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Commentary: Necrobiotic Xanthogranuloma

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Chen and colleagues describe the interesting case of a 68-year-old man presenting with facial and neck edema and mediastinal mass, with eventual diagnosis of Necrobiotic Xanthogranuloma (NXG) and associated plasma cell dyscrasias and lymphoproliferative disorder[1]. The rarity of this condition precludes it from being studied on a large scale, but as cases are reported, with review of the literature as so beautifully done by Chen et al, we can hopefully gain a better understanding of the pathophysiology and treatment.

Necrobiotic Xanthogranuloma (NXG) was first described in 1980 by Kossad and Winkelmann in which they discussed 8 patients with xanthomatous plaques, noted to have monoclonal gammopathy, predominantly IgG kappa type[2]. Since then, more than 100 patients with this disorder have been described, with approximately 80% of them associated with a monoclonal gammopathy.

Clinical Presentation

The clinical picture of NXG is a slowly progressive, destructive and infiltrating xanthomatous plagues and cutaneous lesions with significant tissue destruction and sometimes systemic involvement. The lesions may ulcerate with areas of indurations consisting of yellow or xanthomatous discoloration[3,4]. The plaques and lesions may involve the trunk and extremities, but more than 80% of patients present with periorbital involvement. Most patients have asymptomatic lesions, but symptoms may include pruritis, paresthesias, burning and pain. Lesions mostly appear in patients in their fifth to sixth decades of life, with ranges from 17 to 86 years old[5,6].

Physical findings outside of the skin lesions are often unrevealing, but in the case series by Mehregan, more than 20% had hepatomegaly, and almost 20% had splenomegaly [2]. Hematologic involvement may include neutropenia, cryoglobulinemia, hypocomplementemia, and hyperlipidemia (3). Systemic involvements have included multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, lymphoplasmacytic lymphoma or waldenstrom, lung, and heart[7–12]. However, the most common association is a plasma cell dyscrasias monoclonal gammopathy of unknown significance (MGUS), with up to 80% of patients having IgG type with either Kappa or Lambda light chain. Chen et al reports the first case of concurrent plasma cell dyscrasias and a lymphoproliferative disorder, albeit very low involvement.

Diagnosis and Pathophysiology

A histopathologic review of the lesion is important. Histologically, NXG is characterized by granuloma formation within the subcutaneous and dermal layers, with focal areas of necrobiosis. The granulomas consist of multinucleated giant cells of several types. Cholesterol clefts within the areas of necrobiosis give the foamy appearance that is often seen. Other characteristics and finding are well described by Chen and Balagula[1,11]. Given

the association with MGUS, hematologic malignancies and disorders, serum immunoglobulins and free light chains are necessary in addition to routine complete blood and metabolic counts. A bone marrow biopsy with immunophenotyping, cytogenetic and molecular studies and CAT scan of the chest, abdomen and pelvis may be necessary depending on physical exam and blood tests results. While still poorly understood, the causes that have been proposed are well documented by Chen et al and Balagula et al[1,11].

Management

Management of NXG has included watch-and-wait in asymptomatic patients, to surgery, radiation, plasmapheresis, Intralesional corticosteroids, and systemic and cytotoxic agents such as chlorambucil, melphalan, interferon alpha-2b, cyclophosphamide, methotrexate, hydroxychloroquine, azathioprine, nitrogen mustard, and high dose steroids in symptomatic patients[4,5,12]. Treatment responses have been variable with recurrences in many cases. Most recently, the use of lenalidomide with dexamethasone in a patient with NXG and smoldering myeloma showed resolution of lesions after 3 months of treatment with a durable response with no occurrence at 12 months[13]. Also we have reported a complete response to thalidomide and dexamethasone in a patient with NXG and smoldering myeloma(10% bone marrow plasma cells) with extensive skin lesions, with persistent complete response 3 years after cessation of treatment[14]. One case of autologous stem cell transplant (ASCT) with high dose melphalan, with durable response, was reported[15]. Thalidomide, lenalidomide (immune modulatory drugs) and ASCT are treatment modalities for multiple myeloma, a hematologic malignancy with monoclonal gammopathy, with overall response rates of 80–90% and complete responses of 40–50%[16]. Thalidomide, lenalidomide and bortezomib (a proteosome inhibitor) in combination with steroid, are considered first line agents in the treatment of patients with multiple myeloma, and are increasingly being studied in other hematologic disorders such as non-Hodgkin's lymphoma, Hodgkin's lymphoma, waldenstrom and other lymphoproliferative disorders, and acute and chronic leukemias. These drugs may hold promise in maintaining long term duration-free of symptoms and preservation of skin integrity. The length of systemic treatment has not been defined. Duration of treatment has ranged from 2 to 24 months. In the case series using lenalidomide and thalidomide, duration of treatment were 3 and 24 months respectively.

Conclusion

NXG is a rare disorder, with slowly progressive, but often disfiguring skin lesions, often associated with hematologic disorder, with the most common being MGUS. Accurate diagnosis of the lesions and appropriate further testing is necessary to appropriately choose treatment strategy. While 80% of patients may not need any treatment or may only require topical agents and local procedures, a select group of symptomatic patients with disfiguring skin lesions and or systemic involvement may require systemic therapy. The oral novel agents with lenalidomide and thalidomide in combination with dexamethasone may proof beneficial in these patients. As more cases get reported, we hope to better understand the pathophysiology and treatment of this disorder.

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