Necrobiotic Xanthogranuloma of the Extremities With Paraproteinemia and Without Periorbital Involvement at Presentation

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We report a rare case of necrobiotic xanthogranuloma (NXG) of the extremities with paraproteinemia and without periorbital involvement at presentation in a 58-year-old white woman. A combination of oral cyclophosphamide and oral dexamethasone was attempted, but the patient then developed a left intraorbital lesion. Treatment was not successful in that the gammopathy did not improve and the patient continued to develop more lesions.

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Necrobiotic xanthogranuloma (NXG) is a rare inflammatory histiocytic disease of the skin and often is associated with paraproteinemia.[1] The disease has been well-documented in the literature (approximately 100 cases).[2,3] Necrobiotic xanthogranuloma appears to have no sex predilection and the average age of appearance is 56 years (range, 17–85 years).[4] Most reported cases have presented in the periorbital area.[5,6] We report a rare case of NXG/paraproteinemia that initially manifested in the extremities.

Case Report

A 58-year-old white woman presented in 2004 with a high-grade fever of 3 weeks' duration. At the time of presentation, she was diagnosed with a cytomegalovirus infection and was noted to have a few violaceous and erythematous subcutaneous nodules on her arms (Figure 1) and thighs. A slightly increased total serum protein level of 8.4 g/dL (reference range, 6.0–8.0 g/dL) also was noted. Her laboratory profile in 2005 did not reveal any abnormalities other than a rise of total serum protein to 8.6 g/dL (γ-globulin, 4.5 g/dL [reference range, 0.7–1.6 g/dL]). In mid-2006, her total serum protein level was 9.2 g/dL (γ-globulin, 5.1 g/dL), and quantitative immunoglobulin assay was requested. The results were as follows: IgG, 3314 mg/dL (reference range,

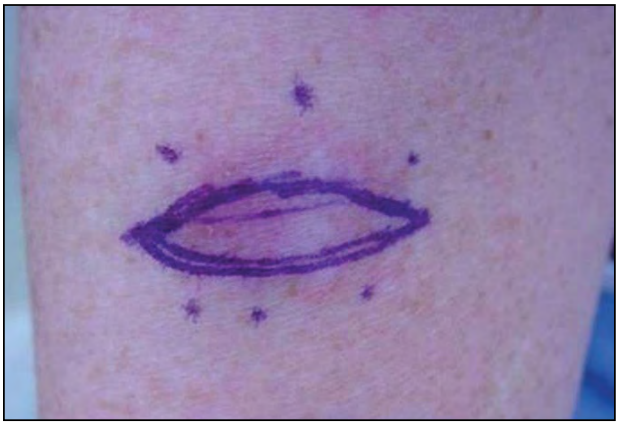

Figure 1. Gross appearance of the lesion showing an erythematous subcutaneous nodule.

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650–1600 mg/dL); IgA, 190 mg/dL (reference range, 40–350 mg/dL); IgM, 188 mg/dL (reference range, 54–300 mg/dL); and serum M-spike (shown by immunofixation to be IgG κ light chain), 2.2 mg/dL (reference range, 0.33–1.94 mg/dL). In late 2006, the following results were obtained: IgG, 3240 mg/dL; IgA, 189 mg/dL; IgM, 148 mg/dL; serum M-spike, 2.8 mg/dL; β_2-microglobulin, 2.3 mg/L (reference range, 1.2–2.8 mg/L); urine total protein, 90 mg/dL (reference range, 0–10 mg/dL); blood urea nitrogen, 9 mg/dL (reference range, 8–23 mg/dL); and plasma creatinine, 0.8 mg/dL (reference range, 0.6–1.2 mg/dL).

The patient continued to do well until early 2007 when she began for the first time to develop ophthalmologic concerns that were diagnosed as episcleritis. The patient was treated with topical corticosteroids, which gave her some temporary relief but did not resolve the issue. Also, the patient's subcutaneous nodules (3 lesions on the upper extremities, 1 lesion on the left thigh, and 1 lesion on the abdomen) had continued to grow, with the largest lesion being on her left forearm. Skin lesions were asymptomatic and she received no treatment. When the patient was referred to our dermatology clinic in late 2007, a subcutaneous nodule measuring 4.5×1.8×1.3 cm on the left arm was resected (Figure 2). Histopathologic examination revealed palisading arrays of foamy histiocytes throughout the dermis in company with large zones of degenerated collagen fibers and inflammatory cells (Figures 3 and 4). The lesion was diagnosed as NXG.

Because of the known association between NXG and monoclonal gammopathies, the patient underwent further evaluation, including a bone marrow aspiration biopsy, which showed 7% to 8% plasma cells. In late 2007, quantitative immunoglobulin assay showed the following results: IgG, 4040 mg/dL; IgA, 154 mg/dL; IgM, 1122 mg/dL; serum M-spike, 2.8 mg/dL; β_2-microglobulin, 2.3 mg/L; and free κ to γ light chain ratio, 3.7 (reference range, 0.26–1.65). Blood urea nitrogen was 11 mg/dL and plasma creatinine was 0.8 mg/dL. The skeletal survey showed no evidence of lytic bone disease. According to the results of bone densitometry, the patient was osteoporotic in her left hip. A diagnosis of monoclonal gammopathy of undetermined significance was made.

A recommendation was made to start the patient on a combination of oral cyclophosphamide (250 mg weekly for 4 weeks) and oral dexamethasone (20 mg twice daily on days 1 to 4 and 12 to 15). The patient then developed a localized left intraorbital NXG and worsening of skin lesions. Her monoclonal gammopathy, however, remained relatively stable.

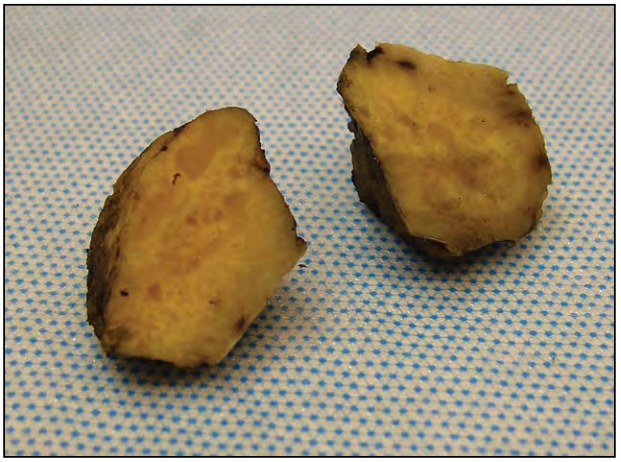

Figure 2. A resected subcutaneous nodule with uneven density showing a smooth yellow cut surface.

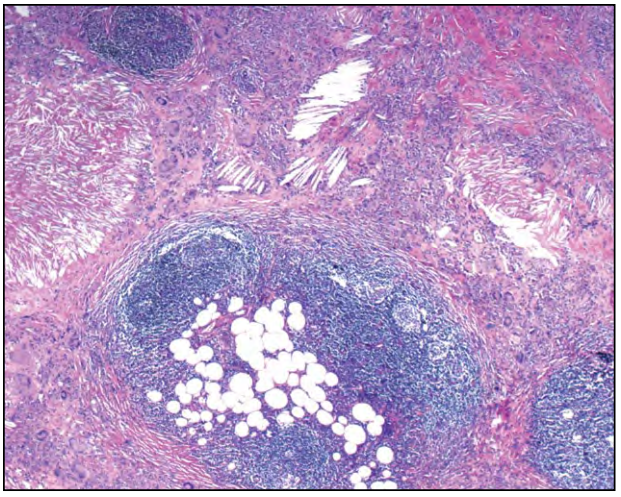

Figure 3. Subcutaneous zones of necrobiosis with interspersed lymphoid infiltrate and cholesterol clefts (H&E, original magnification ×40).

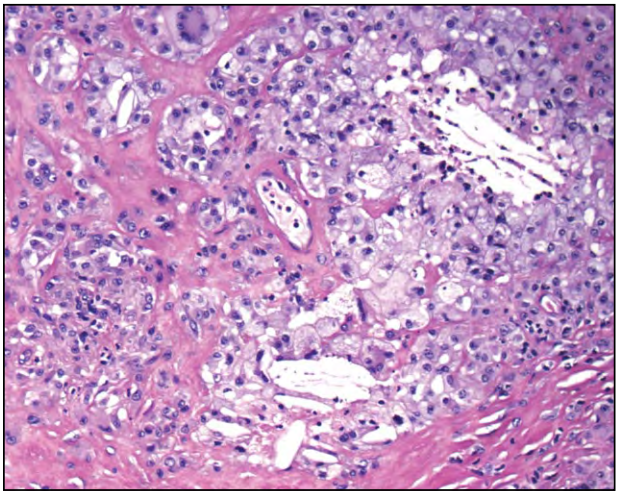

Figure 4. Fibrosis, cholesterol clefts, histiocytes, foam cells, and rare multinucleated giant cells (H&E, original magnification ×200).

Comment

The characteristic cutaneous lesions of NXG are slowly progressive and infiltrating yellow-brown xanthomatous nodules and plaques with destructive growth and a tendency for ulceration. Infiltrated plaques may show telangiectasia and central clearing or atrophy.[7] Lesions usually are asymptomatic but can be associated with tenderness, pruritus, and burning. The characteristic histopathologic finding is palisading granuloma with foam cells, Touton giant cells, and foreign body giant cells, cholesterol clefts, and zones of necrobiosis.[8] Histopathologic findings do not seem to have an appreciable correlation with clinical presentation, disease course, or extent of disease.[2] The disease is closely associated with IgG (and occasionally IgA) paraproteinemia. Monoclonal IgG κ light chain is the characteristic paraprotein of NXG.[9] Necrobiotic xanthogranuloma may rarely be associated with other conditions, such as conjunctivitis, keratitis, scleritis, uveitis, ectropion, and granulomatous infiltration of different organs such as the pharynx, lungs, epiglottis, larynx, bronchi, skeletal muscles, kidneys, liver, and spleen.[4,10] Necrobiotic xanthogranuloma is often confused both clinically and histologically with other granulomatous and xanthomatous entities.[11]

The periorbital region is the most commonly involved region of the skin in NXG.[5,6] The neck, trunk, and proximal limbs are occasionally involved, almost always accompanied by periorbital involvement.[12] Our patient first presented with arm and thigh involvement, and only after several months developed periorbital lesions. Involvement of extremities with no periorbital involvement at the first presentation is rare in NXG; our research from a PubMed search of articles indexed for MEDLINE using the term *necrobiotic xanthogranuloma* found only 15 such cases.[2,3,12-18] Our patient is the seventh case of NXG of the extremities with paraproteinemia and without periorbital involvement at presentation.[3,12,16-18]

There is no first-line treatment of NXG. Case reports describe treatment with excision, corticosteroids, alkylating agents such as melphalan and chlorambucil, plasmapheresis, interferon alfa, and bone marrow transplantation.[19,20] In a study of 17 NXG patients, the combination of low-dose corticosteroids and chlorambucil was the most effective treatment modality.[2] Our experience with administration of cyclophosphamide and corticosteroids was disappointing and the patient continued to develop new dermatologic lesions.

REFERENCES

1. Kossard S, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol*. 1980;3:257-270.
2. Wood AJ, Wagner MV, Abbott JJ, et al. Necrobiotic xanthogranuloma: a review of 17 cases with emphasis on clinical and pathologic correlation. *Arch Dermatol*. 2009;145:279-284.
3. Spicknall KE, Mehregan DA. Necrobiotic xanthogranuloma. *Int J Dermatol*. 2009;48:1-10.
4. Mehregan DA, Winkelmann RK. Necrobiotic xanthogranuloma. *Arch Dermatol*. 1992;128:94-100.
5. Rose GE, Patel BC, Garner A, et al. Orbital xanthogranuloma in adults. *Br J Ophthalmol*. 1991;75:680-684.
6. Codère F, Lee RD, Anderson RL. Necrobiotic xanthogranuloma of the eyelid. *Arch Ophthalmol*. 1983;101:60-63.
7. Ugurlu S, Bartley GB, Gibson LE. Necrobiotic xanthogranuloma: long-term outcome of ocular and systemic involvement. *Am J Ophthalmol*. 2000;129:651-657.
8. Williford PM, White WL, Jorrizzo JL, et al. The spectrum of normolipemic plane xanthoma. *Am J Dermatopathol*. 1993;15:572-575.
9. Venencie PY, Doukan S, Vieillefond A, et al. Necrobiotic xanthogranuloma with paraproteinemia [in French]. *Ann Dermatol Venereol*. 1992;119:825-827.
10. Umbert I, Winkelmann RK. Necrobiotic xanthogranuloma with cardiac involvement. *Br J Dermatol*. 1995;133:438-443.
11. Johnston KA, Grimwood RE, Meffert JJ, et al. Necrobiotic xanthogranuloma with paraproteinemia: an evolving presentation. *Cutis*. 1997;59:333-336.
12. Mcgregor JM, Miller J, Smith NP, et al. Necrobiotic xanthogranuloma without periorbital lesions. *J Am Acad Dermatol*. 1993;29:466-469.
13. Chang SE, Lee WS, Lee MW, et al. A case of necrobiotic xanthogranuloma without paraproteinemia presenting as a solitary tumor on the thigh. *Int J Dermatol*. 2003;42:470-472.
14. Chandra S, Finklestein E, Gill D. Necrobiotic xanthogranuloma occurring within linear morphoea. *Australas J Dermatol*. 2002;43:52-54.
15. Betts CM, Pasquinelli G, Costa AM, et al. Necrobiotic xanthogranuloma without periorbital involvement: an ultrastructural investigation. *Ultrastruct Pathol*. 2001;25:437-444.
16. Chave TA, Hutchinson PE. Necrobiotic xanthogranuloma with two monoclonal paraproteins and no periorbital involvement at presentation. *Clin Exp Dermatol*. 2001;26:493-496.
17. Smith HG, Sargent LA, Lundgrin DB. Necrobiotic xanthogranuloma of the chest wall. *Dermatol Online J*. 2006;12:12.
18. Yasukawa K, Kato N, Hamasaka A, et al. Necrobiotic xanthogranuloma: isolated skeletal muscle involvement and unusual changes. *J Am Acad Dermatol*. 2005;52:729-731.

19. Torabian SZ, Fazel N, Knuttle R. Necrobiotic xanthogranuloma treated with chlorambucil. *Dermatol Online J*. 2006;12:11.
20. Goede JS, Misselwitz B, Taverna C, et al. Necrobiotic xanthogranuloma successfully treated with autologous stem cell transplantation [published online ahead of print January 11, 2007]. *Ann Hematol*. 2007;86:303-306.