Rituximab in the management of juvenile pemphigus foliaceus

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Abstract

Background: Pemphigus foliaceus (PF) is a blistering disorder most commonly presenting in middle age. As PF is restricted to the superficial epidermis, it is considered more benign than other pemphigus diseases. However, progression to severe disease is not uncommon. Although rituximab's efficacy has been well-documented in adults with refractory PF, little data is available on its role in adolescents.

Purpose: We describe a patient with juvenile PF treated with rituximab and review the literature for similar cases.

Methods: PubMed was searched for the terms: antibody, B cells, blistering, CD20, foliaceus, juvenile, pemphigus, rituximab, immunosuppression. As the first reported case of rituximab treated pemphigus was in 2001, only cases from 2001 and after were included. Juvenile PF was defined as disease diagnosis between ages 12-17.

Results: Five cases have been reported. The indication for rituximab in most cases was refractory PF unresponsive to systemic glucocorticoids and non-steroidal adjuvant therapies. All cases demonstrated significant improvement or complete remission and most experienced no adverse events.

Conclusions: Rituximab appears to be both well tolerated and efficacious for refractory juvenile PF. Therefore, it may be considered for severe cases of PF to avoid side effects associated with conventional glucocorticoid therapy.

Keywords: antibody, B cells, blistering, CD20, foliaceus, juvenile, pemphigus, rituximab, immunosuppression

Introduction

Pemphigus foliaceus (PF) is an autoimmune disorder that is characterized by acantholysis and intraepithelial blisters [1, 2]. Although it is usually considered a relatively benign disease in the pemphigus family of blistering disorders, disease severity ranges widely and may cause considerable morbidities, including electrolyte imbalances, increased catabolism, and life-threatening loss of fluids and proteins [3].

PF classically presents in adults from the ages of 40 to 60 years old, with no gender predilection. Excluding endemic PF (fogo selvagem), which is found in North Africa, Turkey, and South America, PF occurs rarely in adolescents [4, 5]. However, occasional reports of non-endemic juvenile PF have been described [6, 7]. Given the serious morbidities that may be associated with severe PF, the occurrence of this disease in adolescents is of special concern.

The utility of systemic glucocorticoids for the initial treatment of PF has been well described [8-10]. In addition, several non-steroidal adjuvant therapies, such as azathioprine and mycophenolate, are well-accepted methods of treating PF [11]. However, the management of refractory PF is less clear and several options may be considered when selecting treatments.

Most notably, rituximab has recently been reported to be efficacious for refractory PF and its benefits in adults have been documented in several studies [12, 13]. However, little is known about the role of rituximab in the management of juvenile PF. As severe PF can have significant medical consequences in adolescents, the evaluation of treatment methods

for juvenile PF is of great interest. We present a case of refractory juvenile PF treated with rituximab and review the literature regarding juvenile PF managed with this medication.

A search of the literature revealed that the first reports of rituximab usage in pemphigus were published in 2001. Therefore, only cases of juvenile PF treated with rituximab in 2001 or later were included in this review [14, 15]. We defined juvenile PF as cases in which disease was diagnosed between the ages of 12-17.

Case Synopsis

Our patient is a 17-year-old male who presented to our clinic for evaluation of a rash that had started on his face 10 months beforehand. Prior to the onset of the rash, the patient had an ear infection, which was treated with amoxicillin. The rash was pruritic and over the course of the next 10 months, spread to involve the majority of his body.

Biopsy records from an outside facility suggested superficial pemphigus. The patient had been treated with a variety of topical steroids and systemic medications including prednisone, azathioprine 100 mg twice daily for three months and doxycycline, with continued development of new lesions.

Physical examination showed follicular pustules distributed diffusely over his body and multiple hyperpigmented, grey and violaceous crusted papules overlying pink patches on his dorsal hands and in the webspaces, on his trunk, and on his bilateral cheeks and nose, sparing the nasolabial folds (**Figure 1**).

Mineral oil scraping was negative for scabies and a 4mm punch biopsy of the right thigh was performed. Microscopic examination showed prominent epidermal acanthosis and multifocal areas of eosinophilic spongiosis within the epidermis without acantholysis or vesiculation. Lymphocytic infiltrate with occasional eosinophils was present in the superficial dermis.

Direct immunofluorescence (DIF) was positive for intercellular reaction of the epidermis with IgG and C3 but was negative for reactions with IgM, IgA, C1q, and fibrinogen. Indirect immunofluorescence studies revealed cell surface IgG antibody titers elevated at 1:10,240 on monkey esophagus and 1:2560 on intact human skin substrate. Basement membrane zone IgA and IgG antibody titers were negative. Additionally, titers of antibodies to desmoglein-1 (DSG-1) were elevated at 2225 units by ELISA studies and antibodies to desmoglein-3 (DSG-3) were negative (0 units). These results were consistent with a diagnosis of pemphigus foliaceus, with a photosensitive component based on clinical examination.

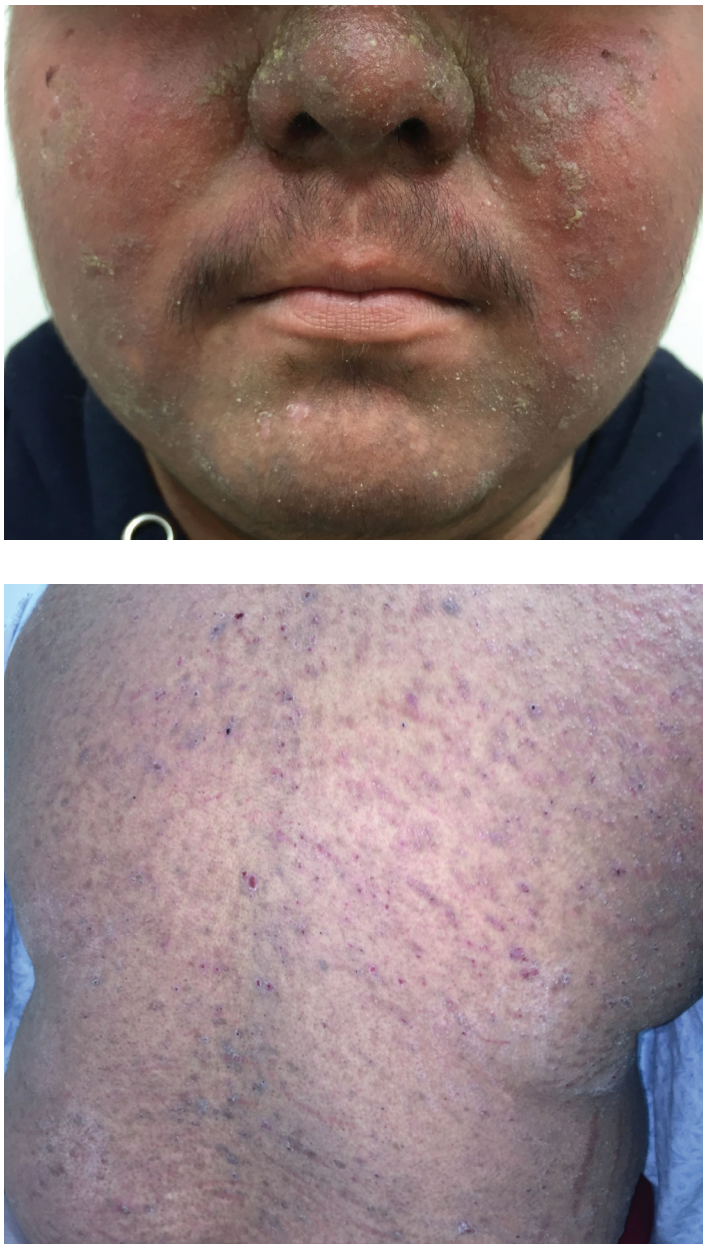

Figure 1. *The 17-year-old male presented with follicular pustules distributed diffusely over his body and multiple hyperpigmented, grey and violaceous crusted papules overlying pink patches on his bilateral cheeks and nose, sparing the nasolabial folds, trunk, and on his dorsal hands and in the web spaces.*

He was started on prednisone 60 mg daily and mycophenolate mofetil 500 mg twice daily, which were increased to 80 mg daily and 1000 mg twice daily, respectively. Sun protection as well as topical corticosteroid treatment were initiated. The patient showed some clinical response to these treatments but was unable to tolerate tapering of the prednisone without experiencing flares. In addition, he missed multiple follow up appointments and did not take mycophenolate for three weeks. He was eventually re-started on mycophenolate at a dose of 1500 mg twice daily. His disease stabilized, but over the next five months, he developed lesions with tapering of the prednisone dose. For this reason, his prednisone was increased and a decision to start rituximab treatment was made.

The patient was treated with one cycle of rituximab, consisting of two 900 mg (375 mg/m2) infusions administered 15 days apart; he was maintained on 1500 mg of mycophenolate twice daily throughout these treatments. He experienced significant improvement of his skin lesions. After his rituximab treatment, the prednisone dose was tapered down to 15 mg daily. At this dose, he developed self-healing lesions, but would flare when the prednisone was decreased below 15 mg daily. As a result, his prednisone was again increased and subsequently tapered to 15 mg daily over the next three months, without the development of any new lesions. He is currently being considered for a second cycle of rituximab.

Case Discussion

Although PF has been well described in adults, it is a rare disorder in adolescents. We conducted a comprehensive search of the literature through PubMed, and since 2001, only four other cases of juvenile PF treated with rituximab have been described [14, 15]. Our patient is the fifth reported case of juvenile PF treated with rituximab (**Table 1**).

The diagnosis of PF is made through clinical evaluation, microscopic examination, and immunologic studies. Clinically, PF is characterized by small, shallow blisters limited to the cutaneous surfaces and rarely involves the mucosa. PF usually occurs in a seborrheic distribution, and common locations include the scalp, face, and trunk. Patients may complain of pain or burning sensation with the cutaneous lesions, but systemic symptoms usually are not prominent [1, 2].

Histologically, PF is characterized by intraepithelial cleavage and acantholysis in the epidermal granular layer [1, 16]. In addition, eosinophils may be present in the superficial dermis [1, 16]. Under DIF, intercellular deposition of IgG in the superficial epidermis can be observed, and ELISA is positive for IgG antibodies to DSG-1 [17, 18].

Although PF is relatively benign compared to other pemphigus variants and often remains localized, lesions may coalesce to involve large areas of the body and can develop into an exfoliative erythroderma [2]. Given the potential for progression to life-threatening disease, treatment of PF, even in its limited stages, is usually recommended.

First-line treatment consists of systemic glucocorticoids such as prednisone or methylprednisolone, which may be pulsed or non-pulsed; studies have had varying results regarding the superior efficacy of either approach [19].

Although systemic glucocorticoids are efficacious for PF, significant long-term adverse effects are deterrents for prolonged use of these medications, especially in adolescents [20, 21]. Therefore, nonsteroidal adjuvant therapies, such as azathioprine, dapsone, and mycophenolate, may also be used [11].

In cases refractory to first-line glucocorticoids and non-steroidal agents, therapies such as cyclophosphamide, intravenous immune globulin (IVIG), and plasmapheresis have been attempted, with varying results [11]. More recently, rituximab has been used for the treatment of refractory PF and several studies have documented its efficacy in adult patients [12, 22]. However, data on the usage of this medication in juvenile PF are limited and to the best of our knowledge, the five cases described in this report constitute the largest study of rituximab usage in juvenile PF (**Table 1**).

All five cases of rituximab-treated juvenile PF occurred in males. The average age at rituximab initiation was 14 years (age range 12-17 years) and the average

Table 1. *Summary of all cases of reported juvenile PF treated with rituximab since 2001.*

Case	Age/ Sex	Disease duration (mo.) at time of rituximab initiation	Previous therapy	Indication for rituximab	Rituximab dose	Concomitant therapies	Follow up (mo.)	Adverse events	Responseb	Relapse or flare after rituximab; mo.	Pre-Rx anti-DSG-1c	Post-Rx anti-DSG-1c	Ref
1[a]	16/M	36	AZA, C, D, MTX	RD	500 mg x 2	AZA, C	20	None	CR	Y; 20	811.1	42.07	15
2[a]	13/M	36	AZA, C, D	RD, SD	500 mg x 2	AZA, C	15	None	CR	Y; 9	131.87	0.53	15
3[a]	12/M	36	C	Contrain-dication to convention-al therapy; iatrogenic Cushing	500 mg x 2	C	8	None	PR	N	1333.70	146.33	15
4	12/M	135	D	RD	300 mg x 2	AZA	12	None	CR	N	244.6	48	14
5	17/M	22	AZA, CL, DX, F, P, T	RD	375 mg/m^2 x2	MP, P	11	None	SI[d]	N/A	2225	950	C

[a] Cases 1-3 were reported to have Ikeda Severity Scores of 5, 8, and 4, respectively.

[b] Response was assessed using the criteria for partial remission and complete remission, from the consensus statement released by the International Pemphigus Committee [29].

[c] Units are U/ml unless otherwise specified.

[d] Although our patient experienced significant improvement with therapy, he did not meet criteria for partial remission [29].

AZA=azathioprine; C=corticosteroids (unspecified); CL=clobetasol; C=current report; CR=complete remission; D=dexamethasone pulse; DA=dapsone; DX=doxycycline; DSG-1=desmoglein-1; F=fluocinolone acetate; H=hydrocortisone; MPD=methylprednisolone; MP=mycophenolate; MTX=methotrexate; P=prednisone; N=no; NR=not reported; RD=refractory disease; Ref=reference; SD=severe disease; SI=significant improvement; T=triamcinolone; Y=yes

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disease duration prior to starting rituximab therapy was 53 months (range 22-135 months).

The indication for rituximab treatment was refractory disease for all cases except one, in which the patient had contraindications to conventional therapies [15]. Prior to the initiation of rituximab, the patients were treated with agents such as azathioprine, dapsone, methotrexate, and topical and systemic corticosteroids.

All patients experienced complete or near-complete resolution of PF disease activity with rituximab treatment and all cases showed significant decreases in DSG-1 titers on follow up ELISA. However, three of the five cases did eventually experience relapse, including the current reported case (average follow-up time period 13.2 months), [15]. In addition, there were no adverse events reported.

As all five cases experienced significant improvement of their PF, by both clinical and immunologic criteria, rituximab appears to be efficacious for the treatment of juvenile PF. Since most of these cases had been refractory to treatment by other immunomodulatory agents, their response to rituximab suggests that treatments specifically targeting the pathways mediated by plasma cells may be more efficacious in comparison to generalized immunosuppression [15]. This observation is consistent with the pathogenesis of PF, which involves autoantibodies targeted against DSG-1.

Additionally, rituximab's superior efficacy may relate to long-lasting B cell depletion, which has been observed to occur following rituximab treatment [23, 24]. These effects may be further compounded by rituximab's preferential reduction of autoreactive plasma cells, in comparison to other immunomodulatory agents that appear to decrease a greater proportion of pathogen-specific plasma cells [25, 26]. Although it is thought that plasma cells do not express CD20, Huang et al. [26] found that auto-reactive antibodies are produced by short-lived plasmablasts that do express CD20, in contrast to pathogen-specific antibodies that are primarily produced by long-lived plasma cells. These observations may explain why rituximab is able to preferentially reduce autoantibodies.

There is no established optimal dosing of rituximab for treatment of PF, but in adults, lymphoma dosing (375 mg/m2 once weekly for four weeks) or rheumatologic dosing (two 1000 mg infusions two weeks apart) are often used [27, 28]. As data on rituximab dosing for PF in adolescents is limited, the therapeutic guidelines for these cases are less clear. As demonstrated by the significant improvement or remission of disease in all five patients in this review, rituximab appears to be efficacious for the treatment of refractory or severe juvenile PF. However, the dosages varied widely among the participants and none used the traditional lymphoma or rheumatologic dosing methods. Thus, although rituximab has demonstrated clear efficacy in juvenile PF, more studies are indicated in order to optimize administration.

Conclusion

Although PF is less severe than other diseases in the pemphigus family, its potential for progression to severe disease and the associated complications makes this disease of particular concern in adolescents. Juvenile PF, though rare, can carry significant morbidity, especially in cases of refractory disease. Rituximab appears to be efficacious in the treatment of refractory juvenile PF and mechanisms by which rituximab exerts its efficacy may involve preferential suppression of autoreactive antibody production. However, relapses still occur with relatively high frequency after rituximab treatment, indicating that scheduled, periodic treatment with rituximab may be needed in some cases to attain sustained remission. Nevertheless, given it is well tolerated, rituximab should be considered for treatment of severe or refractory juvenile PF, as well as for patients in whom the avoidance of glucocorticoid side effects is desired.

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