Necrobiotic xanthogranuloma with type 1 cryoglobulinemia mimicking necrobiosis lipoidica in a young woman with myeloma

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Key words: myeloma; necrobiosis lipoidica; necrobiotic xanthogranuloma; type 1 cryoglobulinemia.

INTRODUCTION

Necrobiotic xanthogranuloma (NXG) is a rare condition currently classified as a non–Langerhans cell histiocytosis and associated with an underlying paraproteinemia (most commonly IgG-κ) in approximately 80% of patients.[1] Recent diagnostic criteria have been proposed, including 2 major criteria of clinical and histopathologic features consistent with NXG and 2 minor criteria of paraproteinemia, plasma cell dyscrasia, and/or other associated lymphoproliferative disorder and periorbital distribution of cutaneous lesions in the absence of a foreign body, infection, or other identifiable cause.[2] Necrobiosis lipoidica (NL) is a rare, chronic granulomatous disease historically associated with diabetes mellitus, although the strength of that association has been called into question.[3] Other reported associations include hypertension, dyslipidemia, and thyroid disease.[4] It is almost exclusively seen on the lower extremities (98% of the anatomic locations specified) of women (84% of the affected patients), according to a recent multicenter retrospective review, and can be very difficult to treat.[4,5]

In this study, we report a patient with ulcerated, atrophic, yellowish, peripherally telangiectatic plaques on the bilateral lower extremities almost perfectly simulating NL that was, in fact, NXG from myeloma with an associated type 1 cryoglobulinemia.

Abbreviations used:

NL: necrobiosis lipoidica
NXG: necrobiotic xanthogranuloma

CASE REPORT

A 33-year-old Caucasian woman with a past medical history significant for BRCA2 heterozygosity and a family history significant for maternal breast cancer presented for a second opinion for the evaluation of a painful, worsening, ulcerating rash on the bilateral lower extremities that had been present for 4 years and, in recent months, had started to involve her right upper extremity and lower abdomen (Figs 1 and 2). Her face and neck were not involved. A biopsy obtained from the right posterior thigh on initial presentation to an outside nondermatologist clinician in 2016 was read as a palisaded granulomatous dermatitis with increased mucin on Alcian blue staining, consistent with granuloma annulare; an independent review of the slide by in-house dermatopathology was favored to represent NL, although the histologic findings were somewhat ambiguous and granuloma annulare remained a diagnostic possibility. Conservative treatments with compression stockings, topical 0.05% clobetasol ointment under occlusion, 0.1% tacrolimus ointment, 100-mg oral doxycycline daily for 2 months, and intralesional triamcinolone were all attempted, with progression of the disease. Her hemoglobin A1c and thyroid-stimulating hormone levels were within normal limits; she was up to date on mammograms and breast magnetic resonance imaging, given her BRCA2 status. In anticipation of starting a more aggressive systemic therapy, a complete metabolic panel and blood count were obtained and were notable for an elevated

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Funding sources: None.
IRB approval status: Not applicable.
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JAAD Case Reports 2022;21:195-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.01.008

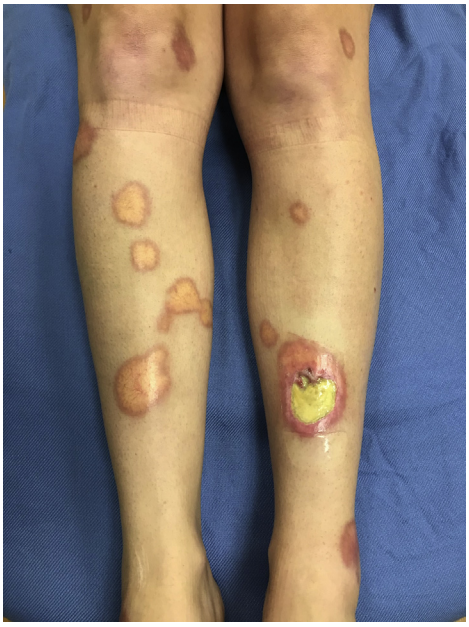

Fig 1. Centrally yellowish, peripherally telangiectatic and indurated plaques on the bilateral lower extremities, including an ulcerated plaque on the left shin.

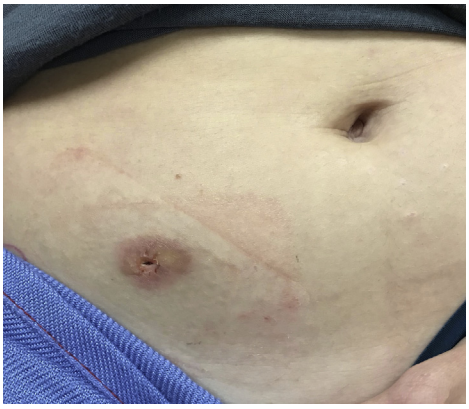

Fig 2. A dusky, smooth, pink-brown plaque on the right side of the lower abdomen (focal ulceration is from prior biopsy).

globulin gap of 5.3 (upper limit of normal, 4.0; total protein level, 8.7 g/dL; upper limit of normal, 8.2 g/dL) and albumin level of 3.4 g/dL (lower limit of normal, 3.6 g/dL). The serum calcium and hemoglobin levels and platelet counts were within normal limits; the white blood cell count was low, at 4000/mL (lower limit of normal, 4.2); and the mean corpuscular volume was high, at 101.1 fL (upper limit of normal, 100.0). Serum protein electrophoresis was performed to better characterize this protein elevation and revealed a lambda-restricted IgG monoclonal gammopathy measuring 2.2 g/dL. Serum cryoglobulins were obtained, and immunofixation was positive for type I cryoglobulinemia.

In light of the patient's gammopathy, repeat skin biopsies were obtained from the most recently developed lesions on the right forearm and inferior abdomen; they showed dermal to subcutaneous sclerosis with intermixed granulomatous inflammation, with areas of cholesterol clefting and large multinucleated giant cells, consistent with necrobiotic xanthogranuloma (Fig 3). Yeast-like spherules of amorphous eosinophilic material were noted focally in a small but deep dermal vessel and stained positively with Von Kossa and negatively with Grocott methenamine silver, Gram, Fontana-Masson, and mucicarmine (Fig 4). These were believed to be dystrophic calcifications, although it is unknown if these were due to her underlying NXG, type 1 cryoglobulinemia, or trauma from prior biopsy/ulceration. A repeat skin biopsy and blood draw for fungal cultures and extensive fungal laboratory workup, including cerebrospinal fluid analysis, were obtained by Infectious Disease and Neurology departments to rule out a potential contributing deep fungal infection were negative. Hematology was consulted and obtained a bone marrow biopsy that revealed a light-chain restricted plasma cell myeloma involving 10% to 12% of essentially normocellular bone marrow, mild normocytic anemia with absent bone marrow stainable iron, and background trilineage hematopoiesis with slight megakaryocytic hyperplasia. Flow cytometry, karyotyping, and fluorescent in situ hybridization were within normal limits. The patient was started on monthly single-agent daratumumab and dexamethasone for fertility conservation, with bortezomib added during cycle 4 to augment the response.

DISCUSSION

Seventy-five percent to 80% of patients with NXG will have periorbital or other facial involvement; extrafacial involvement can occur on the upper and lower extremities, trunk, and even genitals.[2,6] Extracutaneous necrotizing granulomas most commonly present in the eyes, liver/spleen, lymph nodes, and sinuses, although tracheal, brain, parotid, lung, heart, and skeletal muscle involvement have also been reported.[2,7] In addition to myeloma, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, Hodgkin lymphoma, and lymphoplasmacytic lymphoma have all been observed in association with NXG.[8] Concomitant type 1 cryoglobulinemia is not uncommon, with approximately one-fourth of screened patients demonstrating positivity in multiple studies.[8,9] We are not aware of any studies in which histopathologic evidence of dystrophic calcification

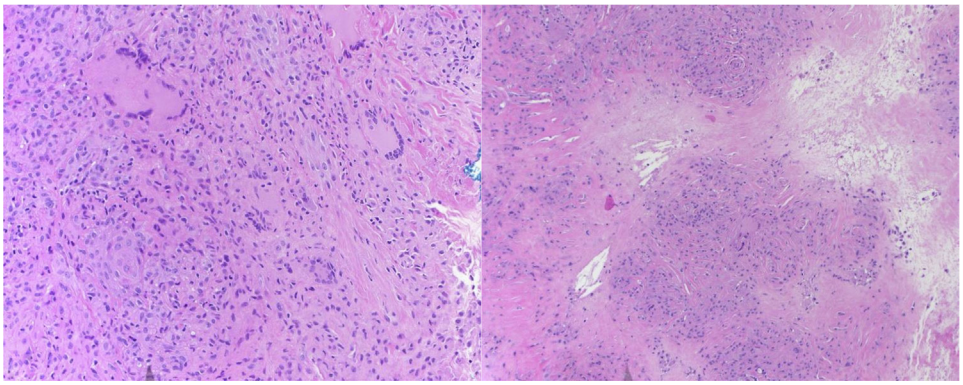

Fig 3. Granulomatous inflammation with areas of cholesterol clefting and large multinucleated giant cells.

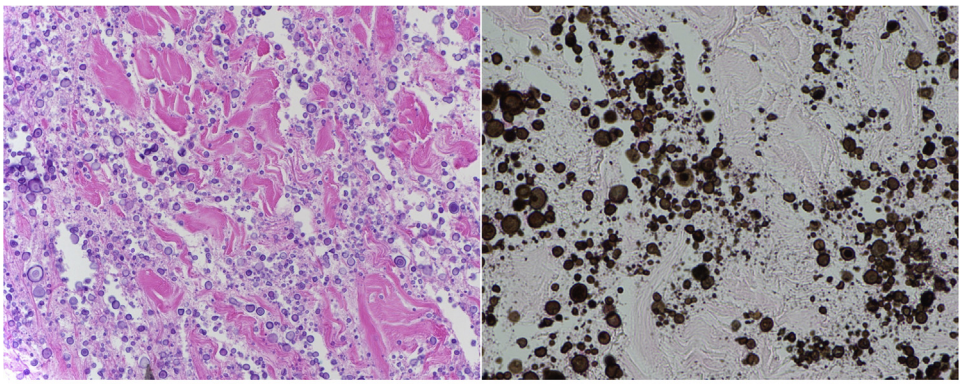

Fig 4. Yeast-like spherules of amorphous eosinophilic material (**A**) and positive Von Kossa stain (**B**), consistent with dystrophic calcifications.

resembling yeast-like spherules has been observed on skin biopsy in patients with NXG or type 1 cryoglobulinemia. We are, furthermore, not aware of any increased risk of myeloma in patients carrying BRCA2 mutations, which makes our patient's young age at presentation all the more exceptional.[10]

NXG simulating NL on the bilateral lower extremities of a young woman may be an unrecognized presentation. In atypical presentations of NL (such as those with truncal involvement), skin biopsy and further evaluation based on screening laboratories are warranted.

Conflicts of interest

None disclosed.

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