Successful Use of Rituximab for Cutaneous Vasculitis

Lorinda Chung, MD; Alisa A. Funke; Eliza F. Chakravarty, MD, MS; Jeffrey P. Callen, MD; David F. Fiorentino, MD, PhD; Stanford University School of Medicine, Stanford, Calif (Drs Chung, Chakravarty, and Fiorentino), and University of Louisville School of Medicine, Louisville, Ky (Ms Funke and Dr Callen)

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 23-year-old woman presented with recalcitrant purpuric macules and papules on her forearms, legs, and abdomen. At the age of 13 years, she presented to an outside facility with renal failure of unknown etiology requiring hemodialysis followed by living-related kidney transplantation at the age of 14 years. Renal biopsies had not been performed. The patient did well until 1 year later, when she experienced an upper respiratory illness followed by a new petechial rash on her bilateral lower extremities that was thought to be clinically consistent with Henoch-Schönlein purpura. Although her initial rash resolved without additional therapy, she continued to experience intermittent purpuric eruptions that were associated with abdominal pain, arthritis, and arthralgia. Over the next several years, her rash became persistent, progressed to involve her forearms and abdomen, and was accompanied by hematuria and increases in serum creatinine levels. She had no pulmonary or neurologic symptoms. Her condition did not respond to trials of prednisone (up to 40 mg/d), cyclosporine (100 mg twice daily), azathioprine (100 mg/d), and etanercept (50 mg twice weekly). Mycophenolate mofetil was not tolerated owing to angioedema.

When the patient first presented to our clinic in February 2004, she had purpuric macules and papules over her forearms, thighs (Figure 1), legs, and abdomen. Medications at that time included prednisone (10 mg/d), cyclosporine (100 mg twice daily), azathioprine (100 mg/d), lisinopril, atenolol, and erythropoietin. A skin biopsy specimen showed leukocytoclastic vasculitis with perivascular C3 deposition but without detectable IgG or IgA on direct immunofluorescence. Subsequent biopsy of her renal allograft showed no evidence of vasculitis or deposition of immunoreactants (data not shown). Significant laboratory test results included the following values: hematocrit, 29% (reference range, 35%-47%); C4, 10.4 mg/dL (reference range, 20-59 mg/dL); C3, 88 mg/dL (reference range, 86-184 mg/dL); rheumatoid factor, 48 IU/mL (reference value, <20 IU/mL); erythrocyte sedimentation rate, 60 mm/h (reference value, <20 mm/h); and creatinine, 1.4 mg/dL (124 µmol/L) (reference value, <1.2 mg/dL [<106 µmol/L]). Urinalysis revealed microscopic hematuria but no casts. The results of the following laboratory investigations were normal or negative: determination of serum cryoglobulin levels, protein immunofixation electrophoresis, antinuclear antibody and antineutrophil cytoplasmic antibody tests, serologic tests for hepatitis B and C, urinary protein electrophoresis, and stool guaiac tests.

CASE 2

A 43-year-old woman was referred for treatment of “refractory” chronic cutaneous small vessel vasculitis (CSVV). At the age of 28 years, she had non-Hodgkin lymphoma (NHL), large B-cell type, which was localized to her neck and had been successfully treated with 4 courses of nitrogen mustard, vincristine, prednisone, and procarbazine followed by radiation therapy. Cutaneous vasculitis first developed 14 months before the patient presented to us at the age of 41 years. In October 2003, pruritic lesions developed on her thighs but resolved within a few days. One month later, a second episode, which affected her legs and feet, also resolved spontaneously. In December 2003, she had another episode, which was treated with oral methylprednisolone (tapered from 24 to 0 mg over 7 days), with improvement, but the lesions again recurred. An oral con-
traceptive was her only medication when the vasculitis began. Shortly after her initial presentation, a skin biopsy specimen demonstrated leukocytoclastic vasculitis. The findings of direct immunofluorescence of a subsequent skin biopsy specimen obtained 6 months later were suggestive of vasculitis, revealing fibrinogen and C3 deposition in a perivascular and a superficial vessel location, respectively. The results of tests for all other immunoglobulins were negative. A chest x-ray film did not show any signs of recurrent lymphoma.

The patient was treated with dapsone (up to 200 mg/d) and hydroxyzine (25 mg nightly), but her condition continued to flare. Further laboratory evaluation revealed a hemoglobin level of 10.8 g/dL and a hematocrit of 32.1%. The level of rheumatoid factor was 110 IU/mL (reference value, <15 IU/mL). Other laboratory values, including cryoglobulin, cryofibrinogen, and complement (total, C3, and C4) levels, were within normal limits. Computed tomography showed inguinal and mediastinal lymphadenopathy, and positron emission tomography demonstrated hypermetabolic lymph nodes within the subcarinal and perihilar regions. Subsequent mediastinoscopy with lymph node biopsy showed paracortical hyperplasia, monocytoid B-cell hyperplasia, and an excess of Λ-positive plasma cells; however, the findings of a bone marrow biopsy were unremarkable. The patient did not improve with combination therapy with colchicine (0.6 mg twice daily) and dapsone (100 mg/d) at an outside facility, and she began a regimen of dexamethasone pulse therapy and doxepin. She again presented to us with multiple purpuric macules and papules coalescing into patches and plaques that almost completely involved the lower extremities, buttocks, abdomen, and flanks (Figure 2). She did not have hepatosplenomegaly or palpable lymphadenopathy. Laboratory evaluation showed a rheumatoid factor level of 891 IU/mL (reference range, 0-13.9 IU/mL); an antinuclear antibody titer of 1:80, speckled pattern (borderline); an elevated C-reactive protein level (24.7 mg/L [reference range, 0.0-4.9 mg/L]); and a positive qualitative cryofibrinogen finding. The results of all other tests, including anticardiolipin antibodies, cryoglobulin, Westergren erythrocyte sedimentation rate, antineutrophil cytoplasmic antibodies, anti-Ro(SS-A) antibody, anti-La(SS-B) antibody, hepatitis panel, and serum and urinary protein and immunofixation electrophoresis, were within normal limits.

Our patients had severe, progressive CSVV. As long as potentially associated pathogenic factors have been addressed (eg, infection, malignancy, medications, or inflammatory diseases), persistent skin lesions warrant therapy.
Although dapsone and/or colchicine therapy can often be effective, other systemic immunosuppressive agents, including methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, cyclophosphamide, and intravenous immunoglobulin, may be required. Patient 1 had persistent, long-standing idiopathic disease that failed to improve with prednisone, cyclosporine, azathioprine, and etanercept therapy. Patient 2 had CSVV with a history of NHL that flared after tapering doses of corticosteroids and was resistant to treatment with dapsone or colchicine. Treatment with methotrexate, azathioprine, or other cytotoxic/immunosuppressive agents was not recommended because of the patient’s cancer history.

Rituximab has been approved for the treatment of CD20+ B-cell lymphoma, but some small, open-label case series and individual case reports have found that it is effective in patients with certain forms of vasculitis. To our knowledge, there have been no reports of its being used for the treatment of patients with CSVV. However, because it is likely that many forms of CSVV are due to immune complex deposition in the dermal blood vessels, and because B cells are a source of immune complexes, we elected to proceed with anti-B-cell therapy in our patients.

Patient 1 received 2 intravenous infusions (1 g on days 0 and 14) of rituximab without pulse oral or intravenous corticosteroids, and there were no other changes in her concomitant medications. Rituximab therapy was well tolerated, with no adverse events noted. The patient experienced a steady reduction in her cutaneous lesions over the following 10 weeks. Four months later, her CD19+ B-cell level was 12/µL (reference range, 100-500/µL). By 5 months, she was completely free of purpuric lesions and was able to reduce her dosage of prednisone therapy to 7.5 mg/d without recurrence (Figure 3). The results of urinalysis normalized, and her creatinine level decreased to 1.1 mg/dL (97 µmol/L).

Patient 2 received 4 weekly infusions of 375 mg/m² of rituximab inducing remission in a patient with hepatitis C virus–associated cryoglobulinemic vasculitis that responded to a single 4-week course of rituximab.

A clinical trial of 15 patients with difficult-to-treat type II mixed cryoglobulinemia demonstrated a rapid response of cutaneous manifestations to rituximab therapy, with purpura disappearing in 11 of 12 patients, skin ulcers healing in 5 of 5 patients, and complete resolution of widespread urticarial vasculitis in 1 patient. During 6 months of follow-up, purpura recurred in 2 patients and ulcers recurred in 1 patient; however, all 3 patients responded to a second course of rituximab. The patient with urticarial vasculitis was still in remission 31 months after a single course of rituximab. There is a case report of rituximab inducing remission in a patient with hepatitis C virus–associated cryoglobulinemic vasculitis and NHL. Another case report demonstrated the efficacy of rituximab therapy in a patient who nearly underwent an amputation because of an ulcerative lesion that was associated with type II mixed cryoglobulinemia.

In addition to type II mixed cryoglobulinemia, antineutrophil cytoplasmatic antibody–associated vasculitis, Wegener granulomatosis, and microscopic polyangiitis have responded to rituximab therapy in clinical trials and case series. In a series of 3 patients with Wegener granulomatosis, there was a recurrence of symptoms after complete remission, but subsequent courses of rituximab resulted in significant improvement.
Rituximab has demonstrated corticosteroid-sparing effects,1,6 and there are very few reports of significant adverse effects in the literature. Rituximab therapy is generally well tolerated by patients with autoimmune diseases, with a lower incidence of infusion-related reactions than has been observed in patients with NHL.9,24 Zaja et al6 reported cases of thrombosis of the retinal artery and pan- nicultis that spontaneously resolved. Other infusion-related adverse effects that have been reported include mild angioedema, polyarthritids, dizziness, and hypertension.3 Other than the 1 incident of a burning sensation during an infusion, which resolved by slowing the rate, our patients tolerated rituximab therapy well.

Rituximab is approved for the treatment of NHL but has shown efficacy in a variety of autoimmune diseases and some forms of vasculitis. The present article, unlike many others that have reported on the use of rituximab in vasculitis associated with systemic conditions, demonstrates the efficacy of rituximab therapy for refractory CSVV of unknown etiology. We believe that rituximab therapy might be a safe, effective treatment for CSVV that is nonresponsive to traditional therapies. Further controlled studies are necessary to evaluate the appropriate dosing regimen and long-term efficacy of rituximab therapy for cutaneous vasculitis.

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Correspondence: David Fiorentino, MD, PhD, Department of Dermatology, Stanford University, 900 Blake Wilbur Dr, Stanford, CA 94305 (Fiorentino@stanford.edu).

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