Inflammatory vaginitis associated with long-term rituximab treatment in a patient with multiple sclerosis

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SUMMARY
We describe inflammatory vaginitis as a potential side effect of long-term rituximab treatment for multiple sclerosis in the absence of any other systemic disease or underlying malignancy. More studies are needed to characterise the incidence of inflammatory vaginitis among women on long-term rituximab therapy.

BACKGROUND
Rituximab, a chimeric monoclonal antibody directed against CD20 expressed on B lymphocytes and resulting in B lymphocyte depletion, has been demonstrated to reduce, the frequency of multiple sclerosis (MS) relapses and new brain lesions on MRI in patients with relapsing-remitting MS (RRMS). Rituximab has been approved since 1997 for haematological and autoimmune disorders and is commonly prescribed as an off-label treatment for MS.

Vulvovaginal pyoderma gangrenosum (PG) has been described in case reports of women with haematological and rheumatological diseases on rituximab. The clinical features of vulvovaginal PG are painful vulvar and/or perianal ulcerations. Biopsies most characteristically find neutrophilic dermatoses. The cause of PG is still not well understood, but it is generally considered to be the result of an abnormal immune response or altered neutrophil chemotaxis. Patients are treated with intravenous Ig or immunosuppressive treatment and cessation of rituximab.

A retrospective analysis from 2017 reported inflammatory vaginitis in 8 out of 263 patients on prolonged rituximab therapy for anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitis (table 1). Mean time on continuous B lymphocyte depletion was 3.5 years. Another additional treatment was not described. Rituximab withdrawal to allow B lymphocyte recovery was necessary in some patients.

Likewise, a recent retrospective case–control analysis reported the development of inflammatory vaginitis among 16 out of 454 patients on long-term rituximab treatment for autoimmune disorders (table 1). The patients were diagnosed with vasculitis 11–19 months after starting rituximab and many of the patients received additional treatment with cyclophosphamide as part of their induction protocol. With the return of B lymphocytes after discontinuation of rituximab, most women reported resolution of symptoms.

In this article, we present a premenopausal woman with MS, who developed inflammatory vaginitis while receiving rituximab to treat MS.

CASE PRESENTATION
A woman in her 20s presented with a 6-month history of severe vaginal discharge, vaginal pain, irritation and dyspareunia. The patient was diagnosed with RRMS 31 months previously. She had received five doses of rituximab, which corresponds to 30 months of B cell depletion based on a schedule of one dose every 6 months. She had not been on any other immunomodulatory treatment prior to starting rituximab and her MS was a clinically and radiologically stable. She had no history of vaginitis and there was no history of fever, abdominal or urinary symptoms. There were no prior infections, late-onset neutropenia or hypogammaglobulinaemia episodes, which are well-described side effects of rituximab therapy at the onset of vaginal symptoms. Full blood counts throughout her disease management consistently showed normal values for serum white cell count (WCC), T lymphocyte count, haemoglobin, platelets, and liver and renal function.

INVESTIGATIONS
Pelvic examination identified copious yellow-grey-coloured discharge and vaginal inflammation (erythema and irritation). The vulva skin was normal. The vaginal pH was not measured.

The examination of the vaginal fluid showed a higher number of WCCs than epithelial cells present. There were no lactobacilli present, an indicator of a suboptimal vaginal flora. The patient was tested...
negative for sexually transmitted infections (table 2). Aerobic and fungal cultures were also negative. Biopsies taken from the vagina showed spongiosis and mixed neutrophilic, lymphocytic and eosinophilic inflammation as well as focal erosions, covered by fibrin and granulocytes. Immunohistochemistry for herpes simplex and varicella-zoster viruses was negative.

TREATMENT AND OUTCOME

The patient was initially treated with metronidazole and vaginal clindamycin without any effect on her symptoms. She then received budesonide (glucocorticosteroid) foam daily with partial improvement of symptoms. Due to the severity of symptoms, rituximab was discontinued resulting in the return of circulating B cells after 5 months (from 0.0010 to 0.023 × 10^9/L, normal range 0.09–0.57 × 10^9/L). At this time, the patient reported complete resolution of symptoms.

Learning points

- Inflammatory vaginitis is a potential complication of long-term rituximab therapy.
- Women on rituximab-therapy should be screened for vaginal symptoms.

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**Table 2** List of investigations and results

| Investigation                        | Results          |
|--------------------------------------|------------------|
| Vaginal ultrasound scan              | Normal uterus and ovaries |
| Vaginal swab                         | Negative         |
| Bacterial and fungal culture/stain   | Negative         |
| Phase contrast microscopy of vaginal fluid | Increased no of WCCs, small epithelial cells without lactobacillus species. |
| Sexually transmitted infection       | Negative         |
| Varicella zoster virus                | Negative         |
| Cervical cytology screening          | Normal cells     |
| Vaginal biopsy                       | Spongiosis, mixed neutrophilic, lymphocytic, and eosinophilic inflammation and focal erosions, covered by fibrin and granulocytes. Special stains for spirochaetes, fungi and viruses are negative. |

PCR-analysis for

- Varicella Zoster virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus−1 and –2, human herpesvirus−6 to –7 and –8.
- WCC, white cell count.

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