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Lenalidomide for the Treatment of Cryoglobulinemia and Undifferentiated Spondyloarthropathy in a Patient With Multiple Myeloma

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Cryoglobulinemia refers to the presence of one or more immunoglobulins that precipitate at temperatures below 37°C and redissolve on rewarming. It is classified into 3 types based on immunochemical characteristics of the paraprotein. Type I is a monoclonal immunoglobulin that is most often associated with Waldenstrom macroglobulinemia, lymphoma, multiple myeloma (MM), and monoclonal gammopathy of unknown significance (MGUS).¹ The cutaneous manifestations of cryoglobulinemia include palpable purpura, livedo reticularis, ischemic necrosis, and cutaneous ulcerations.¹ Here, we report a case of cryoglobulinemia in a patient with undifferentiated spondyloarthropathy and multiple myeloma, who was successfully treated with lenalidomide.

A 43-year-old white man presented with history of recurrent episodes of anterior uveitis and progressive limping secondary to lower back and buttock pain. His physical examination showed only mild tenderness and swelling of the right midfoot. Erythrocyte sedimentation rate (ESR) was 54 (<15), human leukocyte antigen B27 was positive, and magnetic resonance imaging of the lumbosacral spine was consistent with left sacroiliitis (Fig. 1). A diagnosis of undifferentiated spondyloarthropathy was made and he was managed conservatively with nonsteroidal anti-inflammatory medications.²

One year later, he developed recurrent sinopulmonary infections. Extensive workup revealed elevated serum monoclonal IgG to 2.82 g/dL (<0.20) and 43% plasma cells in the bone marrow. The diagnosis of International Staging System stage I MM was made based on beta-2 macroglobulin level of 1.8 mg/L and serum albumin level of 3.6 g/dL. Hgb concentration was 10.8 g/dL (>13), calcium level was 9.0 mg/dL (<10.4), and no overt lytic lesions were detected on the skeletal survey. Therapy was deferred given the absence of end organ damage.³

Three months later, he developed a flare of the inflammatory arthritis manifested by worsening right foot and left hip pain and new rashes. Physical examination noted limited left hip range of motion secondary to pain, right foot swelling, and livedo reticular type of rashes associated with necrotic plaques and ulcerations on the bilateral lower extremities.

ESR was now 134 and hepatitis C viral antibody was negative. Type I cryoglobulinemia was diagnosed with a cryocrit of 8% (<0.5% volume) and pathologic findings of ischemic and thrombotic vasculopathy with extensive fibrin deposition and red blood cell extravasations on skin biopsy (Fig. 2).

Low dose prednisone therapy was first attempted without significant clinical improvement in several weeks and his cryocrit was now 25%. Plasmapheresis was initiated and his cutaneous symptoms partially improved. Lenalidomide, 25 mg by mouth once a day 3 weeks on and 1 week off, and weekly dexamethasone pulse, 40 mg by mouth, were then started and continued for 4 cycles. The skin ulcers healed, his livedo reticular rash resolved, and his cryocrit became negative. Interestingly, his hip and foot pain also resolved; physical examination revealed diminished right foot swelling; and the ESR post-treatment became undetectable. The serum monoclonal IgG was now is 0.76 g/dL and repeat bone marrow biopsy showed 3% plasma cells. He subsequently underwent consolidative bone marrow transplantation and remained symptom free 8 months after treatment with lenalidomide.

Treatment options for patients with Type I cryoglobulinemia occurring in the setting of MM or MGUS include systemic corticosteroid therapy with or without alkylating agents.¹ Plasmapheresis has been used in severe or life threatening cases of cryoprecipitation or serum hyperviscosity syndrome. However, it is inconvenient and produces only transient decrease in cryoglobulin level.⁴ Lenalidomide is a new generation antiangiogenic and immunomodulatory drug related to thalidomide, an inhibitor of the tumor necrosis factor (TNF) alpha pathway.⁵ It has enhanced TNF-alpha inhibitory activity and tumor cytotoxicity, and fewer side effects of deep vein thrombosis and peripheral neuropathy than thalidomide. It is now used as a first-line treatment for MM and myelodysplastic syndrome.³

This is the first reported case of human leukocyte antigen B27 spondyloarthropathy and Type I cryoglobulinemia treated successfully with lenalidomide. Review of the literature revealed only 2 other cases of paraproteinemia-associated Type I cryoglobulinemia treated with thalidomide. Neither of these 2 cases had associated inflammatory arthritis.^{6,7} The first unique feature of our case is that lenalidomide appears to have activity in both HLA B27 spondyloarthropathy as well as Type I cryoglobulinemia. This could be explained mechanistically by the involvement of TNF-alpha pathway in both disease processes, and supported by clinical observations that inflammatory arthritis can be associated with MGUS and MM.⁸ The second unique feature is that the exacerbation of his inflammatory spondyloarthropathy was temporally associated with the development of cryoglobulinemia. It is possible that cryoglobulin crystals may be contributing to the worsening of arthropathy as suggested by a recent report.⁹ The arthropathy in that patient responded to oral and intra-articular corticosteroids, and MM was subsequently diagnosed and treated with lenalidomide.⁹ In summary, on the basis of our limited experience and literature review, lenalidomide may have a potential role in the treatment of inflammatory spondyloarthropathy as well as Type I cryoglobulinemia associated with paraproteinemia.

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FIGURE 1. Magnetic resonance imaging of the sacroiliac joints, T2-FLAIR sequence showing edema in the left SI joint (arrow).

FIGURE 2.
Skin biopsy showing fibrin deposition and red blood cell extravasations (arrows).