Case Report: Treatment of Refractory Pemphigus Foliaceus with Rituximab

The origin of the term pemphigus is the Greek word pemphix, a reference to a blister or bubble. Pemphigus foliaceus is characterized histologically as an intraepidermal blister formation secondary to a cell-cell adhesion loss of keratinocytes (acantholysis). The blisters are found on the skin and typically spare the mucosa. The blisters are described as fragile and easily ruptured, which can lead to crusting and scaling.

Similar to pemphigus vulgaris, systemic glucocorticoid therapy, oftentimes given in conjunction with a nonsteroidal immunosuppressant like azathioprine, is the mainstay of initial treatment. In some instances, however, pemphigus foliaceus does not respond to this therapy and dermatologists should be aware of management options for refractory cases. Rituximab has been documented as an effective treatment option for those particular patients. Following is a case of a patient who showed minimal improvement with the mainstay therapy, but dramatically improved with rituximab.

A previously healthy 40-year-old Hispanic male presented with a six-month history of painful skin lesions on his face, scalp, back, chest, neck, and arms. He had no known Brazilian ancestry. This patient initially saw another dermatologist who did a thorough workup before his retirement. Lab results demonstrated rare Gram-positive cocci, and a negative ANA. The other lab results were essentially normal. Indirect immunofluorescence and antibody titers were not done, as he had no insurance. Two skin biopsies from the back were performed, which revealed subcorneal acantholysis with an intact roof. Rare dyskeratotic keratinocytes were present. Periodic acid-Schiff stain was negative for fungal organisms. Direct immunofluorescence studies revealed IgG with strong staining of epidermal keratinocyte surfaces. This first dermatologist presented the case at grand rounds and made a treatment plan of prednisone and azathioprine. The patient reported that this treatment helped for about two months but did not cause a complete remission of the lesions, and that eventually the lesions became worse than before treatment.
When the patient presented to our office, he had multiple large, scaly, crusted, blistering erosions with active oozing on an erythematous base on his scalp, back, face, chest, buttocks, and groin (Figures 1 and 2). His mucosa was normal. He had several intact vesicles on his lower back with very thin roofs that appeared to be stratum corneum. His condition was so painful and uncomfortable that he could not sit nor put on a shirt. Instead, he wrapped himself in a bed sheet. The patient was extremely photosensitive and could not perform his work-related duties during the recent spring and summer. We switched to methotrexate and triamcinolone acetonide injections as he was not improving with prednisone and azathoprine. Unfortunately, these medications provided minimal improvement over the next few weeks. Subsequently, we took a more aggressive approach and the patient was given two 1-gram infusions of rituximab, 15 days apart. The patient’s condition improved significantly (Figures 3 and 4) and he was able to return to his regular activities without any limitations.

LITERATURE REVIEW

IgG antibodies against keratinocytes is believed to cause pemphigus. The autoantibodies, which are quantitated by enzyme-linked immunosorbent assay (ELISA), are directed against desmogleins, transmembrane desmosomal glycoproteins. Desmoglein 1 is expressed more in the superficial epidermis and desmoglein 3 is more commonly found in the basal and parabasal layers of the epidermis as well as the squamous layer of mucosa. The desmoglein compensation theory explains that desmoglein 1 and desmoglein 3 support each other when they are coexpressed in a cell. However, in certain cell types or layers, desmogleins are vulnerable to autoantibodies as the two desmoglein types do not compensate. In pemphigus foliaceus, autoantibodies against desmoglein 1 result in a superficial epidermal cell separation. Pemphigus vulgaris results from autoantibodies against desmoglein 1 and desmoglein 3 causing both deeper epithelial separation and mucosal involvement.

Pemphigus foliaceus has several distinguishing characteristics from pemphigus vulgaris. The acantholytic blisters in pemphigus foliaceus are higher in the epidermis, compared to pemphigus vulgaris, causing more superficial blisters and commonly spare mucosa. Pemphigus foliaceus, rarely presenting with intact blisters, displays more crusting, scaling, and extensive exfoliation. The lesions are usually found on the face, scalp, and upper trunk similar to our patient. Due to the severity of the disease, physicians must use an aggressive and well-organized approach to treat pemphigus foliaceus starting with systemic glucocorticoid ther-
apy either with or without a nonsteroidal immunosuppressant. Around 60 to 80 percent of patients should achieve initial improvement with these agents. In refractory cases, treatment options include cyclophosphamide, rituximab, intravenous immunoglobulin (IVIG), immunoadsorption, and plasmapheresis.

Given the pathophysiology of pemphigus foliaceus, we felt rituximab would be an effective option for this patient. Rituximab is a monoclonal antibody directed against the antigen CD20 on B-cells, which decreases antibody-producing B lymphocytes. With B-cell depletion, there is a decline in pathologic autoantibodies directed against desmogleins. Also, as an indirect correlation on B lymphocyte decline, there may be a decrease in autoreactive CD4+ T cells.

A few studies have been performed to determine the optimal rituximab dosage. Early studies suggested dosages for treating B-cell lymphoma, which was 375mg/m². A 2007 multicenter study examined 21 patients with either corticosteroid-refractory disease, severe contraindications to corticosteroids, or had at least two relapses despite adequate corticosteroid treatment. Eighteen of the 21 patients had complete remission in three months, nine patients relapsed, and 18 patients were disease-free after 34 months. Despite having decreased circulating B lymphocytes, serum levels of IgG were normal. In 2011, a retrospective study of 27 patients showed that weekly infusions for three weeks had better outcomes and relapse rates than fewer treatments.

Rituximab has been used and shown effective in treating pemphigus foliaceus at a dose used for rheumatoid arthritis, which was two 1,000mg infusions separated by two weeks. With this regimen, fewer infusion sessions are needed and a lower dose of rituximab is used compared to the B-cell lymphoma dose. In a 2012 single-center observational study, 42 patients were treated with rituximab and followed for up to five years. Thirty-six of 42 patients had a complete remission and were off corticosteroids within six months from rituximab treatment. Six patients required an addition rituximab infusion after six months leading to a complete response. Despite 20 patients experiencing a relapse, all had a complete response when given an additional 500mg rituximab treatment without corticosteroids. Interestingly, no other immunosuppressants were needed and all relapses were adequately controlled.

Rituximab has also been studied when combined with intravenous immune globin (IVIG). IVIG is thought to protect from a reduced immunoglobulin level, induced by rituximab treatment. In 2006, 11 patients with refractory pemphigus vulgaris were treated with both rituximab and IVIG. No side effects were observed and all patients obtained complete control of the disease. The study concluded that IVIG provided a synergistic effect to rituximab with rituximab eliminating pathogenic antibody-producing B cells and IVIG working to restore depleted CD20 cells, within 10 to 12 months, without pathogenic autoantibodies.

Side effects have been reported with rituximab. In a 2009 review of 136 patients with pemphigus treated with rituximab, roughly 10 percent had severe infections and three percent had fatal infections. Infusion reactions,
which typically occur in the first 30 to 120 minutes of the first exposure, are common with rituximab, affecting in up to 30 to 45 percent of patients. Fewer than 10 percent of these patients experience bronchospasm and/or severe hypotension and less than five percent are reflective of anaphylaxis. Using a gradual increase in infusion rate or premedicating with antihistamines and acetaminophen are used to prevent or reduce infusion reaction severity. Patients with mild-to-moderate risk of hypotension are encouraged to not take their antihypertensive medications on the morning of infusion.

Given its mechanism of action, hypogammaglobulinemia does occur with rituximab treatment. Usually, total immunoglobulin levels remain in the normal range following one course, but repeated courses increase the risk of hypogammaglobulinemia. A 2009 meta-analysis was performed on 1143 patients with rheumatoid arthritis which showed no increase in serious infection in patients treated with rituximab and methotrexate compared to those treated with methotrexate and a placebo. In 2010, clinical trials showed from three to six percent of patients had decreased IgG, but some had rituximab for up to five cycles over six years, which is typically not consistent with pemphigus foliaceus treatment.

CONCLUSION

Our patient experienced a complete resolution of his pemphigus foliaceus (Figures 3 and 4) after two 1-gm rituximab infusions, separated by 15 days. His treatment was uneventful as he did not experience any side effects. It has been three months since these infusions and he has remained clear. Rituximab is a very reliable option to treat refractive cases of pemphigus foliaceus.

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