Vulvovaginal pyoderma gangrenosum associated with rituximab use in 2 patients with rheumatoid arthritis

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INTRODUCTION

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis occurring at a rate of 3-10 per million/year in the general population, with a higher frequency in women. Roughly half of the patients have an associated medical condition, with inflammatory bowel disease, hematologic disorders, and arthritis having the strongest associations.[1] Vulvovaginal involvement is exceedingly rare, with few cases reported in the literature. A recent connection between rituximab use and vulvovaginal PG has been reported, with successful treatment using immunomodulatory medications.[2-5] We report 2 patients who developed vulvovaginal PG while receiving rituximab to treat rheumatoid arthritis (RA) in the absence of any other systemic disease or underlying malignancy.

Abbreviations used:

IVIg: intravenous immunoglobulin
PG: pyoderma gangrenosum
RA: rheumatoid arthritis

CASE REPORTS

Case 1

A 67-year-old female presented with a 10-month history of exquisitely tender, suppurative vaginitis (Fig 1, *A*). She was diagnosed with seropositive RA 6 years previously, and after failing infliximab, etanercept, adalimumab, and abatacept, she had been receiving rituximab infusions and methotrexate for 3 years. Biopsies taken from multiple areas of the vagina/vulva demonstrated ulceration with granulation tissue and mixed inflammation containing many neutrophils. Aerobic and fungal cultures were negative. Initially, methotrexate was discontinued, and the patient was started on prednisone at 1 mg/kg/day. After no clinical improvement at 2 weeks, rituximab was discontinued due to concern for rituximab-associated PG, and doxycycline was added to her regimen. The patient continued to experience ulceration of the vaginal introïtus and distal vaginal canal and was then transitioned to intravenous immunoglobulin (IVIg) at a dosing regimen of 2 g/kg divided over 3 days every 4 weeks. She experienced significant improvement after the first 2 cycles, characterized by resolution of pain, complete healing of ulcerations, and only mild drainage from the vaginal introïtus (Fig 1, *B*). Her infusions were thereafter spaced out to every 8 weeks, and the patient was successfully taken off IVIg after 1 year of therapy, with gradual resolution of erythema and drainage over the course of follow-up, and the final cycle of IVIg occurring at a 12-week interval from the previous (8 total cycles) with no signs of disease rebound. She remains free of active disease after 6 months of subsequent follow-up.

Case 2

An 87-year-old female presented to our clinic with painful vaginal ulcerations lasting for 1 year, in addition to a rectovaginal fistula, which had developed several months prior to our evaluation. She had a 20-year history of seropositive RA treated with methotrexate, sulfasalazine, hydroxychloroquine, cyclosporine, adalimumab, etanercept, and abatacept. Notably, the patient had most recently been receiving rituximab infusions, starting 6 years prior

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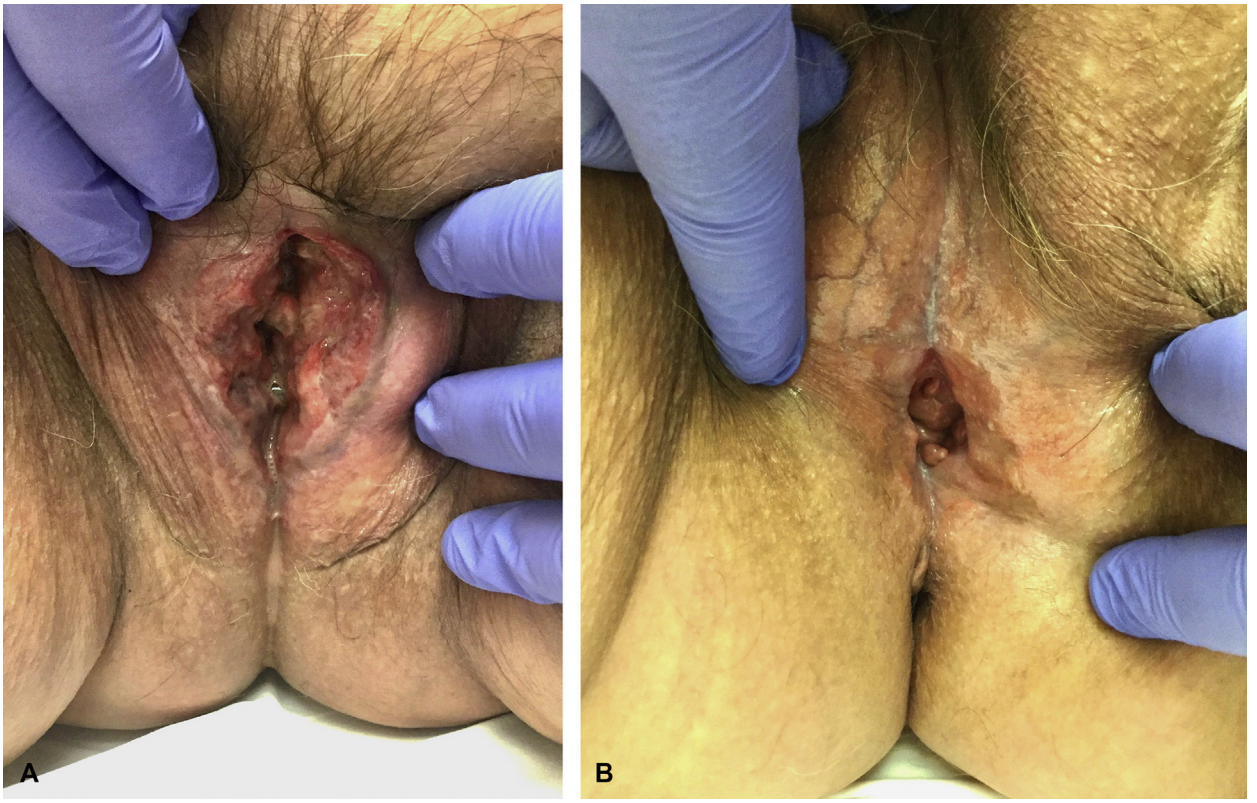

Fig 1. Patient 1: Pre- and post-treatment. **A**, Suppurative vulvovaginal pyoderma gangrenosum prior to removal of rituximab. **B**, Vulvovaginal pyoderma gangrenosum 3 months after removal of rituximab and following 2 cycles of 2 g/kg IVIg. *IVIg*, Intravenous immunoglobulin.

to her condition. A biopsy of the vaginal area demonstrated ulceration with subjacent granulation tissue containing numerous neutrophils. Stains for pathogenic microorganisms and tissue cultures were negative, as was testing for herpes simplex and varicella-zoster virus. The patient was started on a regimen of prednisone at 1 mg/kg daily and topical tacrolimus. Methotrexate was initially discontinued due to concerns of methotrexate-associated mucositis, with no subsequent improvement. After 3 months of treatment with systemic corticosteroids with only mild improvement, dapsone was added to her regimen, and rituximab was transitioned to tocilizumab for control of her RA. The patient's vaginal condition subsequently improved, characterized by healing of many ulcerations and a subjective improvement in pain at the time of last evaluation prior to her death of natural causes.

DISCUSSION

Our cases add to the existing literature regarding the association between rituximab and the unusual vulvovaginal variant of PG. To our knowledge, 9 such cases have been described.[2-5] Of these, 7 patients received rituximab for B-cell systemic non-Hodgkin lymphoma,[2,4] 1 patient for systemic lupus erythematosus,[3] and 1 patient for c-ANCA-positive granulomatosis with polyangiitis.[5] One non-Hodgkin lymphoma patient had an initial diagnosis of mixed connective tissue disease with RA but was found to have diffuse large B-cell lymphoma during further workup before initiating rituximab.[4] Therefore, our cases represent the first in association with RA in the absence of any hematologic disorder. Of note, the development of PG of any site in association with rituximab therapy has recently been demonstrated to be a statistically significant signal on the basis of 32 cases identified in the Food and Drug Administration Adverse Event Reporting System (FAERS) and published case reports describing 14 unique patients.[6] Nevertheless, an association between vulvovaginal PG and rituximab has been described in only a small subset of cases, and none exclusively in the setting of treatment of RA. PG is a diagnosis of exclusion, and our cases conform to the recent diagnostic criteria developed by the Delphi consensus.[7] Limitations of our observations include the known association of RA with

PG. However, vulvovaginal PG is an uncommon entity, and these patients experienced such significant disease response after removal of rituximab from their regimen that a correlation with rituximab is likely. These 2 cases highlight the clinical appearance of this unique entity and help dermatologists recognize this rare disease association.

Conflicts of interest

None declared.

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