Rituximab successful in COVID-19 vaccine-induced refractory pemphigus vulgaris

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Abstract

Coronavirus disease 2019 (COVID-19) is the most prevalent disease in society today, and vaccination is a powerful weapon against COVID-19. However, there have been many recent reports of vaccine-induced skin side effects. Autoimmune bullous reactions caused by the COVID-19 vaccine are rare. We identified a case of refractory PV associated with COVID-19 vaccination that improved after 2 RTX injections.

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ABSTRACT: Coronavirus disease 2019 (COVID-19) is the most prevalent disease in society today, and vaccination is a powerful weapon against COVID-19. However, there have been many recent reports of vaccine-induced skin side effects. Autoimmune bullous reactions caused by the COVID-19 vaccine are rare. We identified a case of refractory PV associated with COVID-19 vaccination that improved after 2 RTX injections.

Key words: Rituximab, COVID-19 vaccine, Pemphigus vulgaris

INTRODUCTION

In March 2020, the World Health Organization declared a global pandemic as coronavirus disease 2019 (COVID-19). It has been reported that the COVID-19 vaccines may cause autoimmune bullous diseases by combining an individual's genetic predisposition state with a hyperstimulated state of the immune system.[1] Pemphigus Vulgaris (PV) is a potentially fatal antibody-mediated autoimmune vesicular skin condition that mostly involves the skin and mucous membranes. Rituximab (RTX) can reduce the cumulative dose and duration of combined glucocorticoids, with significant efficacy and good tolerance, making it the first choice for the treatment of refractory PV.[2]Here, we report a case of refractory PV following the COVID-19 vaccine, which was remission after 2 RTX infusions.

CASE PRESENTATION

A 49-year-old female patient developed a small amount of scattered erythema and blisters on the scalp 2 days following the administration of a first dose of the inactivated COVID-19 vaccine (Sinovac Life Sciences Co., Ltd.), and the blisters were easily ruptured, leaving an eroded surface. The patient did not pay attention to treatment and received a second dose of the COVID-19 vaccine a month later. Subsequently, the skin lesions gradually spread to the whole body. Cutaneous examination revealed multiple erythema and blisters on the scalp, trunk, and extremities, and erosions of the oral mucosa (Fig. 1a–d). The Pemphigus disease area index (PDAI) was 43. The patient was healthy prior to this and without a history of any autoimmunity

disease, medication, or allergy. Histopathological examination of abdominal skin revealed partial necrosis and acantholysis of the epidermis, acantholysis and villiform structures above the basal layer, small platelet infiltration of lymphocytes and histiocytes around the blood vessels in the superficial dermis, and increased individual eosinophils (HE*100) (Fig. 2a). Direct immunofluorescence showed intercellular staining of IgG antibodies (Fig. 2b). High titers of autoantibodies against Dsg1 and Dsg3 were detected in the patient's serum (160.55U/ml and 163.77U/ml, respectively; > 20U/ mL is positive). The neutrophil ratio and C-reactive protein increased slightly, but all other examinations were within normal limits.

Given this, refractory PV was diagnosed and treatment with methylprednisolone at a dose of 40 mg/day was initiated. Cutaneous lesions and the oral mucosa worsened in 2 weeks and methylprednisolone was increased to 60 mg/day. Then successively combine with azathioprine 1g/d, intravenous immunoglobulin 2g/day, and methotrexate 20mg once a week. But satisfactory disease control had not been achieved after six weeks. She adjust her treatment to methylprednisolone 60 mg/day in combination with RTX (500 mg 2 times, 2 weeks apart) after the exclusion of contraindications. This treatment resulted in all the lesions subsiding significantly in the patient's condition within two weeks (Fig. 1e–h). In addition, her blood routine reverted to normal, serum antibodies Dsg1 and Dsg3 were substantially diminished, and pemphigus PDAI score also decreased to 21. She was discharged with the same oral methylprednisolone dose of 40 mg per day.

DISCUSSION

The COVID-19 vaccines can cause a variety of skin conditions, ranging from local swelling, erythema, and delayed local hypersensitivity to generalized reactions such as pruritus, urticaria, multiforme erythema, vasculitis, and bullous disease.[3]Autoimmune bullous reactions due to COVID-19 vaccines are not routine, and only a few cases following the first, second, or third dose have been reported.[4,5]However, the association between the two has not yet been adequately explained. Different procedures such as molecular mimicry, bystander activation or epitope spreading, and inflammatory dysregulation in genetically susceptible individuals appear to be implicated in the start of autoimmunity following vaccinations.[6] Additionally, the humoral pathway through stimulation of B-lymphocytes, which results in the generation of antibodies against structural proteins, is the dominant mechanism by which inactivated vaccines provide immunity.[1]

RTX is a human-mouse chimeric monoclonal antibody against the CD20 antigen of B-lymphocytes. By facilitating mediating antibody and complement-dependent cytotoxicity, it kills or triggers apoptosis in cells and can eliminate B cells.[7] RTX was first proposed for the treatment of refractory or recurrent PV and in patients with contraindications to glucocorticoids in the early 2000s.[8] Subsequent observations in multiple studies have shown that first-line use of RTX combined with glucocorticoids in patients with moderate to severe pemphigus is more effective than prednisone alone, which can help to reduce the dose of glucocorticoids rapidly and with fewer adverse events.[9, 10]

Even while our case might be a coincidence, the temporal relationship between the condition and the COVID-19 vaccine, its rarity, the lack of any known triggers like medicines or infections, and the onset of PV case afterward suggest the potential for connection. And this may be the first instance of refractory PV brought on by effectively treating the COVID-19 vaccination with RTX. Vaccination has shown to be successful in the present fight against the new coronavirus. PV might be a significant adverse event, but we do not advise skipping the covid-19 immunization. Furthermore, more research is required to understand the COVID-19 vaccine's effects, in order to prevent these negative side effects, and maximize patient benefits.

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FIGURE 1 : (a-d) Before treatment, irregular erythema, blister, and erosion were scattered on the back, chest, scalp, and lips. (e-h) After treatment, the original skin lesions were dry and crusted, new skin and pigmentation were visible, the eroded surface of the scalp and lips healed well.

FIGURE 2 . (a) Partial necrosis and acantholysis of the epidermis, acantholysis and villiform structures above the basal layer, small platelet infiltration of lymphocytes and histiocytes around the blood vessels in the superficial dermis, and increased individual eosinophils (HE*100) ; (b) Intercellular IgG network deposition (DIF×40).