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LETTER

Life-threatening rituximab-induced pyoderma gangrenosum successfully treated with intravenous immunoglobulin

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A 29-year-old woman with a 13 year history of proteinase-3–anti-neutrophil cytoplasmic antibody (PR3-ANCA)-positive granulomatosis with polyangiitis (GPA) was admitted to the gynaecological department with an aggravation of persistent, painful genital ulcerations initially interpreted as acyclovir-resistant genital herpes. The patient’s GPA had previously manifested as tracheal granulomas necessitating tracheostomy, but for the past 5 years, she had been in complete remission with biannual rituximab infusions (1000 mg) and low-dose prednisolone (5 mg daily). The last rituximab infusion was given 6 months before admission. Phenotyping of peripheral blood cells on admission demonstrated complete B-cell depletion.

Inspection revealed widespread, deep, and confluent ulcerations with loss of tissue affecting the vulva and vagina. The changes were extensive and consistent with pyoderma gangrenosum (PG). A polymerase chain reaction test for herpes simplex virus was negative. Biopsies revealed a non-specific, predominantly neutrophilic, inflammation without evidence of granulomas, and the condition was interpreted as PG secondary to a microangiopathy, either a rituximab-induced immune reaction or GPA itself. However, the latter was considered less likely, as PG is uncommon in GPA and serum anti-PR3 and anti-myeloperoxidase (anti-MPO) antibodies now were within normal limits. Intravenous methylprednisolone yielded some improvement. The scheduled rituximab infusion was withheld and the patient was discharged.

One week later, the patient presented with symptoms of septic peritonitis, copious vaginal discharge, and more extensive vulvovaginal ulcerations. The white blood cell count was 31.8 × 10^9/L and C-reactive protein 354 mg/L. Laparotomy revealed generalized peritonitis, fibrinous pus, and a small perforation of the terminal ileum, which was treated with a minor resection. She failed to recover on subsequent broad-spectrum antimicrobial therapy and multiple bacterial cultures were negative.

On suspicion of a vasculitic reaction, high-dose intravenous methylprednisolone was given, yielding only mild, transient improvement. Subsequently, the condition deteriorated, with type 1 respiratory failure necessitating mechanical ventilation. Bronchoalveolar lavage demonstrated sterile inflammation.

Sterile cultures and lack of response to antimicrobial treatment supported the theory of a drug-induced microangiopathy manifesting as PG. Intravenous immunoglobulin (IVIG) (2 mg/kg/day) was administered for 3 days, yielding significant clinical improvement with normalization of vital signs and increased ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2). Following gradual resolution of the vulvovaginal and pulmonary changes, the patient was extubated and discharged in complete remission.

The clinical picture in our patient was consistent with PG, probably due to an immunological reaction against rituximab. The patient’s vulvovaginal PG rapidly progressed to multiorgan involvement with inflammatory lung disease and gastrointestinal perforation.

PG is traditionally regarded as an inflammatory, ulcerative skin disorder characterized by neutrophil infiltration, representing an isolated disease entity, or accompanying other inflammatory or neoplastic diseases. The ethiopathogenesis is debated and probably multifactorial. Corticosteroids are usually regarded as the mainstay of therapy, with other immunosuppressive agents currently being investigated (1).

Clinical subtypes of PG include genital and extracutaneous PG, with the latter affecting the lungs and other solid organs (2). Rituximab-induced vulvovaginal PG has previously been observed in six patients (3). As our patient was in complete remission of her GPA, it is highly probable that the severe PG with multiorgan involvement was due to a rituximab-induced microangiopathy (leucocytoclastic vasculitis).

While infusion reaction is the most common side-effect of rituximab, various late-onset adverse events are becoming
recognized (4). Mucocutaneous ulcerations have previously been reported as leucocytoclastic vasculitis and/or PG (3, 4). The pathophysiology of late-onset adverse events of rituximab is debated. Theories include a dysregulated cytotoxic T-cell response secondary to prolonged B-cell lymphopenia (5), rituximab-induced activation of NLRP3 inflammasome (6) or neutrophils (3), or a cross-presentation of apoptotic B cells by dendritic cells causing T-cell activation with subsequent vascular damage (4).

The mechanism of action of IVIG is not fully understood, but may involve neutralization of antibodies, Fc-receptor blockade, complement inhibition, and/or regulation of B, T, and dendritic cells. In this case, the presence of pathogenic anti-rituximab antibodies was unlikely as the patient demonstrated complete B-cell depletion. Because T-cell function is not significantly influenced by rituximab, we hypothesize that the rapid and complete response indicates that IVIG may have inhibited or modulated a T-cell-dependent adverse immune reaction to rituximab (7). IVIG may thus represent an important treatment option in similar rituximab-induced PG or microangiopathic conditions.

The patient’s family has provided written, informed consent for the publication of this case report.

References

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