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Plasmapheresis for Facilitating Readministration of Rituximab After Paradoxical Exacerbation in Pemphigus Vulgaris: A Case Report

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ABSTRACT

Rare reports of post-rituximab exacerbation of pemphigus vulgaris (PV) have been published, with some therapeutic protocols proposed for managing this condition. A 40-year-old female with PV experienced an exacerbation of mucocutaneous lesions following rituximab administration. She failed to respond to conventional immunosuppressive agents, intravenous immunoglobulin, and ocrelizumab, so plasmapheresis was administered. Then, further doses of rituximab were prescribed, and mucocutaneous lesions improved significantly. We propose plasmapheresis as a possible treatment for post-rituximab PV exacerbation, also noting that subsequent doses of rituximab can be safe and effective.

1 | Introduction

Pemphigus is an autoimmune blistering disease that is potentially fatal and caused by autoantibodies attacking desmosomes. In pemphigus vulgaris (PV), autoantibodies attack desmogleins 1 and 3, which are responsible for cell-to-cell adhesion in the epidermis [1].

Pemphigus patients treated with rituximab are categorized into four subgroups: complete responders, partial responders, nonresponders, and paradoxical reactions. The paradoxical reaction of post-rituximab exacerbation of PV is rare [2]. Furthermore, several publications reported disease flare-ups following rituximab administration, including patients with optic neuromyelitis, ulcerative colitis, lymphomatoid papulosis, and bullous pemphigoid [3]. Aryanian et al. reported four patients out of 1245 with PV exacerbation or allergic reaction after rituximab injection (0.3%). Moreover, the rate of PV flare-up following rituximab treatment is 1.12% and 0.38% per patient and cycle of injection, respectively [4].

Several classic therapeutic regimens are suggested for managing refractory PV, such as increasing prednisolone doses, intravenous corticosteroid pulses, and intravenous immunoglobulin administration. Also, early administration of rituximab is associated with a higher chance of complete remission of PV [5]. However, the best treatment for managing a PV flare-up after rituximab injection is not elucidated. We report a refractory

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case of PV in a 40-year-old female who experienced a paradoxical exacerbation of PV after receiving rituximab. After the failure of several standard treatments, rituximab administration following plasmapheresis showed a substantial PV improvement without any allergic reaction or exacerbation.

2 | Case History

A 40-year-old female presented to the dermatology clinic with erosive lesions on the scalp and oral mucosa. She was admitted, and cutaneous biopsy and direct immunofluorescence indicated PV. She was treated with two doses of rituximab (Zytux, AryoGen Pharmed Co; 1000-mg IV infusion at Days 1 and 15), but 2 weeks later, she experienced an exacerbation and rapid spread of her cutaneous lesions to the trunk and extremities. The initial laboratory evaluations were normal, including biochemical tests and serum and urine protein electrophoresis. Notably, the levels of antidesmoglein 1 and 3 antibodies were elevated. Furthermore, imaging studies, including chest and abdominopelvic computed tomography (with and without contrast) and mammography, were all unremarkable.

3 | Methods

With a diagnosis of post-rituximab exacerbation, systemic intravenous corticosteroids (monthly pulses of methylprednisolone

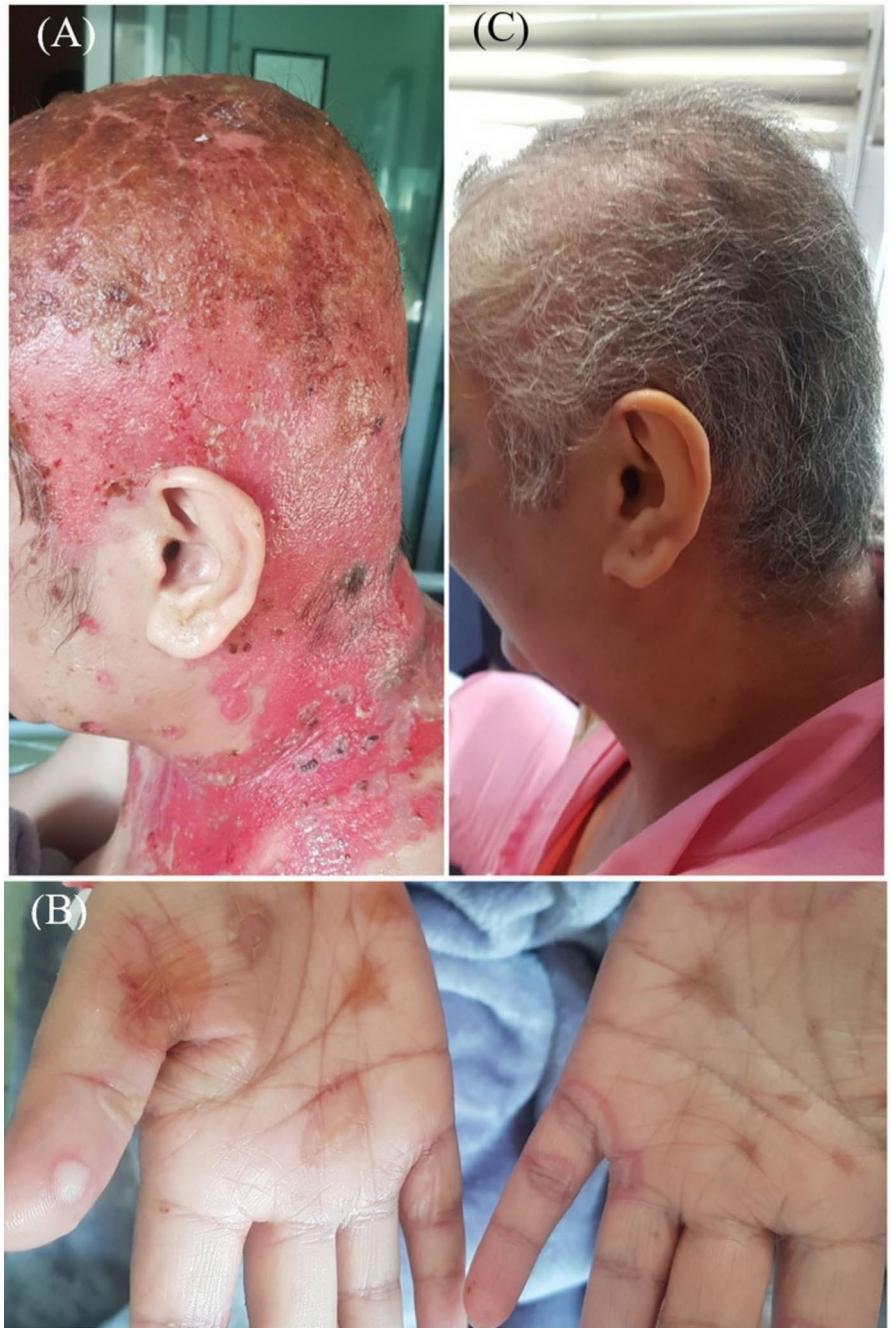

FIGURE 1 | (A, B) Exacerbation of the disease after treatment with rituximab; (C) Improvement of scalp lesions after treatment with intravenous methylprednisolone, then oral prednisolone, and mycophenolate mofetil.

1 g/day × 4 consecutive days for 3 months), oral prednisolone 40 mg/day (except for days receiving intravenous steroid) and mycophenolate mofetil 2 g/day were administered, and the cutaneous lesions improved partially (Figure 1). During treatment, she experienced an abrupt extension of a kaposi varicelliform eruption, which was treated with intravenous and oral acyclovir. Her mucocutaneous lesions of PV were controlled with this therapeutic regimen.

The medications were tapered to 5 mg/day of prednisolone and 1.5 g/day of mycophenolate mofetil during 9 months, after which she experienced a recurrence of scalp lesions. She did not respond to another course of intravenous corticosteroids and also immunoglobulin (IVIg; 400 mg/kg/day × 5 consecutive days for 2 months), so an intravenous dose of cyclophosphamide was administered. With partial improvement, oral cyclophosphamide (50 mg/day) and prednisolone were continued. Six months later, for another exacerbation of scalp and trunk lesions, she was treated with two doses of 300 mg IV ocrelizumab (Xacrel, CinnaGen Co; 2 weeks separated), showing partial improvement of trunk lesions but not scalp lesions (Figure 2). Two months later, plasmapheresis was administered in combination with oral prednisolone and cyclophosphamide. The estimated plasma volume (EPV) for plasmapheresis was calculated using

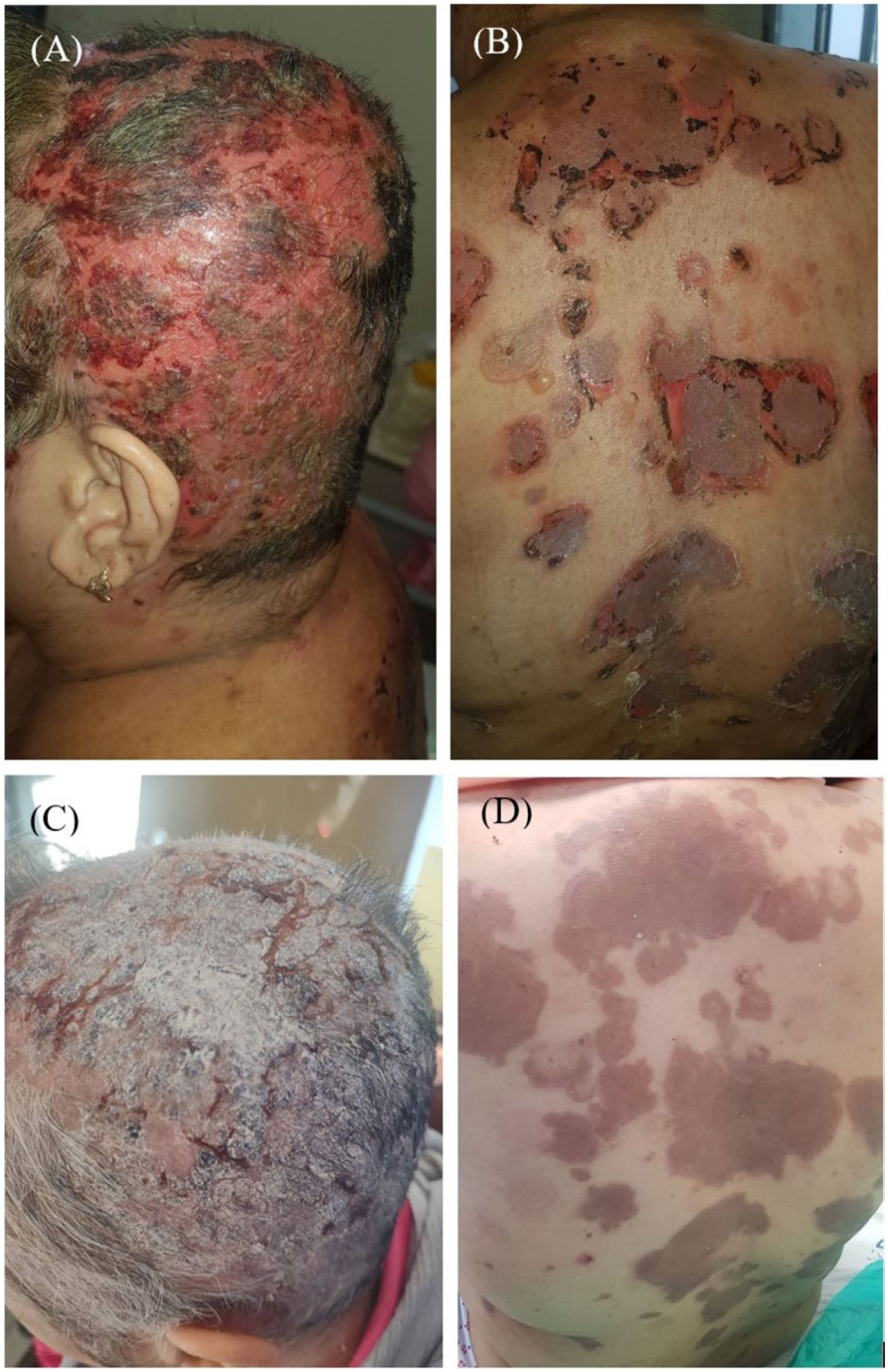

FIGURE 2 | (A, B) Recurrence of scalp and trunk lesions not responding to intravenous corticosteroids and immunoglobulin; (C, D) Partial improvement after treatment with ocrelizumab.

the formula: EPV = [0.07 × weight (kg)] × [1 − hematocrit (Hct)] [6]. Plasma removal was replaced with a mixture of isotonic saline (50% of the volume) and 20% human albumin to prevent fluid overload. Throughout the treatment, hemodynamic parameters were closely monitored, with any complications addressed immediately. The procedure involved five sessions over 10 days, scheduled on alternate days. After five sessions, the Nikolsky sign turned negative, and lesions showed significant improvement. Based on the patient's condition, plasmapheresis was repeated every 3–4 weeks for 3 months.

During her admission for the third session of plasmapheresis, she acquired COVID-19 and was admitted to the COVID-19 ward. She was treated with remdesivir and antibiotics, with cessation of all immunosuppressive medications. Interestingly, the cutaneous lesions resolved 1 month after hospitalization despite ceasing all pemphigus-related medications. In the follow-up visit, 5 months after her admission, she experienced another recurrence of scalp lesions (Figure 3A).

4 | Conclusion and Results

Due to the history of the disease exacerbation following rituximab injection, the patient was initially treated with plasmapheresis. Then, another two doses of rituximab (Zytux, AryoGen Pharmed Co, 1000-mg IV infusion at Days 1 and 15) were administered. The mucocutaneous lesions improved significantly,

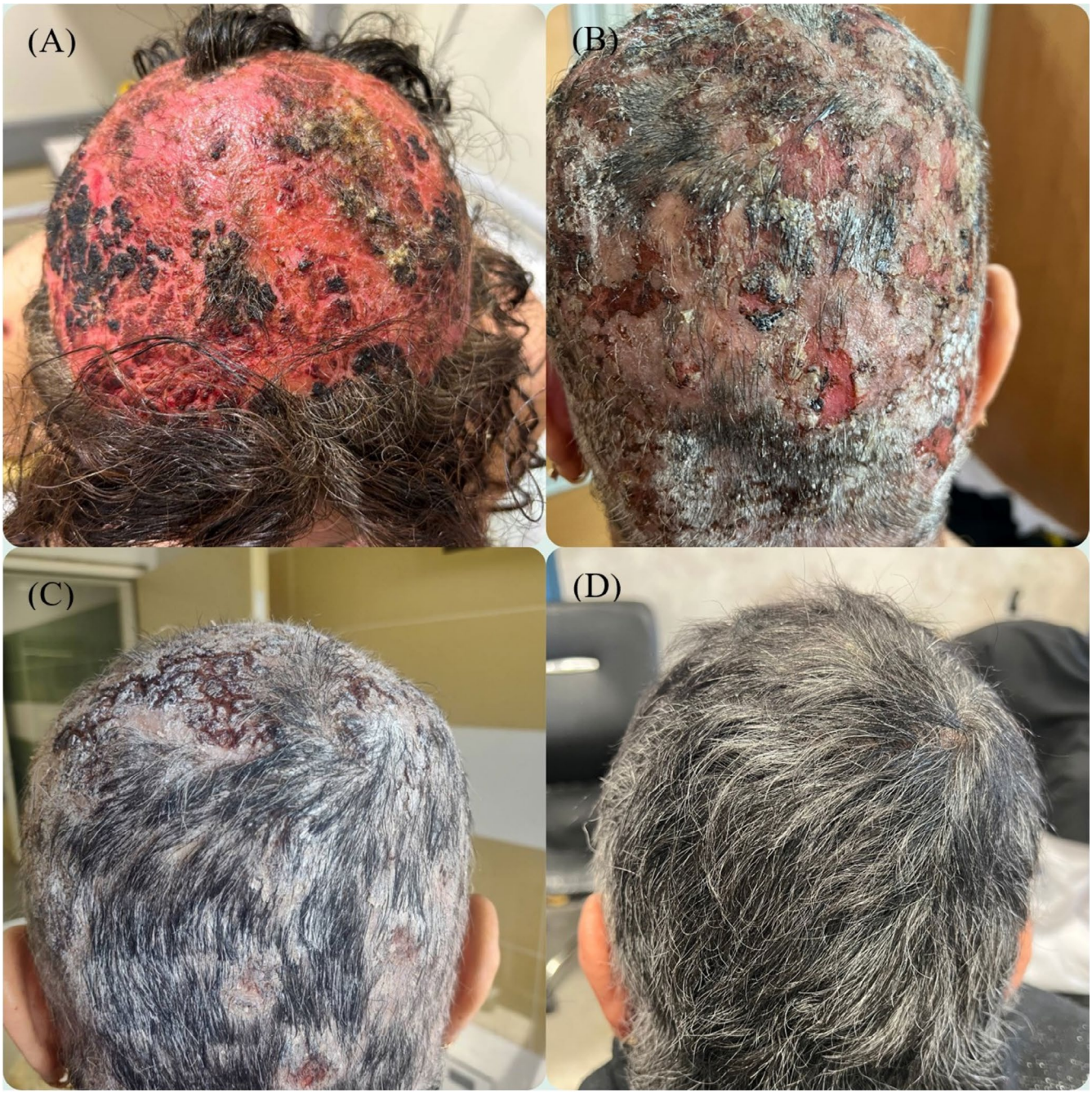

FIGURE 3 | (A) Exacerbation of scalp lesions five months after COVID-19 admission; (B–D) Substantial improvement of scalp lesions after two doses of rituximab following plasmapheresis.

and she did not experience paradoxical exacerbation or any recurrence after 6 months (Figure 3B–D). Considering the patient's history and the positive levels of antidesmoglein 1 and 3 antibodies at month 6, a maintenance dose of 500 mg rituximab was prescribed. A timeline for the course of PV and each treatment duration is depicted in Figure 4.

5 | Discussion

Rituximab substantially reduces pemphigus activity score in 1–3 months. Rituximab infusion resulted in long-term remission by eliminating autoreactive B and T cells, lowering antidesmoglein antibody levels, delaying B-cell maturation, and repopulating immature B cells [7]. Rituximab shortens the stabilization phase, minimizing the need for further steroids [8]. Rituximab is effective for treating PV, though its efficiency may be limited in areas like the gingiva and scalp. Furthermore, some patients experience disease exacerbation following rituximab injection [2]. In our case, the patient was originally treated with rituximab. Following rituximab treatment, the mucocutaneous lesions exacerbated, indicating refractory PV. In one study, the prevalence of post-rituximab exacerbation was 1.12% and 0.38% per patient and cycle [9].

Two therapeutic protocols are proposed for managing post-rituximab PV exacerbation: (1) an increase in prednisolone dosage and (2) intravenous immunoglobulin administration. Both therapeutic regimens are effective in controlling this condition [3]. Furthermore, rituximab can be administered with long-term efficacy after controlling disease exacerbation. Interestingly, post-rituximab exacerbation may not be affected by a therapeutic protocol of rituximab. Also, the presence of previous post-rituximab flare-ups does not inevitably predict exacerbation after injection of the next doses of rituximab [9]. We used plasmapheresis due to a lack of response to an increased prednisolone dose, intravenous methylprednisolone, and intravenous immunoglobulin. Our patient's lesions responded significantly to the standard dose of rituximab after plasmapheresis.

The effectiveness of plasmapheresis for the management of refractory PV has been described. For instance, in a retrospective investigation, 17 recalcitrant cases of PV to high-dose corticosteroids and immunosuppressants were treated with plasmapheresis with substantial improvement [10]. Plasmapheresis removes autoantibodies from the patient's plasma, meaning a rapid response can be achieved [11]. We used plasmapheresis for managing post-rituximab exacerbation of PV and our patient responded substantially to the subsequent doses of rituximab following plasmapheresis.

Several parameters have been proposed as risk factors for post-rituximab PV flare-up, including pemphigus disease area index (PDAI) score (> 28), antidesmoglein 1 level (> 1137 RU/mL), and frequent secondary bacterial infections [12]. In our study, the levels of antidesmoglein 1 and 3 antibodies were substantially increased. These findings may suggest measuring antidesmoglein 1 and 3 antibody levels for PV exacerbation following rituximab administration.

Unfortunately, our patient was hospitalized because of COVID-19, requiring the discontinuation of all immunosuppressive medications and the administration of remdesivir due to an elevated risk of viral sequelae. One month after admission, the patient's cutaneous lesions disappeared despite discontinuing all

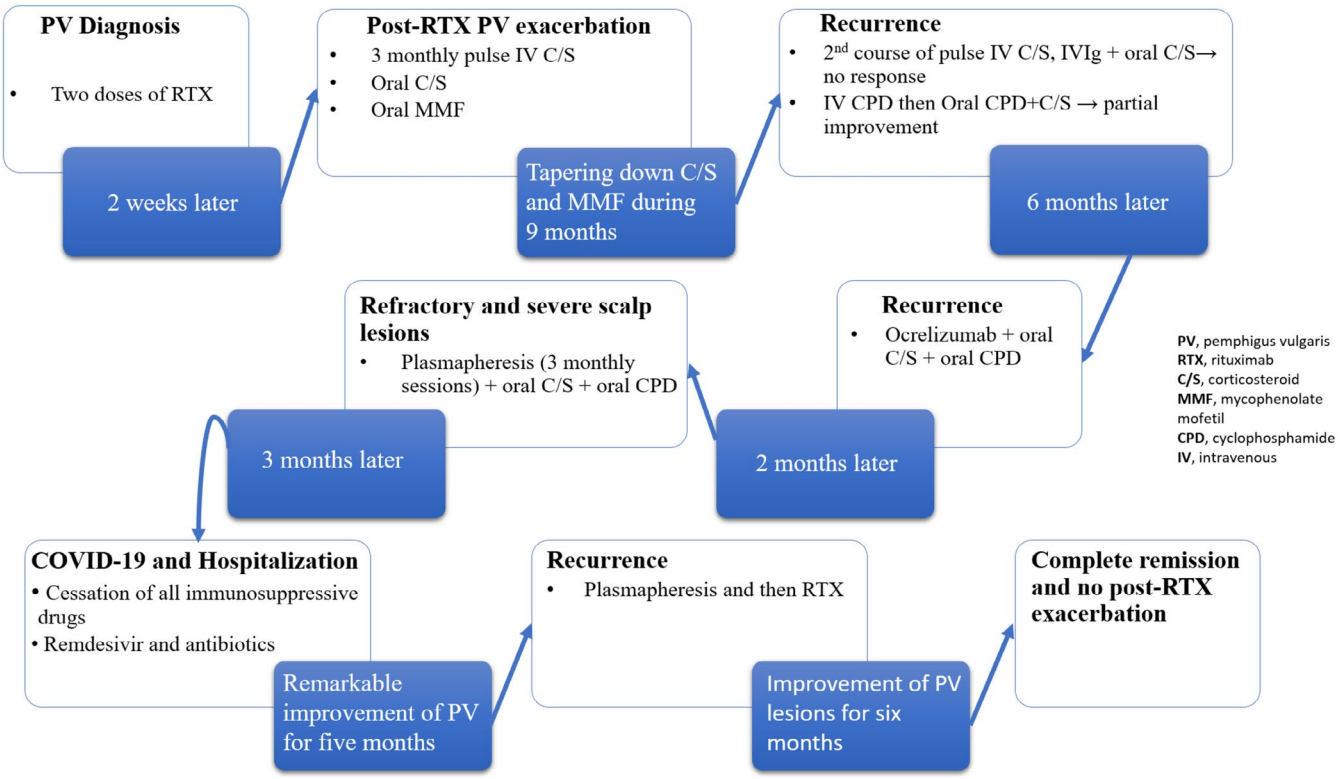

FIGURE 4 | Timeline of pemphigus vulgaris course and the therapeutic regimen that has been used.

medications linked to PV, suggesting that the immune response triggered by the viral infection may contribute to disease remission. However, delaying or discontinuing immunosuppressive therapy is likely to result in adverse clinical consequences [13]. In our case, the patient experienced another recurrence of scalp lesions after five months.

A severe course of COVID-19 is associated with decreased lymphocyte counts. Rituximab reduces the total lymphocyte count as well as the B-cell count. Therefore, during the COVID-19 era, rituximab may exacerbate COVID-19 and lead to an undesirable prognosis [14]. During the COVID-19 pandemic, PV and associated autoimmune bullous disorders were difficult to control. Rituximab and other immunomodulatory medications are crucial in bringing down PV-related mortalities [15] but raise the risk of viral infections, which can trigger a PV relapse [16]. Furthermore, it is well established that combining short-term systemic corticosteroids and rituximab is more beneficial and has fewer side effects (such as infections) than systemic corticosteroids used alone. Compared to corticosteroids alone, adding rituximab does not raise the risk of viral infections [16, 17].

In this study, we report a case of recalcitrant PV exacerbating after rituximab administration, with a good response to the combination of plasmapheresis and rituximab. We propose plasmapheresis as a possible treatment for managing post-rituximab exacerbations of PV. After controlling the condition, the subsequent doses of rituximab were safe for our patient. Nonetheless, large-scale studies are needed to confirm the efficacy of plasmapheresis in managing post-rituximab PV exacerbations.

Author Contributions

Mohammad Reza Pourani: data curation, investigation, writing – original draft. **Sayyed Mojtaba Nekooghadam:** conceptualization, investigation, supervision. **Fatemeh Samadi:** writing – original draft. **Sanaz Soleimani:** conceptualization, investigation, methodology, supervision. **Fahimeh Abdollahimajd:** conceptualization, data curation, investigation, methodology, supervision, writing – review and editing.

Ethics Statement

Ethics code: IR.SBMU.SRC.REC.1403.040.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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