

A case of rituximab-induced pyoderma gangrenosum



Jorge R. Georgakopoulos, BSc,^a Gina Rohekar, MD, FRCPC,^{a,b} and
Fiona E. Lovegrove, PhD, MD, FRCPC^{a,c}
London, Canada

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INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, chronic, ulcerative disorder of the skin. Cutaneous lesions typically progress from painful nodules or pustules into ulcers with overhanging, violaceous borders. Dating back to its first description in the early 1900s, PG is often improperly identified as an infectious process.¹ Today, PG is considered an immune-mediated process because of its close association with autoimmune conditions and favorable response to immunomodulatory drugs.

Diagnosis can be challenging because histopathology is often nonspecific. Therefore, diagnosis of PG relies on a constellation of clinical features and is ultimately a diagnosis of exclusion. Common comorbid disorders, found in approximately 50% of PG cases, include rheumatoid arthritis (RA), inflammatory bowel disease, myelodysplastic syndrome, and hematologic malignancies such as large B-cell lymphoma.^{2,3} Drug-induced PG has been described and is typically associated with interferon or granulocyte-macrophage colony-stimulating factor treatment.⁴

Here we describe a case of rituximab-induced PG that was only appropriately diagnosed and treated after several investigations and interventions that failed to identify the exact disease etiology. Drug-induced PG is exceptionally rare and poorly described, which may account for the delayed diagnosis and management in this case.⁴

CASE REPORT

A 59-year-old previously healthy woman presented to a rheumatologist for symmetrical

Abbreviations used:

PG: pyoderma gangrenosum
RA: rheumatoid arthritis

polyarthritis and a facial rash. Based on her clinical presentation and positive antinuclear antibodies (1:2560), mixed connective tissue disease with RA was diagnosed. Her symptoms were successfully controlled with methotrexate, hydroxychloroquine and low-dose prednisone. Biopsy-proven stage IVB diffuse large B-cell lymphoma was subsequently diagnosed after magnetic resonance imaging identified a psoas mass with invasion of the L1 vertebral body. After 6 rounds of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], prednisolone) followed by radiation therapy, the patient's disease was considered in remission.

Two years after completing chemotherapy and radiation treatment, the patient's rheumatologist prescribed rituximab, 2g every 6 months, for ongoing RA management. Shortly after her first infusion, a single small ulcer was noted on the posterior aspect of one leg, which resolved. Rituximab infusion at 6 months was effective and well tolerated; however, immediately after rituximab infusion at the 12-month mark, the patient had multiple perianal and labial cysts, green vaginal discharge, and a urinary tract infection.

Histopathologic evaluation of a labia minora ulcer identified squamous mucosa with extensive surface ulceration, underlying granulation tissue, and

From Schulich School of Medicine and Dentistry^a and the Department of Medicine, Division of Rheumatology,^b Western University and Lovegrove Dermatology.^c

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Correspondence to: Fiona E. Lovegrove, MD, 140 Oxford Street E, Suite 406, London, Ontario, Canada, N6A 5R9. E-mail: lovegrovederm@gmail.com.

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chronic inflammatory changes. No fungal hyphae, viral inclusions or dysplasia were noted. The patient was referred to general surgery and underwent incision and drainage of a perianal abscess. The patient also received a course of broad-spectrum antibiotics. However, her skin lesions continued to worsen. Subsequent flexible sigmoidoscopy showed nonspecific inflammatory changes and granulation tissue with no signs of malignancy. Magnetic resonance imaging showed a perianal fistula with cranial and caudal extension, indicating a small abscess. The working diagnosis at this time was lymphoma versus Crohn's disease. The patient then underwent examination under general anesthesia with incision, drainage, and debridement of the perianal ulcerative wounds. Postoperatively, the ulcerative wounds progressively worsened despite inpatient wound management. Poor wound healing was presumed to be owing to fecal contamination; as such, the patient underwent a diverting loop ileostomy. The plastic surgery department, which was consulted for wound management, performed tissue debridement and closure with skin graft, which ultimately failed. Fourteen months since their last rituximab infusion, the patient was re-admitted for worsening lesions.

The dermatology department was consulted for diagnosis and discussion of ongoing management. Examination found large full-thickness ulcers covering 30% of the bilateral buttocks surface and vulvovaginal region (Fig 1). Multiple ulcers extended into subcutaneous tissue, and wound edges were overhanging with purple-grey discoloration compared with the unaffected skin. Histopathology derived from in-patient operative procedures was reviewed by an independent dermatopathologist. This report showed "extensive ulceration of the epidermis with underlying edema of the dermis and mixed acute and chronic inflammatory cells ... slight undermining of the inflammation at the periphery of the ulcer is seen. The inflammatory infiltrate composed mainly of neutrophils, lymphocytes and rare scattered multinucleated giant cells." The overall features were nonspecific; however, PG was favoured. The diagnosis of PG was made based on the cutaneous findings, review of histopathology, medical history including RA and large B-cell lymphoma, and the rapid onset of extensive ulcers that worsened with sharp debridement. Immediate management included prednisone, 1 mg/kg orally, and gentle wound care with particular avoidance of sharp debridement.

Two weeks later the patient was discharged from the hospital with significant improvement in cutaneous lesions. Three months after their first dose of prednisone, they returned to the dermatology clinic



Fig 1. Initial visit to the dermatology office and before prednisone therapy. The figure depicts the patient lying on their left side with the upper body extending to the left and lower body to the right. Examination found large full-thickness ulcers covering 30% of the bilateral buttocks surface and vulvovaginal region with purple-grey discoloured wound edges overhanging.

with almost complete healing of all ulcers. The prednisone was tapered over approximately 3 months, and sulfasalazine was initiated as a steroid-sparing agent given the history of RA and lymphoma. Recalcitrant small ulcers on the patient's buttocks were treated with intralesional triamcinolone injection to the active borders. Because of her excellent response to treatment, the patient subsequently underwent reversal of her loop ileostomy.

DISCUSSION

We present a case of rituximab-induced PG that required consultations from multiple inpatient services, several investigations, and failed treatment before the appropriate diagnosis was made. This rare and challenging presentation of PG relied on clinical history, disease course, and cutaneous findings to correctly diagnose rituximab-induced PG. The clinical diagnosis of PG within our case aligns with the recent diagnostic criteria for classic ulcerative PG formulated by Maverakis and Shinkai.⁵ History of rapidly ulcerating lesion with ulceration occurring at sites of trauma, history of RA and large B-cell lymphoma, clinical examination of cutaneous lesions, retrospective review of the histopathology identifying neutrophilic infiltration, and rapid response to treatment formulated our diagnosis of PG. It is important to recognize that initial

morphologic findings could not conclude PG given the nonspecific findings and lack of neutrophilic infiltrate. This ultimately led to tissue manipulation and suboptimal management.

Rituximab is a monoclonal antibody targeted against the CD20 antigen found on the surface of B lymphocytes. Its use is indicated in several diseases, most notably RA and hematologic malignancies. Although rituximab is closely associated with infusion reactions, it is poorly linked with PG. A recent review of PG reported a total of 52 cases of drug-induced PG, none of which were rituximab precipitated.⁴ Rituximab-induced PG has only been reported in 4 studies with 12 cases in total.⁶⁻⁹ All reported cases were in female patients presenting with excessive vaginal discharge, several vulvovaginal ulcerations, a history of hematologic malignancy, and prior exposure to rituximab. This finding is consistent with the clinical presentation of our patient.

To date, there is no gold standard treatment for PG.¹⁰ Given our patient's complex disease presentation, high-dose prednisone at 1 mg/kg/d was initiated because of its rapidity of response. Given the chronicity of PG and our patient's significant medical history that included RA and large B-cell lymphoma, we elected to taper their prednisone and start sulfasalazine, a 5-aminosalicylic acid. This treatment regime proved very effective, and the patient continues to respond well up to 9 months after receiving their first dose of prednisone.

Drug-induced PG is a challenging diagnosis if rechallenge is not undertaken. As such, a limitation to our study includes the assumption that rituximab was the causative agent. We recognize that given the other co-morbidities of RA and B-cell lymphoma, we are unable to conclude that PG was exclusively related to rituximab administration. The diagnosis of rituximab-induced PG was based on the 2 episodes of ulcerative lesions appearing immediately after exposure to rituximab, with lesions resolving once rituximab therapy was held and treatment with systemic steroids was initiated. Based on the Naranjo Adverse Drug Reaction

Probability Scale, it was "probable" that rituximab was the causative agent (score of 5).

This case highlights many of the challenging aspects when diagnosing PG. It emphasizes the importance of having a high suspicion for PG in patients with (1) complex ulcerative lesions that progressively worsen with surgical intervention; (2) comorbid disorders including RA, inflammatory bowel disease, myelodysplastic syndrome, and hematologic malignancies; and (3) histopathology showing neutrophilic dermatosis or, more commonly, nonspecific findings requiring repeat biopsy. Furthermore, clinicians should be aware of vulvovaginal PG in female patients with prior exposure to rituximab, regardless of the duration since their last treatment. Recognizing these patterns will ideally allow for earlier diagnosis and improved patient outcomes.

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