Long-term Plasmapheresis in Conjunction With Thalidomide and Dexamethasone for the Treatment of Cutaneous Ulcers and Neovascular Glaucoma in Recalcitrant Type I Cryoglobulinemia

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Cryoglobulins are cold-precipitating immunoglobulins that occur secondary to lymphoproliferative disorders, chronic viral infections, and autoimmune disorders. The treatment of cryoglobulinemia should target the underlying disorder; however, such an approach may be difficult, and therapeutic options remain limited for type I cryoglobulinemia.

Observations We report a case of recalcitrant type I cryoglobulinemia treated successfully with long-term plasmapheresis in conjunction with thalidomide and dexamethasone. A woman in her 50s with cryoglobulinemia and bilateral lower extremity ulcers of 1 year’s duration developed acute angle-closure glaucoma following the appearance of new macules on her upper extremities. An initial short course of 5 plasmapheresis treatments improved the patient’s cutaneous lesions as well as the glaucoma. Three weekly doses of rituximab were not associated with any evidence of clinical improvement, so thalidomide and dexamethasone were administered as replacement therapy. Because of the increasing pain and persistence of the woman’s ulcers, intensive plasmapheresis was resumed and continued 3 to 4 times per week for approximately 4 months, after which a slow tapering regimen was initiated. This therapy was associated with progressive, rapid healing of the ulcers, stabilization of the skin lesions, and control of the patient’s intraocular pressure.

Conclusions and Relevance The long-term use of plasmapheresis may be a well-tolerated treatment option for therapeutically challenging cases of cryoglobulinemia.

Rituximab, a chimeric monoclonal antibody against CD20, binds to CD20⁺-positive B cells and serves as a therapeutic option typically reserved for refractory cases of cryoglobulinemia. We describe a patient with type I cryoglobulinemia associated with a plasma cell dyscrasia that failed to respond to treatment with rituximab; however, a long-term course of intensive plasmapheresis with thalidomide and dexamethasone induced remission of the patient’s chronic lower extremity ulcers and resolved a rare manifestation of cryoglobulinemia-related neovascular glaucoma.

Report of a Case A woman in her 50s presented to the dermatology clinic with chronic, bilateral lower extremity ulcers. Her lesions started 1 year earlier as nonblanching, erythematous macules that progressed into tender, nonhealing ulcers. She also had experienced, during the previous several years, intermittent epi-
sodes of epistaxis. A skin examination revealed several pretibial areas of nonblanching, nonpalpable purpura and large ulcers with central atrophic eschars (Figure 1).

Laboratory investigation demonstrated the presence of cryoglobulins at a cryocrit value of 17%. Results of tests for hepatitis C antibody and viral RNA were negative. Results of tests for hepatitis B surface and core antibodies were also negative. A review of a previous skin biopsy specimen (obtained 15 months before this examination) from one of her ulcers revealed capillary vascular proliferation containing intravascular periodic acid–Schiff–positive material and no evidence of vasculitis (Figure 2). Serum protein electrophoresis revealed a monoclonal spike with a concentration of 0.34 g/dL (for conversion to grams per liter, multiply by 10), and a bone marrow biopsy specimen showed moderately hypercellular marrow with 10% of the cellularity and 5% of the intertrabecular space composed of plasma cells and an interstitial infiltrate composed of CD20+ and CD3+ cells. Serum immunofixation showed an IgM κ biclonal gammopathy, and immunofixation of the patient’s cryoglobulins revealed an IgM κ monoclonal protein. Together, these findings were interpreted as consistent with type I cryoglobulinemia secondary to a plasma cell dyscrasia.

Six months after her initial clinic visit, the patient developed erythematous, nonblanching macules on her upper extremities that were followed shortly afterward by an episode of acute angle-closure glaucoma in her left eye. An ophthalmologic examination at the time revealed venous engorgement and neovascularization of the iris. There were no signs or symptoms of systemic manifestations of cryoglobulinemia. The patient underwent emergency laser decompression, but 6 months later she developed an exacerbation of glaucoma and received 5 cycles of plasmapheresis using albumin, 5%, and normal saline as replacement fluids. Four units of fresh frozen plasma were included in the replacement fluids during one of these procedures because of a recent retinal hemorrhage. At all other plasmapheresis procedures, she received only albumin, 5%, and normal saline as replacement fluids. This intervention resulted in modest improvement of her glaucoma and lower extremity ulcers.

In the period following plasmapheresis, the pain associated with the patient’s ulcers gradually increased, and she developed new lesions in her pretibial area. Given the significant number of CD20+ B cells in her bone marrow biopsy, trial therapy with rituximab (375 mg/m²/wk) was administered. Her ulcers worsened during this therapy, and rituximab was discontinued after the third dose because of increasing pain from the ulcers.

A trial of oral thalidomide (50 mg/d) and dexamethasone (4 mg/d for the first month, then 40 mg/wk) was then initiated. Plasmapheresis was resumed because of increasing ulcer pain 3 weeks after thalidomide and dexamethasone therapy was begun, starting with 5 treatments every other day. Approximately 6 weeks after the initiation of thalidomide therapy, the patient developed symptoms suggestive of thalidomide toxicity. Thalidomide was replaced with mycophenolate mofetil (500 mg twice daily), which was administered for only 2 weeks. Because the symptoms suggesting thalidomide toxicity improved, thalidomide therapy was restarted 3 weeks after it had been discontinued. Treatment with thalidomide (50 mg/d) and dexamethasone (40 mg/wk) was continued until these medications were stopped 7 months later because of thalidomide-induced neuropathy.

Intensive plasmapheresis 3 to 4 times per week was resumed approximately 3 weeks before thalidomide therapy was restarted and was continued for the next 4 months, after which plasmapheresis was slowly tapered by increasing the intervals between procedures. Additional treatment during the period of intensive plasmapheresis included increased topical debridement with wound care, intermittently using levofloxacin for superficial infections, and topical treatment with papainurea-chlorophyllin ointment and silver dressings.

Before the period of intensive plasmapheresis, little or no improvement of the lower extremity ulcers had been achieved.

Figure 1. Lower Extremity Ulcers Before Initiation of Long-term Plasmapheresis Treatment

Nonpalpable purpura, eschar formation, and large ulcers were present in the pretibial and ankle regions.

Figure 2. Hematoxylin-Eosin Staining of the Left Lower Extremity Skin Biopsy

Notable findings included capillary vascular proliferation and intravascular periodic acid–Schiff–positive material (original magnification ×40).
However, concurrent with the initiation of intensive plasmapheresis, the patient’s lower extremity ulcers showed continued improvement, progressing through healing to complete closure and, at the time of writing, had not recurred. Three months after her last plasmapheresis session, the patient’s ulcers had resolved, with scarring and atrophy on her legs. Cryocrit testing was positive at 7%. Her intraocular pressure remained within normal limits.

Discussion

Plasmapheresis is used for treatment of cryoglobulinemia.1,4,5 In a case series6 of 7 patients with type I cryoglobulinemia in the setting of multiple myeloma, plasmapheresis was recommended for the rapid relief of initial symptoms as an adjunct to systemic therapies. Although there was no evidence of renal involvement, bowel ischemia, peripheral neuropathy, or other systemic manifestations in the present case, the rapid progression of her second episode of acute angle-closure glaucoma led to the use of plasmapheresis rather than a trial of conventional immunosuppressive agents.

Neovascular glaucoma is not a well-known complication of cryoglobulinemia. Nevertheless, we believe that these 2 conditions were related in our patient given the temporal sequence of the exacerbation of her lesions in association with the onset of glaucoma and because plasmapheresis was effective in lowering her intraocular pressure. Iris neovascularization leading to glaucoma has been documented7 in the setting of cryoglobulinemia. Although iris neovascularization typically occurs when the retina undergoes ischemia, such as in diabetic retinopathy or retina vein occlusion, Telander et al7 described 2 cases of iris neovascularization in the absence of retinal ischemia among patients with type I and type II cryoglobulinemia. The authors hypothesized that in these patients the precipitation of cryoglobulins in the cooler peripheral regions of the eye led to anterior segment ischemia and subsequent aberrant angiogenesis in the iris. In one of these patients, treatment with a 5-day course of plasmapheresis and several months of therapy with rituximab and fludarabine also led to improved neovascular findings and decreases in intraocular pressure.

With the present report, we demonstrate that long-term plasmapheresis in conjunction with thalidomide and dexamethasone therapy may induce lasting, complete remission of cutaneous lesions related to type I cryoglobulinemia. Our case suggests that, in addition to the rapid reduction of immunoglobulins and cryoglobulins, long-term treatment with plasmapheresis may have immunomodulatory effects. Because albumin, 5%, replacement was used rather than one administration of fresh frozen plasma, we cannot speculate as to whether similar results would have been obtained if agents such as intravenous immunoglobulins had been used as a primary treatment modality. Thus, when the treatment of the underlying disorder is difficult or not immediately attainable despite treatment with systemic immunosuppressive agents, the manifestations of cryoglobulinemia may be resolved by using plasmapheresis to achieve long-term reduction of immunoglobulins and associated cryoglobulins. As the number of reports of patients with type I cryoglobulinemia who experience failure with rituximab continues to increase,8 the potential benefits for plasmapheresis are important to highlight. This therapeutic modality also may be useful in patients who are unable to tolerate treatment with agents such as thalidomide or in whom systemic adverse effects preclude the long-term use of such agents. However, further studies are needed to evaluate how the safety and efficacy of long-term plasmapheresis compare with current cryoglobulinemia therapies such as immunosuppressive drugs, rituximab, and antiviral agents.

REFERENCES