

Immediate-type infliximab infusion reaction presenting as purpura



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Key words: anti-tumor necrosis factor antibodies; infliximab; purpura; pyoderma gangrenosum and Crohn's.

INTRODUCTION

Immediate-type infliximab infusion reactions occur during or within 1 to 2 hours of an infusion and are well documented in the literature. The most common dermatologic manifestations of immediate-type infusion reactions include urticaria and erythematous rashes. We describe the case of an immediate-type infliximab infusion reaction presenting as purpura.

CASE REPORT

A 35-year-old woman with Crohn's disease and pyoderma gangrenosum presented to an outpatient dermatology clinic with a new-onset skin eruption. The reaction consisted of a purpuric eruption to her arms, abdomen, thighs, and lower legs (Fig 1). The lesions were not blanchable, pruritic, painful, or palpable according to the patient and appeared 30 to 60 minutes after completion of her 16th infliximab infusion. The eruption also recurred after her 17th and 18th infusions. The purpura would persist for 5 to 7 days until they would fade without scarring, erosion, or dyschromia. Laboratory investigations showed a normal prothrombin time/international normalized ratio and partial thromboplastin time, no evidence of thrombocytopenia, a negative antinuclear antibody value, and negative cold agglutinins. The patient was tested 7 years prior for prothrombin 20210A mutation, protein C and S deficiency, factor V Leiden deficiency, antiphospholipid antibody, anti-thrombin III, and lupus anticoagulant, which revealed no abnormalities. The patient was referred to the dermatology department after the purpuric eruptions developed. At the time of her appoint-

Abbreviation used:

TNF: tumor necrosis factor

ment, the lesions had resolved, and she had discontinued the infliximab infusions, thus a biopsy could not be performed. Images of the eruption were viewed and obtained from the patient's phone.

With regard to the patient's infusion history, she was initially started on infliximab by her gastroenterologist for treatment of a Crohn's disease flare, during which she also had pyoderma gangrenosum. She was initially started on infliximab with an induction protocol of 700 mg intravenous (IV) infusion at 0, 2, and 6 weeks. She was then maintained on a 700-mg IV infusion every 6 weeks. After her 13th infusion, the dose was increased by her gastroenterologist to a 1400-mg IV infusion, and the dosing interval was extended to every 8 weeks.

The patient experienced malaise and lightheadedness during each infusion since starting the medication. She received pretreatment with dimenhydrinate and oral steroid at each infusion, which provided improvement of these symptoms. When the purpuric eruption developed, she did not have any new systemic symptoms. The patient received 2 more infusions, after which the purpuric reaction recurred on both occasions. Slowing the infusion rate did not prevent or improve the extent of the reaction. Anti-infliximab antibody levels were measured 5 months later at greater than 20 $\mu\text{g}/\text{mL}$. The patient had been treated with infliximab for a

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Funding sources: None.

Conflicts of interest: None disclosed.

This abstract was accepted as an e-Poster at the Canadian Dermatology Association Annual Meeting June 2017.

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JAAD Case Reports 2018;4:596-8.
2352-5126

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<https://doi.org/10.1016/j.jidcr.2018.05.015>



Fig 1. Immediate-type infusion reaction to infliximab presenting as a purpuric eruption.

total of 2 years. After the purpuric eruption developed with several consecutive infusions, concerns regarding the recurrent reaction resulted in a change in therapy to adalimumab and azathioprine. The patient has not experienced any further purpuric reactions while taking adalimumab.

DISCUSSION

Infusion-related reactions to infliximab have been well documented in clinical trials and in the literature as part of postmarketing surveillance. Immediate-type infusion reactions have been described as those occurring at any time during the infusion or within 1 to 2 hours of its completion.¹ The most frequently observed immediate-type infusion reactions include pruritus, flushing, dyspnea, chest discomfort, hypertension, myalgia, nausea, urticaria, headache, erythematous rash, and dizziness.¹ In large, randomized controlled trials involving patients with inflammatory bowel disease who were treated with infliximab, immediate infusion reactions were reported in the range of 5% to 23%.¹ Most infusion reactions are mild.² In this population, the presence of antibodies to infliximab is associated with a significantly increased risk of acute infusion reactions.³ Episodic dosing has been reported as the main risk factor for the development of antibodies to infliximab,² whereas concomitant

immunosuppressive therapy may decrease the risk of antibody formation and infusion reactions.²

Several reports exist of rare dermatologic manifestations associated with infliximab, most of which are preceded by a clinical latency period after infusions have been initiated. Cutaneous vasculitis presenting as palpable purpura (80% of cases), cutaneous ulcers, nodules, and maculopapular rashes have been reported as rare adverse effects of anti-tumor necrosis factor (TNF) agents as a class. The most common type (90% of cases) is cutaneous leukocytoclastic vasculitis.^{2,4} In a study of 113 patients who had vasculitis after initiating anti-TNF therapy, infliximab was implicated in 42% of cases.⁵ Vasculitis presented as purpura in 57% of cases, was more common in women, and appeared after a mean of 38 weeks of therapy.⁵ Case reports of cutaneous vasculitis describe delayed onset of the rash, occurring more than 12 hours after anti-TNF infusion, often several days after an infusion.⁶⁻⁸ Other skin eruptions documented include necrotizing fasciitis, psoriasiform eruptions, lichenoid dermatitis, red man syndrome, eczematidlike purpura of Doucas and Kapetanakis, and eczematous rashes.⁴ The histologic manifestations of eruptions include interface dermatitis and lichenoid dermatitis.^{4,9}

Infusion reactions and dermatologic manifestations are associated with infliximab therapy and may

be a reason for discontinuing treatment for some patients. The presence of anti-infliximab antibodies, development of the reaction within 60 minutes of the infusion, predictable recurrence after successive infusions, self-resolution within 1 week, and absence of recurrence after switching to adalimumab in this case are consistent with a diagnosis of an immediate-type infusion reaction. In contrast, the eruption did not appear until the 16th infusion, suggesting a clinical latency period, and the individual lesions appeared as purpura, which are more consistent with a vasculitic process. However, the rapid onset after the infusion and predictable recurrence is inconsistent with previous documented cases of vasculitis associated with infliximab. Although rashes have been reported, the term *rash* is nonspecific, and it is important to specify the clinical presentation or histopathologic findings of the reaction and its associated time course.⁹ This case represents a unique immediate-type infliximab infusion reaction presenting as otherwise uncomplicated purpura resulting in discontinuation of infliximab therapy. The etiology is unclear at this time, although the authors postulate the reaction could have been secondary to transient platelet dysfunction.

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