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Case Report

A preventable severe influenza A pneumonia after rituximab therapy for pemphigus vulgaris: a case report highlighting the critical role of vaccination

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ABSTRACT

Rituximab is an effective first-line therapy for pemphigus vulgaris (PV) but causes prolonged B-cell depletion, increasing susceptibility to infections. We report a 38-year-old man with PV who developed severe influenza A (H3) pneumonia 20 days after his second rituximab infusion, having declined influenza vaccination. Prior to rituximab, he received corticosteroids and azathioprine, but lesions persisted. Upon presentation, he experienced headache, myalgia, arthralgia, and fatigue. Laboratory tests revealed lymphopenia and elevated C-reactive protein, and a respiratory viral panel confirmed influenza A H3. Imaging showed bilateral basal infiltrates with ground-glass opacities. The patient required hospitalization, antiviral therapy with oseltamivir, antibiotics, and supplemental oxygen. He recovered without intensive care admission. This case highlights the critical importance of influenza vaccination before rituximab therapy. Vaccination should not be left to patient discretion, and rituximab should never be administered without prior immunization, especially during winter months, to prevent severe or potentially fatal influenza complications.

Keywords: Pemphigus vulgaris, Rituximab, Influenza pneumonia, Vaccination

INTRODUCTION

Pemphigus vulgaris (PV) is an autoimmune blistering disease that was once fatal before the introduction of corticosteroids and immunosuppressive agents.[1] Recent studies and updated guidelines suggest that rituximab can be an effective option as a first-line treatment in PV.[2] Rituximab is a monoclonal anti-CD 20 antibody that has significant efficacy in the treatment of PV by inducing apoptosis of pathological B lymphocytes. After rituximab treatment, B-cell levels decrease to very low levels for 6-12 months, which reduces the body's humoral immune response to foreign antigens and may lead to serious infectious complications.[1]

CASE REPORT

A 38-year-old male patient presented with oral mucosal lesions five months earlier. A biopsy performed at an external center was reported as nonspecific, and direct immunofluorescence (DIF) examination was negative. Desmoglein 1 and desmoglein 3 antibodies were also negative. In patients with initial isolated oral mucosal involvement, autoantibodies may be negative at the early stage.[3] However, due to clinical compatibility with PV the patient was started on methylprednisolone 40 mg/day and azathioprine 100 mg/day. Although the patient weighed 120 kg, a relatively low dose of methylprednisolone was initiated. When the patient presented to our clinic, lesions had spread to the scalp, nose, and back (Figure 1). Repeat biopsies from the scalp and trunk were obtained, along with DIF. Histopathological examination demonstrated suprabasal acantholysis, and DIF revealed immunoglobulin G and complement component 3 deposition, consistent with PV. Desmoglein 1 and desmoglein 3 antibodies were positive. The corticosteroid dose was increased to 0.7 mg/kg/day, and azathioprine was increased to 150 mg/day. Despite two months of this

treatment, new lesions continued to appear, and rituximab therapy was planned. Azathioprine was discontinued and corticosteroid therapy was continued. The patient had no history of comorbid diseases or regular medication use. Laboratory tests revealed normal immunoglobulin G, immunoglobulin M, and immunoglobulin A levels. However, anti-hepatitis B surface antibody and anti-hepatitis B core immunoglobulin G were positive. Following consultation with the infectious diseases department, prophylactic entecavir therapy was initiated. Influenza vaccination was recommended before treatment, but the patient declined vaccination. Twenty days after the initiation of entecavir therapy, the patient was hospitalized for rituximab administration. Complete blood count, biochemical parameters, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were within normal limits. There was no evidence of active infection. Cardiac examination was also normal. The first dose of rituximab (1 g diluted in 1000 ml of normal saline) was administered over six hours. The patient was discharged with prophylactic trimethoprim-sulfamethoxazole administered twice weekly. Two weeks later, the second dose of rituximab was administered, the patient was advised about increased susceptibility to infections and was instructed to use a mask and avoid crowded environments. The corticosteroid dose was tapered by 10 mg every four days and subsequently discontinued. The patient had received corticosteroid therapy for a total of three months. Twenty days after the second rituximab dose, the patient presented with severe headache, arthralgia, myalgia, and fatigue. The lesions associated with PV had completely resolved. He had discontinued corticosteroids three days earlier and reported that his symptoms had begun three days prior to admission. He had no cough, sputum production, chest pain, or dyspnea. Laboratory investigations revealed a CRP level of 107 mg/l and lymphopenia, while D-dimer and other hematological and biochemical parameters were within normal limits. A respiratory viral panel was positive for influenza A H3. Posteroanterior chest radiography demonstrated bilateral basal infiltrates. Thoracic computed tomography showed prominent ground-glass opacities in the basal regions (Figure 2). During follow-up, the patient's oxygen saturation dropped to the 60% range without supplemental oxygen. He was transferred to the pulmonology department. Treatment was initiated with oral oseltamivir 75 mg twice daily, intravenous moxifloxacin 400 mg once daily, intravenous piperacillin-tazobactam 4.5 g three times daily, and nasal oxygen at 2 l/min. Although influenza pneumonia was diagnosed, broad-spectrum antibiotics were also initiated based on current guideline recommendations, due to immunosuppression and suspicion of bacterial co-infection.[4] Treatment was continued for 14 days. CRP level decreased to 8 mg/l, lymphopenia resolved, oxygen requirements decreased, and oxygen saturation improved to 90% without supplemental oxygen. The patient was discharged in good condition. Written informed consent was obtained from the patient for the use of the photographs and clinical information for academic purposes.

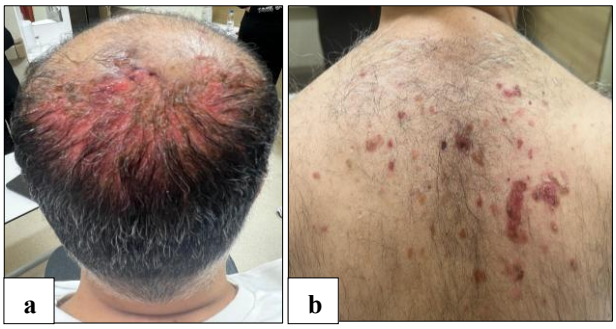

Figure 1 (a and b): Crusted ulcerative lesions on an erythematous base on the scalp and back.

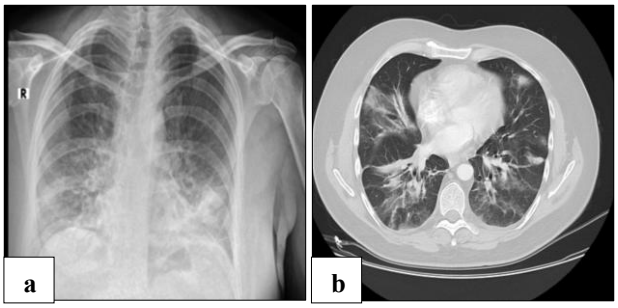

Figure 2 (a and b): Bilateral basal infiltrates on posteroanterior chest radiography, Prominent ground-glass opacities in the basal regions on thoracic computed tomography.

DISCUSSION

In general, infections are reported less frequently in patients receiving rituximab compared with those receiving conventional therapies; however, the risk of severe infection remains real and may be fatal.[2] The standardized mortality rate in rituximab-associated infections was estimated to be 22.6%.[5] In a review, 38 patients were evaluated across 24 studies, revealing a total of 46 infectious adverse events, of which 12 originated from case reports or case series.[1] Viral infections were the most frequently reported followed by fungal infections, whereas bacterial infections were associated with the highest mortality.[6] In another study, coronavirus disease 2019 (COVID-19) and cytomegalovirus infections (CMV) were the most common infections during the first 12 months after treatment, while influenza was reported in 34 of 910 patients.[7]

Influenza infection is one of the leading causes of morbidity and mortality worldwide, particularly among young children, the elderly, and immunocompromised individuals.[8] The World Health Organization recommends annual influenza vaccination for pregnant women, children aged 6 months to 5 years, older adults (≥65 years), individuals with various comorbidities, and healthcare workers.[9] In our country, the social security institution covers the cost of the influenza vaccine for individuals aged 65 years and older, as well as for certain high-risk

groups with documented chronic diseases. In some patients, as in our case, the cost of vaccination may contribute to vaccine hesitancy. Our patient could not receive the influenza vaccination because he was unable to afford the vaccine cost. Therefore, we suggest that influenza vaccination should also be covered by reimbursement, particularly for high-risk young patients receiving immunosuppressive therapies such as rituximab. Although vaccination is considered one of the most successful public health interventions, vaccine hesitancy is increasing in society. Studies investigating the underlying reasons have shown that the most common causes of vaccine hesitancy include lack of knowledge, distrust in vaccines, and the perception that vaccination is unnecessary.[10] In patients who experience vaccine hesitancy, difficulties with pre-rituximab vaccination are also likely to be encountered. Influenza cases usually peak in winter in temperate regions and more complex outbreak patterns occur in tropical and subtropical countries.[11] Influenza pneumonia is a rarely reported in rituximab therapy, but expected viral infection. Current guidelines recommend influenza vaccination two or four weeks before rituximab therapy.[12]

However, despite recommendations in the literature, some patients receive rituximab treatment without prior vaccination due to financial problems and increasing vaccine hesitancy and/or fear. This can lead to severe, and occasionally fatal, influenza pneumonia, as observed in our patient.

CONCLUSION

In conclusion, vaccination prior to rituximab therapy is essential. Influenza vaccination should be included in reimbursement programs for patients receiving immunosuppressive treatments such as rituximab, particularly for those who cannot afford the cost. Patients with vaccine hesitancy due to lack of knowledge or fear should be adequately informed about the importance of vaccination and encouraged to receive it. Additionally, it should be recognized that the risk of influenza infection may be higher following rituximab treatment, especially when administered during the winter months.

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