ORIGINAL ARTICLE

Rituximab as First-line Therapy for Severe Pemphigus: A Case Series and Review of Current Literature

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Summary
Pemphigus refers to a group of life-threatening, autoimmune blistering disease that presents as blisters and erosions involving the skin and mucosa. Systemic corticosteroids and rituximab have been recommended as mainstay therapy for pemphigus vulgaris and pemphigus foliaceus. Herein, we report three cases of pemphigus vulgaris and a case of pemphigus foliaceus treated with rituximab as first-line therapy.

Key words: *Pemphigus, First-line, Rituximab*

Introduction
Pemphigus is a group of life-threatening, autoimmune blistering disease that presents as blisters and erosions involving the skin and mucosa. Systemic corticosteroids and other immunosuppressive drugs have traditionally been considered the mainstay of therapy. High doses and long treatment period of systemic glucocorticoids to achieve adequate clinical response may lead to serious and life-threatening side effects. We hereby report three cases of pemphigus vulgaris and a case of pemphigus foliaceus treated with rituximab, we also included an updated review of the literature.

Case Series

Case 1
SH, a previously healthy 32-year-old indigenous woman, presented with progressively worsening blisters and erosions over her body and oral mucosa for the past 3 months. Physical examination revealed multiple crusted erosions over her face, lips, neck, trunk and limbs involving 30% of her body surface area (BSA) (Figure 1 a &b). Intraoral examination revealed irregular ulcers with erythematous bases. She also suffered from physical deconditioning and muscle weakness with grade 2 sacral pressure ulcer due to prolonged immobilization prior

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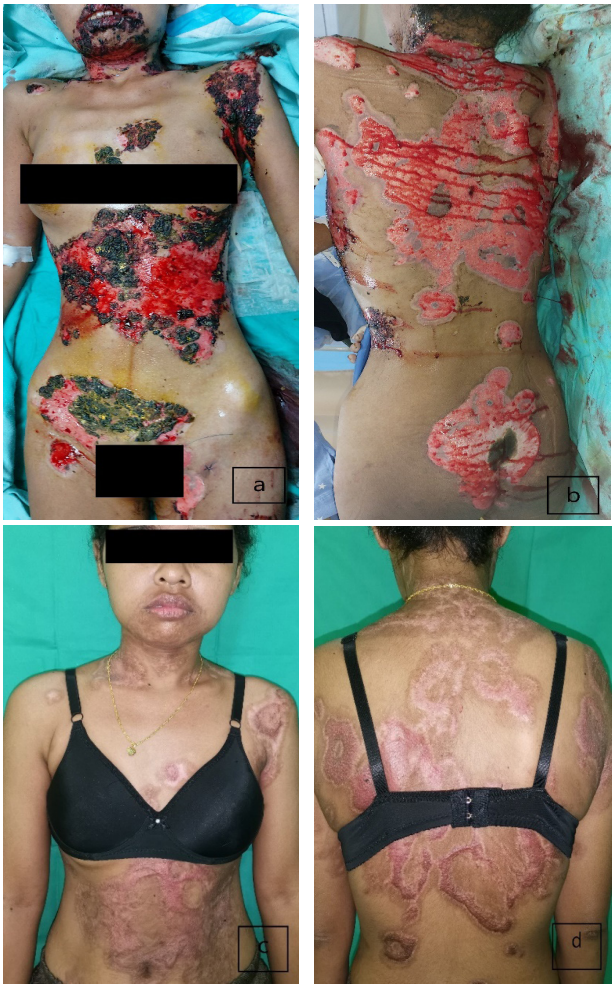
to her hospital admission. Our differential diagnoses were pemphigus vulgaris, drug-induced bullous eruption, and bullous lupus erythematosus.

Laboratory values revealed leucocytosis, hypochromic microcytic anemia, hypoalbuminemia and hypokalaemia. Histopathological examination of a perilesional skin biopsy revealed suprabasal clefting and acantholysis resembling a tombstone appearance. Direct immunofluorescence showed intercellular IgG and C3 deposition in a fishnet-like pattern. A diagnosis of pemphigus vulgaris was thus made.

Figure 1. (a & b) Clinical presentation of the patient showing multiple crusted erosions over her face, neck, trunk and limbs and **(c & d)** after three months during follow-up



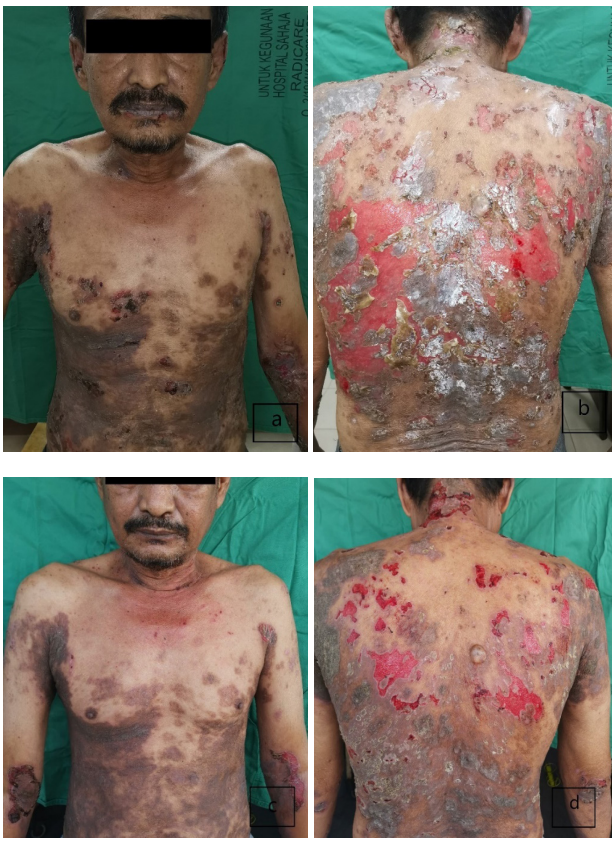
Treatment was initiated with methylprednisolone intravenously 500mg daily consecutively for 3 days, continued by hydrocortisone 100mg three times a day. However, her condition did not show significant improvement. Therefore, rituximab, a monoclonal antibody was given at 1gm intravenously for 2 infusions 15 days apart together with a lower oral prednisolone dose of 25mg daily (0.5mg/kg/day). She showed good and rapid clinical improvement and was subsequently discharged. We managed to taper her prednisolone dose fairly quickly over the next 3 months while azathioprine 50mg a day was added. After one year, her disease remained in remission without any oral or systemic medication.

Case 2

MR, a 59-year-old gentleman, diagnosed via skin biopsy with pemphigus vulgaris three years ago but who unfortunately with a history of poor treatment compliance, presented with generalized painful blisters and erosions over his skin and oral mucosa. Examination revealed multiple raw erosions with areas of peripheral crusting over his trunk and limbs, involving 20% BSA (Figure 2: a & b). There were also multiple erosive, desquamative lesions over lips, buccal mucosa and palate. Blood investigations were unremarkable apart from hypoalbuminemia. A repeat skin biopsy was not performed.

He too was treated with IV methylprednisolone 500 mg daily for three consecutive days. Subsequently, rituximab was given, due to poor clinical response, in addition to 0.5mg/kg/day oral prednisolone. He showed marked and rapid improvement over the following three days and was discharged well. He was still having mild disease activity on follow-up at 3 months and mycophenolate mofetil was added while prednisolone was quickly tapered off.

Figure 2. (a & b) Clinical presentation of the patient showing multiple crusted erosions over his trunk and limbs and **(c & d)** upon discharge at day 15



Case 3

MN, an otherwise healthy 20-year-old gentleman, presented with progressively worsening blisters and erosions all over his body for the past 3 months. Examination revealed thick-crusted erosions over his face, neck, trunk, and limbs. There was also bilateral non-cicatrizing conjunctivitis with mucopurulent discharge. Blood investigations revealed leucocytosis, normocytic normochromic anemia, hypokalaemia and hypoalbuminemia. Other laboratory values were unremarkable. Our differential diagnoses included pemphigus vulgaris, pemphigus foliaceus and drug-induced bullous eruption. Histopathological examination of an intact blister showed suprabasilar cleaving with acantholysis. Direct immunofluorescence showed intercellular deposition of IgG and C3 in a fishnet pattern. Thus, a diagnosis of pemphigus vulgaris was promptly made.

Due to the severity of his disease, he was given rituximab as first-line therapy, at 1000mg intravenously given as 2 infusions 15 days apart. He too, was discharged fairly early with 0.5mg/kg/day prednisolone and low-dose azathioprine. We managed to wean off prednisolone within 6 months and azathioprine within a year. At 18 months follow up, he remains disease-free and without any oral or topical treatment.

Case 4

ZS, a 59-year-old woman with type II diabetes mellitus, hypertension, erythrodermic psoriasis with symptomatic palmoplantar pustulosis despite methotrexate since 2018, presented with generalized raw erosions and flaccid blisters without mucosal involvement. Our differential diagnoses were pemphigus vulgaris, pemphigus foliaceus, subcorneal pustular dermatosis and generalized pustular psoriasis. Skin biopsy revealed subcorneal clefting containing acantholytic epidermal cells and occasional neutrophils. Immunofluorescence study showed intercellular IgG and C3 deposited in a fishnet-like pattern. Thus, a diagnosis of pemphigus foliaceus was made.

However, despite an initial treatment of intravenous methylprednisolone pulse of 500mg daily for three days followed by oral prednisolone 1mg/kg/day and azathioprine 150mg daily, she still suffered a severe relapse even with minimal tapering of prednisolone six months later. Rituximab was thus electively given, similar to the patients above. This time, prednisolone could be tapered off quickly within six months without azathioprine. At the time of writing 15 months later, she is in complete remission without any systemic or topical treatment whatsoever.

Discussion

Pemphigus is a heterogenous group of autoimmune, blistering, and potentially life-threatening cutaneous disorders. It is characterized by acantholysis, resulting in intraepithelial blisters in mucous membrane and the skin. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the two most common forms of pemphigus. PF is attributed to IgG autoantibodies directed desmoglein 1

(Dsg1) while autoantibodies against desmoglein 3 (Dsg3) are characteristic for mucosal PV and autoantibodies against Dsg1 and Dsg3 have been linked to mucocutaneous PV.

Treatment of pemphigus has historically been a challenge. Systemic corticosteroid is recommended as first-line treatment options for pemphigus. Adjuvant steroid-sparing immunosuppressants such as azathioprine, mycophenolate mofetil (MMF) or cyclophosphamide among others are often added for disease control. However, long-term immunosuppressive therapy especially corticosteroid can lead to serious adverse reaction. Moreover, a number of patients are also resistant to conventional therapy.

Rituximab is a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes. Hitherto, rituximab was reserved for pemphigus refractory to conventional therapies or patients who develop severe adverse reactions to conventional immunosuppressants.[1] Multiple literatures have shown that rituximab is a valuable treatment for refractory pemphigus.[2-12] Following that, European Academy of Dermatology and Venereology guideline recommends rituximab as a third-line therapy from 2015.[13]

Literatures have also reported successful experience with rituximab and corticosteroids as first-line combination therapy for pemphigus, however most of the previous studies only included a limited number of patients.[14-17] More recently, Pascal Joly *et al*, through a prospective open-label randomized trial, with a high level of evidence, has shown the clinical efficacy of rituximab as first-line agent for pemphigus.[18] Pemphigus patients were randomly assigned to receive oral prednisolone , 1.0 or 1.5mg/kg/day tapered over 12 to 18 months (prednisolone alone group) or intravenous rituximab combined with oral prednisolone, 0.5 to 1.0mg/kg/day tapered over 3 or 6 months (rituximab plus short-term prednisolone group). This is the most robust data regarding the use of rituximab as first-line agent as it shows the first-line use of rituximab plus short-term prednisolone for patients with pemphigus is more effective than using prednisolone alone, with fewer adverse events. Moreover, it shows that rituximab can be regarded as the most important advance after the arrival of corticosteroid in the treatment of pemphigus. All these had led to the recommendation of rituximab as first-line treatment in new onset moderate-to-severe pemphigus by an international panel of experts in the management of pemphigus.[19] Rituximab was also shown to be superior to MMF in producing sustained complete remission in patients with PV.[20]

The common dosing of rituximab for pemphigus were based on the lymphoma or the rheumatoid arthritis (RA) protocol. The RA protocol consists of 2 infusions of 1000mg, 2 weeks apart while the lymphoma protocol consists of 4 weekly infusions of 375mg/m2. There are also different regimen with low-dose rituximab given as 2 infusions of 500mg, 2 weeks apart with or without concomitant use of immunoadsorption or intravenous immunoglobulin.[21] However, there is still no universally accepted dosing protocol for pemphigus. The recommended course of rituximab by the international panel of experts consists of either the RA protocol or the lymphoma protocol.[19] Although some studies suggest a potential benefit of the lymphoma protocol for pemphigus, uncertainties remain regarding specific dosing modalities. In a retrospective cohort study published in 2019, lymphoma protocol was shown to be associated with higher odds of achieving complete remission off therapy (CROT) as compared to the RA protocol.[22] Another meta-analysis showed no superiority of lymphoma protocol over the RA protocol in all outcomes.[21] While other study showed superiority of the RA protocol in achieving a higher response rate.[23] Modified regimen with half the dose of conventional RA protocol has also been shown to be effective for pemphigus.[24] The RA protocol however has the advantage of lower cost compared to the lymphoma protocol.[1] The RA protocol was used in our patients with pemphigus as it was the regimen used by Pascal

Joly et al in their study (the study with the most robust data), however we did not proceed with the maintenance infusion at month 12 and 18 due to financial limitation.

Before initiating rituximab, special attention needs to be paid for possible contraindication in all patients. Rituximab is contraindicated in patients with hypersensitivity to rituximab or other murine proteins, active severe infections and severe heart failure (New York Heart Association class IV).[25] Infusion related reactions (IRR) are adverse events associated with the use of rituximab, occurring within 24hours after drug infusion. Mild to moderate IRR may include fever, skin rash, pruritus and nausea among others while more severe reactions include hypotension, angioedema, bronchospasm, hypoxia and cardiac related disorders.[26] Our patients were all given prophylaxis comprising paracetamol, chlorpheniramine and corticosteroid to prevent the occurrence of IRR. Other adverse reactions related to rituximab may include infections, hematological abnormalities and mucocutaneous reaction among others.[27,28] Fortunately, all of our patients did not suffer from any adverse reactions except for MN who suffered from bacteraemia during his complicated hospital stay.

In regards to the need of maintenance rituximab therapy, patients with high Pemphigus Disease Area Index [PDAI] score and low changes in anti-desmoglein antibody values have higher risks of relapse and may benefit from maintenance rituximab infusion at 6 months.[29] Dosing of maintenance rituximab therapy varied among different literature. An infusion of 500mg-1000mg can be repeated at 6 months or only at 12 months.[18,30,31] Besides rituximab as maintenance therapy, the use of azathioprine as maintenance therapy was shown to be beneficial in prolonging the duration of remission in patients who received rituximab as initial therapy.[32] Two of our patients with newly diagnosed PV are in remission after being put on azathioprine as maintenance therapy following rituximab as initial therapy.

Finally, concerns have been raised regarding the prolonged immunosuppressive effect of rituximab, which could last at least 6 months, especially during the ongoing novel coronavirus disease (COVID-19) pandemic.[33] Literatures have shown that rituximab therapy is associated with more severe COVID-19.[33-36] Therefore, the attending physician has to offer individualised care and take into account the severity of the disease and potential benefits or risks of prescribing rituximab therapy to patients with pemphigus. In proven cases of COVID-19, glucocorticoids, rituximab and other steroid-sparing immunosuppressive agents should be discontinued. In this setting, the administration of intravenous immunoglobulin has been proposed as a potential option for pemphigus patients with COVID-19 and flare of disease.[37] Dealing with vaccination for COVID-19, the American College of Rheumatology recommends vaccination 4 weeks prior to next scheduled rituximab cycle, and to delay rituximab 2-4 weeks after final vaccination dose if disease activity allows.[38]

Conclusion

Our local experience has shown that rituximab is an effective and safe therapy for both newly diagnosed and refractory severe pemphigus, and should be considered as a first-line treatment option.

Conflicts of Interest Declaration

The authors have no conflict of interest.

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Table 1. Literature review of rituximab as first-line therapy for pemphigus

Author, year, country	Methodology	n	Study period	RTX dosing regimen	Glucocorticoid	CAT	Conclusions
Agarwal A, et al,[14] 2018, USA	Retrospective case control study	40	1999-2015	1000mg day 0, 14. May repeat cycle after 12 months.	RTX group Total prednisolone - 177.2 mg/mo CAT group Total prednisolone - 141.3 mg/mo	+	Rituximab significantly reduces the monthly prednisolone requirement among CAT-resistant PV patients similar with CAT-responsive patients.
Ingen-Housz-Oro S,[15] et al, 2015, France	Case reports	5	-	1000mg day 0, 14 or 375mg/m2.	Topical high-potency corticosteroids	-	Concomitant use of rituximab and high-potency topical corticosteroids could be considered as treatment for PV in some patients with contraindications to use of high doses of systemic corticosteroids.
Vinay K,[16] et al, 2017, Switzerland	Retrospective study	31	2008-2016	1000mg day 0, 14.	Prednisolone 0.5-1.0 mg/kg/day	+	Complete remission off therapy was more likely to be achieved by patients receiving rituximab earlier in the disease course (<6 months) and as first-line steroid-sparing adjuvant.
Chen DM,[17] et al, 2020, France	Open-label, randomized controlled trial	36	2010-2012	1000mg day 0, 14.	Prednisolone group -1.0 to 1.5 mg/kg/day RTX plus short term prednisolone group -0.5 to 1.0 mg/kg/day	-	In patients with moderate-to-severe PV, rituximab plus short-term prednisolone was more effective than prednisolone alone with less corticosteroid exposure.
Joly P et al,[18] 2017, France	Prospective, multicentre, parallel-group, open-label, randomised trial	90	2010-2012	1000mg day 0, 14 and 500mg at months 12 and 18.	Prednisolone group -1.0 to 1.5mg/kg/day RTX plus short term prednisolone group - 0.5 to 1.0 mg/kg/day	-	First-line use of rituximab plus short-term prednisolone for patients with pemphigus is more effective than using prednisolone alone, with fewer adverse events.

RTX, rituximab; CAT, conventional adjuvant therapy; mo, months.

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