

# Vulvovaginal pyoderma gangrenosum in association with rituximab



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**Key words:** association; pyoderma gangrenosum; rituximab; vulvovaginal.

## INTRODUCTION

Pyoderma gangrenosum (PG) is an uncommon inflammatory and ulcerative skin disease with 4 major clinical forms: ulcerative, vesicular-bullous, pustular, and superficial granulomatous/vegetative. Lesions are painful and most frequently occur on the lower extremities, although they can occur anywhere, including mucus membranes and peristomal sites. The pathophysiology of PG is speculative, but proposed mechanisms include loss of innate immune regulation or altered neutrophil chemotaxis.<sup>1</sup> Biopsies most characteristically find neutrophilia, and the concept of neutrophil dysregulation has also been supported by the clinical response that may be seen with the use of antineutrophilic agents including colchicine and dapsone.

Rituximab is a monoclonal antibody directed against the CD20 antigen on the surface of mature B cells. Rituximab was first approved for the treatment of low-grade B-cell non-Hodgkin lymphoma (NHL) in 1997 and now carries indications for chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris. In addition to its approved therapeutic indications, rituximab may be efficacious in other immunobullous dermatoses, systemic lupus erythematosus (SLE), cutaneous lupus erythematosus, chronic graft-versus-host-disease, and dermatomyositis.<sup>2</sup> To our knowledge, only a few cases of vulvovaginal PG associated with rituximab use have been reported and none within the dermatologic literature.

### Abbreviations used:

IVIG: intravenous immunoglobulin  
NHL: non-Hodgkin lymphoma  
PG: pyoderma gangrenosum  
SLE: systemic lupus erythematosus

## CASE REPORT

A 24-year-old woman was referred to the dermatology department for the evaluation of groin ulcerations. She was diagnosed with SLE 2 years prior with a history of arthritis, serositis, and pancytopenia in the context of a positive antinuclear antibody (1:2560, speckled), rheumatoid factor, and antibodies against ds-DNA, SSA, SSB, RNP, and chromatin. Her rheumatologist prescribed hydroxychloroquine, but she continued to have fevers and pleurisy. Mycophenolate mofetil was added but was presumed to be responsible for alopecia and was subsequently discontinued. Rituximab (two 1000-mg doses given 2 weeks apart) was then initiated because of persistent lupus activity. Two months after these infusions, abscesses and painful ulcerations developed in the pelvic region that expanded to involve the vaginal labium, perineum, and perianal area over the course of 2 weeks. She also had 2 fistulas, one of which communicated with the anus. These lesions were felt to represent necrotizing fasciitis, prompting multiple surgical procedures, which ultimately worsened the wounds. A diverting colostomy was created to allow for healing of the area, followed by multiple

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Funding sources: None.

Conflicts of interest: None disclosed.

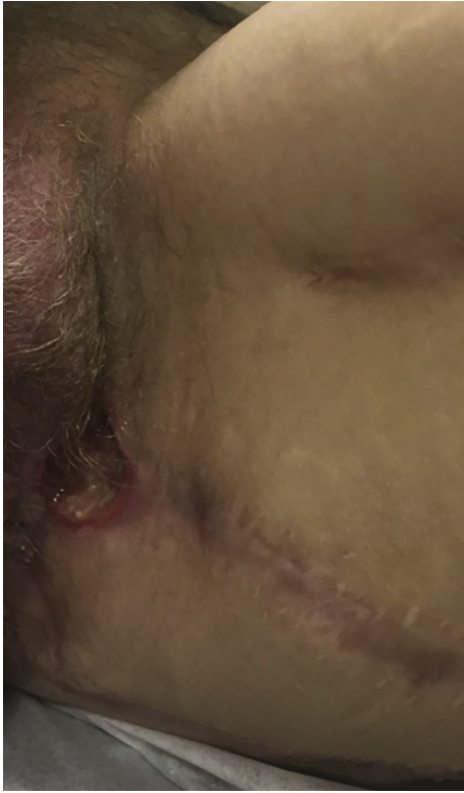
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JAAD Case Reports 2018;4:907-9.

2352-5126

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<https://doi.org/10.1016/j.jdcrr.2018.09.001>



**Fig 1.** Vulvovaginal PG. Edema and ulceration of the left labium majus.

reconstructive procedures of the perineum. She received another 1000-mg rituximab infusion for her lupus 6 months after the initial course, which was associated with dehiscence and exacerbation of the wounds.

On initial evaluation, there was edema of the labia majora with a well-demarcated ulceration on the left labium majus (Fig 1). It was tender and non-indurated. The left medial thigh had scarring from prior instrumentation/grafting. There was no oral mucosa or ocular involvement. Biopsy of the posterior vaginal wall found ulcerated mucosa with granulation tissue formation and marked acute and chronic inflammation. Biopsy of the left labium majus found ulcerated squamous mucosa with underlying acute and chronic inflammation, granulation tissue, and fibrosis; Gomori methenamine silver stains were negative. Tissue cultures of multiple lesions performed on several occasions were negative for fungi and acid-fast bacilli. Results of a colonoscopy were normal. Complete blood counts throughout her disease management consistently showed normal values for white blood count, hemoglobin, platelets, mean corpuscular volume, and differential counts; serum protein electrophoresis showed a normal pattern with no monoclonal

gammopathy; and anticyclic citrullinated peptide antibodies were negative. The clinical presentation, workup, and histopathologic findings supported the diagnosis of vulvovaginal PG, first occurring and then flaring in temporal association with the administration of rituximab. The patient was started on prednisone, 30 mg/d, cyclosporine, 3 mg/kg (titrated to 5 mg/kg) daily, tacrolimus 0.1% ointment, and silver sulfadiazine cream. All lesions healed completely, and over the course of 1 year she was able to taper off prednisone and cyclosporine, without additional flares.

## DISCUSSION

Vulvar PG has not been widely reported in the literature. According to a 2015 case series, over the last 2 decades there have only been 9 documented cases of vulvar PG that were not associated with the use of rituximab.<sup>3</sup> An additional 7 cases of rituximab-associated vulvar PG have been reported in patients with B-cell NHL,<sup>3,4</sup> and one case was reported in a patient with PR3-ANCA-positive granulomatosis with polyangiitis.<sup>5</sup> Our patient's vulvar ulcerations were also consistent with PG, in this instance associated with rituximab used for SLE management (Table 1).

Clinicians should be aware of this association, particularly when confronted with severe, refractory noninfectious genital ulcerations. The latency between initiation of rituximab and the development of PG is variable and may be quite prolonged, so recognizing the association might be difficult. The interval was 2 months in our patient; clinical details in prior reports are imprecise on this point but suggest time spans of 3 months, 1 year, and up to 10 years. Late-onset adverse reactions to rituximab (including interstitial pneumonitis and bowel obstruction/perforation) do occur and have been previously reviewed.<sup>6</sup> Moreover, rituximab has been described to induce psoriasis, with onset typically several months after initiation of therapy.<sup>7</sup>

Rituximab has also been used with success in the management of PG,<sup>8</sup> and a survey of German dermatologists reported management of PG with rituximab by respondents either often (2%) or rarely (24%).<sup>9</sup> Nevertheless, the experiences noted in our report would suggest caution using this agent for PG.

A few mechanisms have been proposed by which rituximab might contribute to development of PG. Some mechanisms posit potential effects of rituximab on neutrophil activation or maturation.<sup>3</sup> Alternatively, prolonged B-cell lymphopenia caused by rituximab may lead to a dysregulated cytotoxic T-cell response.<sup>5</sup> Oligoclonal T-cell expansion in both ulcer edges and blood of patients with PG has

**Table I.** Documented cases of rituximab associated vulvovaginal PG

Patient age (patient no.)	Initial condition treated with rituximab	Clinical findings	Management of PG	Study
51(1)	Follicular NHL	Ulceration of vulva, destruction of labia majora, extension into vagina with discharge, necrosis and hemorrhage	Prednisone and minocycline	Walsh et al <sup>4</sup>
62(2)	B-cell NHL	Ulceration of vulva with pain and discharge. Perianal irritation with mucous discharge and diarrhea.	Prednisolone and azathioprine with good response, switched to IVIG*	Selva-Nayagam et al <sup>3</sup>
50(3)	B-cell NHL	Pruritus, discomfort, pain, urinary frequency and urgency	Prednisolone, IVIG	Selva-Nayagam et al <sup>3</sup>
56(4)	B-cell NHL	Heavy discharge with development of painful ulceration of vulva and diarrhea	Prednisolone and azathioprine with no response, switched to IVIG	Selva-Nayagam et al <sup>3</sup>
60(5)	B-cell NHL	Painful urination, vaginal burning, and discharge	Prednisolone, not tolerated by patient. Switched to high dose methotrexate. <sup>†</sup>	Selva-Nayagam et al <sup>3</sup>
51(6)	B-cell NHL	Vulvar bleeding, pain, and ulceration	Prednisolone, minocycline	Selva-Nayagam et al <sup>3</sup>
74(7)	B-cell NHL, autoimmune hemolytic anemia	Ulceration of vulva with heavy discharge	Topical 10% hydrocortisone cream to vulva and intravaginally	Selva-Nayagam et al <sup>3</sup>
29(8)	PR3-ANCA—positive granulomatosis with polyangiitis	Deep vulvar and vaginal ulceration with vaginal discharge	High-dose methylprednisolone with no response, switched to IVIG	Vikse et al <sup>5</sup>
24(9)	SLE	Edema and ulceration of vulva	Prednisone, cyclosporine, tacrolimus ointment	Our patient

\*Patient had cytomegalovirus and BK virus so prednisolone and azathioprine were discontinued and patient was treated with IVIG.

<sup>†</sup>High-dose methotrexate was 30 mg/wk.

been described in the literature,<sup>10</sup> suggesting that T cells play a role in PG development, possibly through cytokine signaling or an antigenic stimulus.<sup>10</sup>

Vulvovaginal PG can greatly affect the psychosocial aspects of a patient's quality of life; however, once recognized, it can be effectively treated. When a role for rituximab is suspected, therapy with oral glucocorticoids, cyclosporine, or intravenous immunoglobulin (IVIG) may prove effective.

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