Clinical Medicine Insights: Dermatology

CASE REPORT

Clinical Response of Necrobiotic Xanthogranuloma to Treatment of Underlying Paraproteinemia with Lenalidomide

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Abstract: Necrobiotic xanthogranuloma (NXG) is a rare, chronic, histiocytic panniculitis associated with underlying paraproteinemia. This paraproteinemia, with monoclonal gammopathy of undetermined significance (MGUS), may be followed without treatment. We report a 62-year-old female with a history of progressive nodular and ulcerated lesions for many years who failed local and intralesional treatments. The skin lesions progressed to ulceration. Her paraprotein levels reduced when the underlying monoclonal gammopathy was treated with lenalidomide and dexamethasone. Healing and resolution of the skin lesions was seen in conjunction with reduction in serum paraprotein levels. Symptomatic skin lesions warrant treatment of the underlying paraproteinemia in the patient with NXG and MGUS. Treatment with lenalidomide and dexamethasone was successful in this patient.

Keywords: paraproteinemia, necrobiotic xanthogranuloma

Clinical Medicine Insights: Dermatology 2011:4 43–46

doi: 10.4137/CMD.S7858

This article is available from http://www.la-press.com.

Introduction

Necrobiotic xanthogranuloma (NXG) is a rare, chronic, histiocytic panniculitis known to be associated with paraproteinemia. Clinical features consist of indurated papulonodules and plaques of yellow-brown and violaceous coloration that often atrophy and ulcerate. Histopathology of the lesions shows a granulomatous infiltration of the dermis and subcutaneous tissue, containing multiple foam cells, Touton giant cells, and cholesterol clefts in the presence of degenerating collagen. The skin lesions may be asymptomatic but may progress to ulceration with pain. With no clear guidelines, treatments have ranged from chemotherapeutic drugs, commonly alkylating agents like chlorambucil or melphalan, to surgical excision, intralesional and systemic corticosteroids, and radiation, with variable success. A recent case report chronicled successful treatment with lenalidomide and dexamethasone. This case, from the same institution, independently employed the same treatment strategy with equal success.

Case Report

A 62-year-old Caucasian female with a 20-year history of neutropenia and at least a four-year history of progressive scattered lesions on her extremities was referred to dermatology. She had been injected numerous times with intralesional steroids. On physical examination, the patient was noted to have multiple 1–3 cm lesions with dusky-red and yellow coloration on her bilateral lower extremities, as well as new indurated and erythematous lesions on her left upper arm and right shoulder. On her right outer thigh, an ulcerated lesion with central crusting was apparent. Several lesions ascending to her left hip showed atrophy secondary to previous steroid injections. A punch biopsy of the new lesion on her left arm was obtained, yielding pathological findings of granulomatous dermatitis and panniculitis, compatible with NXG.

Following pathological diagnosis, a workup was initiated to identify possible underlying etiologies. In light of the association between NXG and gammopathy, serum protein electrophoresis was obtained, revealing an elevated serum paraprotein of 1.4 g/dL (0.00–0.00) and reduced serum albumin at 3.8 g/dL (4.2–5.3). Serum IgG was 2730 mg/dL (700–1600) and urine protein electrophoresis showed 2 mg/day of IgG kappa M protein. Additional laboratory values included a white blood cell count of 2200 cell/μL (4.0–11.0) with 40.6% neutrophils (42.0–66.0) and 17.4% lymphocytes (2.0–7.0). Hemoglobin was 12.1 g/dL (4.0–5.5), and erythrocyte sedimentation rate was 46 mm/hour (0–20). Blood urea nitrogen and creatinine were both within the reference ranges.

When previous records were obtained, it became clear that 14 years previously she had been found to have a paraprotein level of 1.0 and had since been observed for presumed monoclonal gammopathy of unknown significance (MGUS). Hematology was consulted for evaluation and management recommendations. Further observation was deemed appropriate.

A month later, she presented complaining of an uncomfortable new lesion. Examination revealed a 2×1.5 cm ulcerated lesion with surrounding erythema on the right thigh, draining yellow purulent material. She was treated for four weeks with cephalexin 500 mg three times daily with no response.

At this time, the decision was made to begin treatment of the gammopathy with lenalidomide 20 mg daily for 21 days with dexamethasone 36 mg each morning for four days on and four days off. For antithrombotic prophylaxis, aspirin 81 mg every other day was begun. At three weeks of treatment, serum paraprotein levels had reduced to 0.9 g/dL and serum IgG was within the reference range at 1600 mg/dL. Adverse effects reported by the patient at this time included insomnia, diarrhea, and a reduction in blood pressure.

Upon completion of a second course of the regimen, she displayed no new lesions and marked improvement of the existing lesions, although they retained their dusky yellowish hue. Four months later, serum paraprotein levels had further reduced to 0.2 g/dL. Physical examination six months post-treatment revealed atrophy and fading of the lesions as well as a significant reduction in palpability (Fig. 1).

Discussion

While there is no consensus for treatment of NXG, its association with paraproteinemia in 80% of patients is well established. With a chronic course, its management often proves challenging. This case provides an example of focused management of the underlying paraproteinemia and subsequent resolution of cutaneous disease.

The patient's skin findings were associated with underlying MGUS, a benign clonal immunoglobulin elevation. It is not believed to be an antecedent of

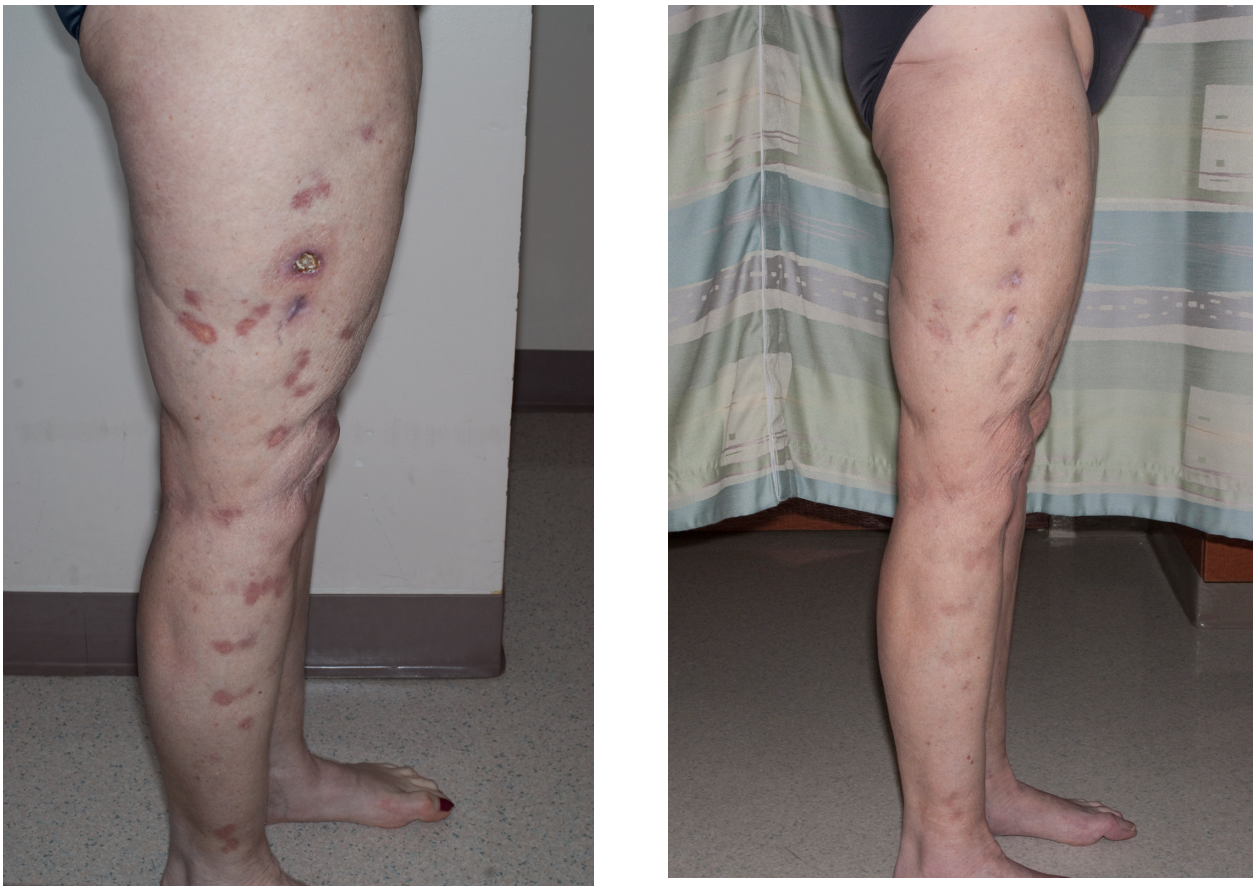

Figure 1. (**A**) Red-yellow nodules with ulceration of NXG before treatment. (**B**) Healing and resolution of skin lesions after treatment of underlying paraproteinemia.

malignancy, but an indicator of dysregulated B cell expansion. While asymptomatic patients typically do not require treatment, close monitoring is necessary because around 15% of patients with MGUS will eventually develop myeloma. Likewise, asymptomatic skin lesions do not necessitate treatment. However, if lesions ulcerate to nonhealing open wounds they become portals of infection and foci of pain, requiring treatment.

The suggested pathophysiology of NXG involves the formation of paraprotein-lipid complexes that likely precipitate a foreign body reaction and granuloma formation in the skin, as well as xanthoma formation resulting from cholesterol esterification in macrophages. Based around this model, chemotherapeutic agents have been used to reduce the level of paraprotein with subsequent improvement of cutaneous disease. Multiple reports have shown success with the use of alkylating agents, particularly chlorambucil. This patient was treated with lenalidomide and dexamethasone and experienced resolution of cutaneous lesions in association with a reduced paraprotein load.

Lenalidomide is an anticancer drug with immunomodulatory, antiangiogenic, and apoptotic properties. It is approved by the US Food and Drug Administration for the treatment of multiple myeloma and myelodysplastic syndromes. While related to thalidomide, lenalidomide causes lower rates of sedation, constipation, and neuropathy. Myelosuppression is the most frequently reported side effect. The association with thromboembolism, particularly when combined with dexamethasone, calls for mandatory antithrombotic prophylaxis. Due to potential teratogenicity, reliable forms of contraception and pregnancy testing are necessary in women of childbearing age, as well as registration in a restricted distribution program.

We have now had two patients at this institution whose paraproteinemia was being followed without treatment who developed symptomatic NXG skin lesions unresponsive to local and intralesional treatment. We consider that these skin lesions were

persistent, progressive, and unresponsive to treatment directed at the skin. Considering the clinical discomfort and appearance of these lesions and the potential for these skin lesions to be portals of infection, we believe the benefits of systemic treatment outweigh the potential side effects. We submit that treatment of the underlying paraproteinemia in these patients resulted in improvement and clearing of the skin lesions and that symptomatic skin lesions warrant such treatment.

Disclosure

Written consent was obtained from the patient to reproduce information and photographs for this article. Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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