs. Photograph courtesy of William Beuerlein, DO (Jacksonville, Florida).

A complete blood cell count and comprehensive metabolic panel were unremarkable. A lumbar puncture, chest radiograph, blood cultures, urinalysis, and urine cultures did not identify a clear infectious cause for the rash, though the workup for infection did raise concern about active cytomegalovirus (CMV) infection with colitis and pneumonitis. Computed tomography of the head showed no acute hemorrhage.

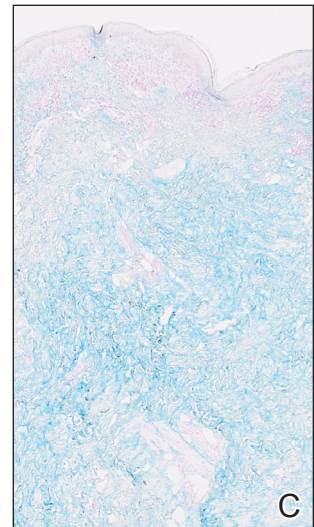
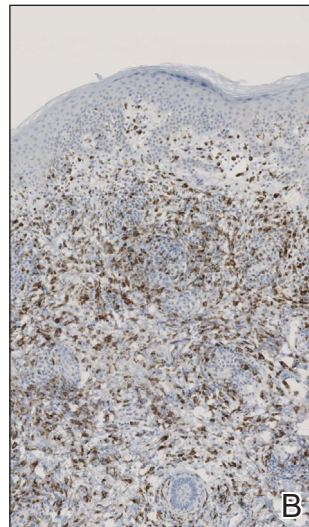
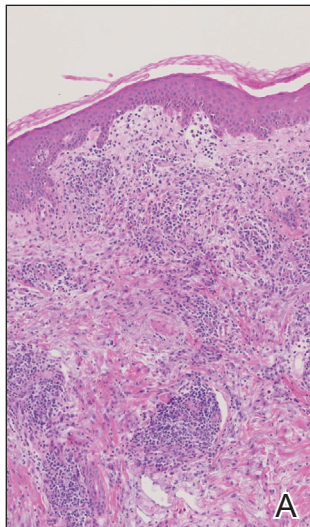
Dermatology was consulted and determined that the appearance of the rash was most consistent with a lichenoid drug eruption, likely secondary to vedolizumab that was administered 1 week before the rash onset. Analysis of a skin biopsy revealed a dense dermal histiocytic and lymphocytic infiltrate in close approximation to blood vessels, confirmed by immunohistochemical staining for CD45, CD43, CD68, CD34, c-KIT, and myeloperoxidase (Figures 2A and 2B). Colloidal iron staining of the specimen revealed no mucin (Figure 2C).

Taken together, the clinical presentation and histopathologic findings were determined to be most consistent with RGD, IGD type, with secondary vasculitis due to vedolizumab. The patient was treated with triamcinolone ointment and low-dose prednisone. Vedolizumab was discontinued. The rash resolved several weeks after cessation of vedolizumab.

## Comment

This case describes the development of RGD, IGD type, as an AE of vedolizumab for the treatment of IBD. Reactive granulomatous dermatitis encompasses a spectrum of cutaneous reactions that includes the diagnosis formerly distinctly identified as IGD.<sup>11</sup> This variety of RGD is characterized by histologic findings of heavy histiocytic inflammation in the reticular layer of the dermis with interstitial and perivascular neutrophils, lymphocytes, and histiocytes, as well as the absence of mucin. Interstitial granulomatous dermatitis-type reactions commonly are associated with autoimmune conditions and medications,

**FIGURE 2.** A, Histopathology of a punch biopsy revealed a dense dermal infiltrate of mostly chronic inflammatory cells (H&E, original magnification  $\times 400$ ). B, Histiocytes cuffed blood vessels on immunohistochemistry (CD68, original magnification  $\times 400$ ). C, There was an absence of mucin with colloidal iron stain (original magnification  $\times 4$ ). Photographs courtesy of William Beuerlein, DO (Jacksonville, Florida) and Angela Niehaus, MD (Winston-Salem, North Carolina).



with accumulating examples occurring in the setting of other biologic therapies, including the IL-6 receptor inhibitor tocilizumab; the programmed death receptor-1 inhibitor nivolumab; and the tumor necrosis factor  $\alpha$  inhibitors infliximab, etanercept, and adalimumab.<sup>12-15</sup>

Although our patient represents CMV infection while being treated with vedolizumab, the relationship between the two is unclear. Development of CMV infection while receiving vedolizumab has been reported in the literature in a patient who was concurrently immunosuppressed with azathioprine.<sup>16</sup> In contrast, vedolizumab administration has been utilized as a treatment of CMV infection in IBD patients, either alone or in combination with antiviral agents, with successful resolution of infection.<sup>17,18</sup> Additional observations of the interaction between CMV infection and vedolizumab would be required to determine if the onset of CMV infection in this patient represents an additional risk of the medication.

Identifying a relationship between a monoclonal antibody therapy, such as vedolizumab, and RGD, IGD type, might be difficult in clinical practice, particularly if this type of reaction has not been previously associated with the culprit medication. In our patient, onset of cutaneous findings in relation to dosing of vedolizumab and exclusion of other possible causes of the rash supported the decision to stop vedolizumab. However, this decision often is challenging in patients with multiple concurrent medical conditions and those whose therapeutic options are limited.

## Conclusion

Ulcerative colitis is not an uncommon condition; utilization of targeted monoclonal antibodies as a treatment strategy is expanding.<sup>2,19</sup> As implementation of vedolizumab as a targeted biologic therapy for this disease increases, additional cases of IGD might emerge with greater frequency. Because IBD and autoimmune conditions have a tendency to coincide, awareness of the reaction presented here might be particularly important for dermatologists managing cutaneous manifestations of autoimmune conditions, as patients might present with a clinical picture complicated by preexisting skin findings.<sup>20</sup> Furthermore, as reports of RGD, IGD type, in response to several monoclonal antibodies accumulate, it is prudent for all physicians to be aware of this potential complication of this class of medication so that they can make educated decisions about continuing monoclonal antibody therapy.

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