Rituximab Therapy in Severe Juvenile Pemphigus Vulgaris

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Juvenile pemphigus vulgaris (PV) is a rare and often misdiagnosed condition. Although PV frequently is severe in children, a substantial portion of the morbidity and mortality associated with juvenile PV has been attributed to treatment. This report demonstrates the efficacy of rituximab therapy in juvenile PV. We report 2 cases and review the literature. Rituximab treatment was effective in helping to control 2 recalcitrant cases of juvenile PV without inducing the adverse effects associated with other adjuvant therapies. Rituximab should be considered when treating resistant cases of PV in pediatric populations to avoid the long-term side effects of other immunosuppressive treatments.

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In 1999, Bjarnason and Flosadottir[1] examined the incidence and outcomes of juvenile pemphigus vulgaris (PV) and found only 46 reported cases. Although rare and frequently misdiagnosed, this condition affects both sexes equally, with a median age of onset of 12 years. Juvenile PV develops through the same mechanism as the adult form, with autoantibodies, typically immunoglobulin G, targeting the desmosomal proteins to produce intraepithelial mucocutaneous blistering.[1] The long-term prognosis and outcomes of children with PV is unknown[1]; however, it is recognized that a substantial portion of the morbidity and mortality associated with PV is due to treatment. Therefore, it is imperative to develop safer treatment regimens, especially in pediatric cases where the adverse effects of the current therapies can have long-term implications.

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Serum transfer and knockout mice studies gave evidence to both the antibody-mediated mechanism and target antigen in PV.[2,3] Short-lived plasma cells that continuously are generated by specific memory B cells or long-lived plasma cells in the bone marrow that do not require restimulation are believed to be the source of these autoantibodies.[4,5] Current PV treatments are designed to target either the various cells involved in autoantibody production or the autoantibodies themselves.

Rituximab, a chimeric anti-CD20 monoclonal antibody that binds and depletes B cells, has been reported to be an effective treatment in adult PV.[6-13] CD20, a 33- to 37-kDa nonglycosylated transmembrane phosphoprotein, is expressed on the surface of pre–B cells, mature B cells, and many malignant B cells, but not on plasma cells or bone marrow stem cells.[14] The side effects of rituximab therapy are limited; thus, it may offer an effective and safe treatment alternative in children with PV. We discuss our experience with rituximab therapy in 2 pediatric patients with severe PV.

Case Reports

Patient 1—A 16-year-old black adolescent girl was diagnosed with PV in June 2001. She initially presented with oral lesions heralded by pain and halitosis, followed by skin erosions in the head and neck area after minor trauma. Hematoxylin and eosin staining of a skin biopsy specimen and immunofluorescence examination were diagnostic for PV. The patient was treated with intramuscular corticosteroids initially, followed by oral prednisone and mycophenolate mofetil, with continued progression and worsening of disease. She was first seen at Johns Hopkins Hospital for refractory disease in December 2001. Mycophenolate mofetil was discontinued and she was started on azathioprine. The patient showed substantial improvement with oral prednisone and azathioprine 200 mg daily. In May 2002, the patient was in remission and prednisone was tapered. Bone density and imaging studies demonstrated avascular necrosis of the hip that

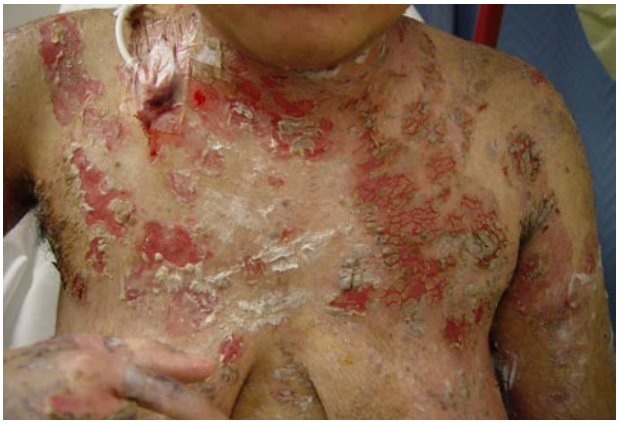

Figure 1. Flaccid and broken bullae with widespread erosions developed with failure of therapy with systemic steroids, mycophenolate mofetil, azathioprine, and intravenous immunoglobulin.

likely was secondary to systemic steroid use. The patient continued receiving azathioprine 200 mg daily, with no new lesions or adverse reactions noted.

In April 2003, the patient developed an acute flare, with recurrence of oral ulcerations spreading to her lips, scalp, and upper back following an upper respiratory tract viral infection the week prior. She was restarted on prednisone 40 mg and treated urgently with high-dose intravenous immunoglobulin (IVIG) at 2 g/kg. She received 6 courses of IVIG, with continued worsening of disease (Figure 1). Despite combined treatment with prednisone 80 mg, azathioprine 200 mg, and IVIG, she developed generalized disease with total body blistering and required emergent admission to Johns Hopkins Hospital.

Rituximab therapy was started in September 2003 at a dosage of 375 mg/m^2 weekly for 4 weeks. Immediate improvement was not seen, and more extensive lesions were noted on the trunk and extremities as well as worsening pain. For that reason, 6 cycles of plasmapheresis were given over 2 weeks in an attempt to more acutely lower antibody levels. The patient showed substantial improvement by the end of the second week.

The patient showed a slow and steady recovery over the subsequent weeks. By 6 months after rituximab treatment was initiated, the patient had only small asymptomatic lesions of the buccal mucosa. Over the next month, she began to develop new lesions in the mouth. In March 2004, she underwent another cycle of rituximab therapy at the same dosage (375 mg/m^2 weekly for 4 weeks). Following treatment, she had no new active disease. The persistent erosions on her skin continued to heal and she ultimately was completely tapered off of systemic steroids. She remained on azathioprine 200 mg daily maintenance therapy.

Patient 2—A 16-year-old black adolescent girl, previously misdiagnosed with Behçet disease after experiencing oral erosions for 2 years that responded to intermittent systemic steroids, was admitted to the outside hospital with hematemesis and severe oral lesions in March 2005. She subsequently developed bullae and vesicles on the hands, abdomen, and lower back. The patient was misdiagnosed with varicella-zoster virus, though viral culture results had been negative. Crops of lesions continued to develop despite the addition of valacyclovir and foscarnet to her therapeutic regimen. Dermatology was consulted and a biopsy and direct immunofluorescence examination were performed, with results consistent with PV (Figure 2). Prednisone 1 mg/kg daily was started and the patient was transferred to Johns Hopkins Hospital.

On arrival, the patient displayed flaccid blisters, bullae, and desquamating epithelium over most of her body (Figure 3). Examination of the oral cavity revealed erosions on the buccal mucosa, gingiva, and hard palate. The Nikolsky sign was positive. The patient required intubation and intravenous narcotics for pain control, and *Pneumocystis carinii* pneumonia prophylaxis and local wound care was initiated. Mycophenolate mofetil 40 mg/kg daily (divided dose) was added to the therapeutic regimen, with little response of her cutaneous manifestations. She received 6 cycles of plasmapheresis; on completion, she was treated with rituximab 375 mg/m^2 weekly for 4 weeks.

The patient's cutaneous lesions began to improve. She was extubated but still required substantial doses of narcotics for pain control. In June 2005, 3 weeks after receiving rituximab therapy, resolution of the patient's lesions appeared to plateau. Her CD20 cell level was zero. In July 2005, adjuvant treatment with IVIG 2 g/kg was initiated and the patient's skin again began to improve. She required less pain medication and began working with physical therapy to get out of bed after 5 months of hospitalization. The patient continued to develop a few isolated blisters on her extremities. In August 2005, mycophenolate mofetil was discontinued and azathioprine 250 mg daily was started. Two additional doses of IVIG were administered 6 and 10 weeks after her first infusion. The patient was discharged in September 2005 on azathioprine 250 mg after more than 6 months of hospitalization. She subsequently failed azathioprine therapy secondary to elevation in liver function test results; she then was managed on tapering prednisone and monthly IVIG infusions.

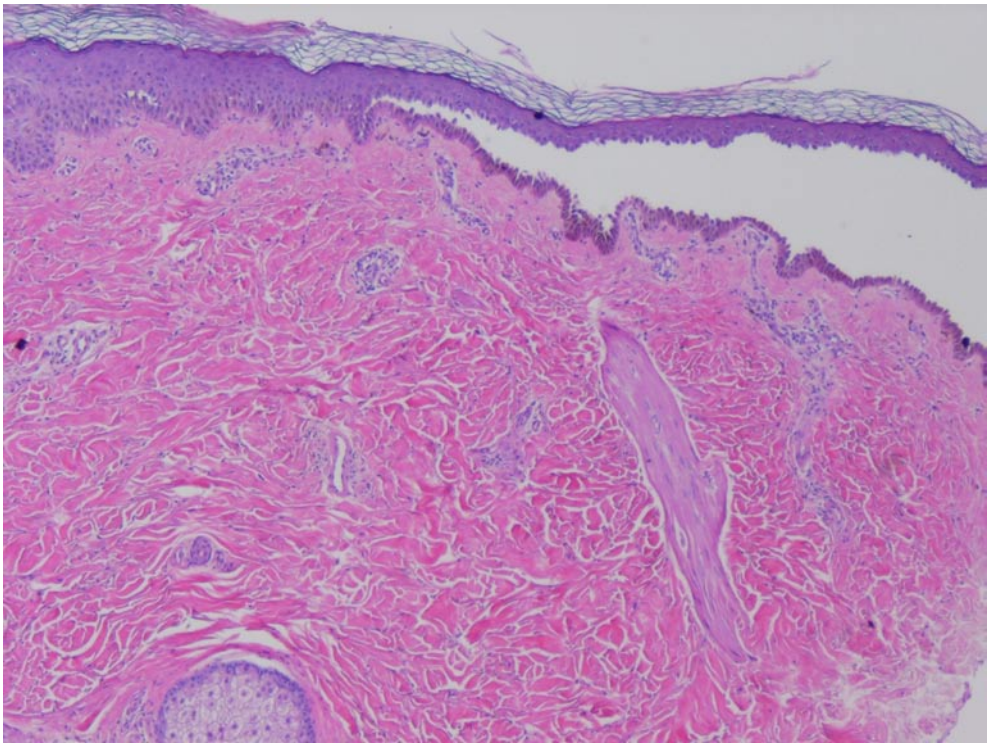

Figure 2. Suprabasilar clefting of the epidermis. The vesicle roof is intact and viable. The subjacent dermis contains a mild perivascular lymphocytic infiltrate (H&E, original magnification ×40).

Comment

Most of the current therapies for PV are immunosuppressive—they either lower autoantibody levels by targeting proliferating B and T cells or they suppress the inflammatory response induced by the antibodies.[15] Approximately 75% of patients can discontinue therapy after 10 years, which underscores the lengthy duration of immunosuppressive regimens required before remission.[16] Seventy-five percent of experts initially treat pemphigus with prednisone and 25% use adjuvant therapies such as azathioprine (44%), mycophenolate mofetil (20%), cyclophosphamide (16%), and methotrexate (8%).[17] In aggressive cases, removal of circulating autoantibodies has been accomplished only with IVIG or plasmapheresis.[18] Treatment decisions are based on the prescriber's view of efficacy as well as on the medication's side-effect profile.

Before the introduction of corticosteroids in the 1950s, the mortality of PV was 75% (likely underestimated).[15] Although systemic corticosteroids remain the mainstay of treatment, their principal side effects include diabetes mellitus, osteoporosis, adrenal suppression, peptic ulcers, weight gain, Cushing syndrome, increased susceptibility to infection, cataracts, mood changes, and myopathy. The most common side effects in children are growth retardation, Cushing syndrome, and infection.[1]

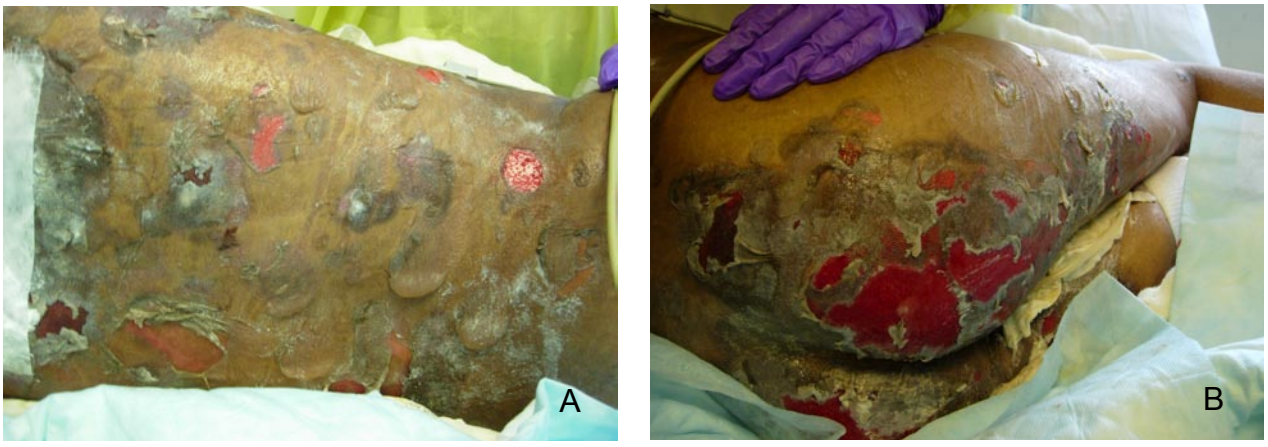

Figure 3. Large bullae and sheets of desquamating epithelium over the back (A) and buttocks (B), with extensive underlying erosions.

Our first patient developed avascular necrosis of the hip that likely was secondary to prolonged systemic steroid use.

Azathioprine is a well-established adjuvant therapy used in the treatment of PV that has been shown to have a steroid-sparing effect and remission rates of 28% to 45% in adults.[19] Azathioprine has been the most widely used adjuvant therapy in children, with 7 cases of treatment, all without side effects.[1] Oral cyclophosphamide is associated with neutropenia, alopecia, gastrointestinal tract disturbances, thrombocytopenia, increased transaminases, secondary infertility, potentially hemorrhagic cystitis, and bladder carcinoma. There are 2 reported cases of its use in children,[1] but because of its side-effect profile, it is avoided in pediatric cases.

Plasmapheresis also has been used in the treatment of PV; plasmapheresis in combination with pulse corticosteroids was reported in one case of childhood PV, with good results.[18,20] In severe adult PV, repeated large-volume plasmapheresis substituted with immunoglobulin-free albumin solutions followed by subsequent high-dose cyclophosphamide and low-dose immunosuppressive agents for several months were effective in treating the disease.[21] According to Euler et al,[21] the rationale behind this approach was to induce proliferation of pathogenic clones by clearing the circulating immunoglobulin, followed by partial deletion of the clones by maximal pulse immunosuppression.

In 1997, rituximab was approved by the US Food and Drug Administration for treatment of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin lymphoma. Its efficacy also has been reported in a number of autoimmune diseases including refractory idiopathic thrombocytopenic purpura, myasthenia gravis, and Wegener granulomatosis.[22] In pediatric populations, rituximab use in adolescents with systemic lupus erythematosus showed improvements in disease markers and symptoms.[23] Reports of rituximab in children with autoimmune thrombocytopenia and/or hemolytic anemia and lymphoproliferative disorders after organ transplantation also have appeared in the literature.[24]

Reports of rituximab use in PV, like other adjuvant therapies, have been limited to case reports. In all cases, the dosage was the same as that of the standard lymphoma protocol, 375 mg/m^2 once weekly for 4 doses, and all patients were adults. In its first reported use, rituximab resulted in partial remission of refractory PV in a 30-year-old woman.[13] One patient with disease involving 70% body surface area had complete clearing for 40 weeks after rituximab administration.[8] Other groups reported clinical improvement within 1 to 2 weeks of rituximab treatment in patients with refractory pemphigus[7,9,11] and complete remission in one patient 3 months after therapy was discontinued.[10]

Our treatment regimen was based on the approach by Euler et al[21] to substitute rituximab for cyclophosphamide after plasmapheresis. The use of rituximab in our patients, however, did not lead to as dramatic a response as that reported among adults. In fact, our patients required additional therapy to control their disease.

There are some unique characteristics in our patients that may account for these differences. First, most of the adults studied already were on an immunosuppressive regimen prior to beginning rituximab therapy. Therefore, these patients already possessed decreased levels of autoimmunity prior to initiating treatment. Although our first patient was receiving azathioprine at the time she received rituximab, our second patient had only just begun prednisone and mycophenolate mofetil, and she had not had a sufficient amount of time to see a therapeutic response. Therefore, she required additional immunosuppressive adjuvant therapy compared with the first case.

Second, the rarity of PV in children often results in delayed diagnosis and recognition only after a more advanced clinical presentation. Studies have demonstrated that serum levels of pemphigus autoantibodies correlate with the clinical disease activity.[2,25] Our second patient presented with severe disease, suggesting that her autoantibody levels were higher than those seen in the typical adult case. Although rituximab can induce potent immunosuppression by targeting B cells, as indicated by the CD20 cell count in our second patient, only IVIG and plasmapheresis can remove the circulating pathogenic immunoglobulin. In this regard, IVIG is safer, with a better side-effect profile.

The adverse effects of rituximab are limited. Concern mostly has focused on the risk of infection with prolonged B-cell suppression; one case of a child developing meningitis after treatment has been reported.[26] Replacement IVIG has been used prophylactically in rituximab-treated infants and when immunoglobulin G levels fell below reference range in older children.[27] Our patients were receiving prophylactic antibiotics as well as aggressive wound care during treatment. Additionally, our second patient was given adjuvant IVIG after her rituximab infusion. Other reported adverse reactions include fever and chills, nausea, pruritus, bronchospasm, and dyspnea, which typically present during the first infusion.[22] Most of these adverse reactions respond to slower infusion rates or temporarily halting the infusion. Premedication with acetaminophen and

an antihistamine is recommended to prevent or minimize adverse reactions.[28] Rare side effects include neutropenia, interstitial pneumonitis, bronchospasm, and angina pectoris.[29] One patient in a 3 PV patient series did develop fatal *P carinii* pneumonia 4 months after finishing rituximab therapy while receiving cyclophosphamide and prednisone, but it is unclear if this event was directly related to rituximab.[7] Neither of our patients experienced any adverse affects related to rituximab therapy.

Rituximab induces cellular death by binding to CD20 without the need for conjugation to toxin.[30,31] CD20 is thought to function as a calcium channel subunit[32] and in the activation of B cells from gap_0 to gap_1 phase.[33] As mentioned, rituximab selectively depletes B cells while sparing progenitor cells. Because the origin of autoantibody in PV is unknown, it is difficult to know the precise mechanism of rituximab in patients with PV. A temporal correlation of rituximab initiation with clinical improvement and an associated reduction in anti–desmoglein 3 antibody titers has been shown.[7,9,12] Although the duration of rituximab response in PV is unknown, a phase 2 study examining 28 patients with non-Hodgkin lymphoma reported a median time to progression of 8.1 months and a median duration of response of 5.9 months.[34]

While preparing this manuscript, Kong et al[35] reported the successful treatment of childhood PV with rituximab. Our series, therefore, adds greater evidence for the use of rituximab in pediatric PV, demonstrating efficacy in 2 recalcitrant cases without the adverse effects reported with the use of other adjuvant therapies. Further investigation is warranted to identify those patient and clinical disease characteristics that would benefit greatest from this therapy.

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