A 75-year-old woman was referred to the hematology clinic for a 2-year history of erythematous skin lesions. One year after the initial lesions erupted, physical examination showed extensive xanthomatous plaques with erythematous borders on the neck, chest, breasts, abdomen, arms, thighs, and eyelids (Figure 1A). She had no associated systemic or focal symptoms. Initial biopsy at this time was interpreted as consistent with atypical granuloma annulare. However, lesions were not responsive to topical or intralesional corticosteroids or ultraviolet B phototherapy. Nine months after the initial biopsy, a repeat biopsy was performed, which revealed alternating areas of granulomatous infiltrate and eosinophilic necrobiosis filling the dermis. These were associated foamy macrophages, variably lipidized multinucleated giant cells (including Touton type), and prominent cholesterol clefts. Overall, the findings were consistent with necrobiotic xanthogranuloma (NXG) (Figure 2A and B). Unfortunately, diagnostic delays are not uncommon owing to the rare nature of NXG. Approximately 2 years after the initial development of skin lesions, a hematologic workup was performed. Serum electrophoresis with immunofixation revealed an immunoglobulin G (IgG) lambda monoclonal paraprotein of 0.7 g per deciliter. Renal function and blood counts were normal. Marrow evaluation was notable for increased lambda light-chain–restricted plasma cell and lymphoplasmacytic B-cell populations, shown to be clonally related. Fludeoxyglucose (18F) positron emission tomography/computed tomography (18F-FDG PET/CT) demonstrated FDG avidity of cutaneous lesions (Figure 1C) and showed no suspicious osseous foci of myelomatous disease. She was diagnosed with an underlying smoldering myeloma.

FIGURE 1. Discrete yellow indurated plaques with erythematous borders on the chest, breasts, and extremities pre- (A) and post-treatment (B), with associated fludeoxyglucose (18F) avidity on positron emission tomography/computed tomography (C).
The NXG was initially treated with myeloma-directed therapy. Her lesions demonstrated marked response to initial treatment with lenalidomide + dexamethasone (Figure 1B), completing a total of 5 cycles, which was discontinued because of neutropenia. She was transitioned to bortezomib + dexamethasone x 6 cycles, again complicated by neutropenia. Similarly, ixazomib + dexamethasone and pomalidomide + dexamethasone were not tolerated, prompting abandonment of myeloma-directed therapy. She was subsequently treated with monthly intravenous immune globulin (IVIG) 1 g/kg, which has been well tolerated and extremely effective.

Necrobiotic xanthogranuloma is a rare disorder, categorized as a cutaneous non-Langerhans cell histiocytosis, often associated with a paraproteinemia, typically of IgG isotype. It often presents as a paraneoplastic syndrome in the setting of an underlying hematologic neoplasm such as a plasma cell dyscrasia, lymphoma, or—rarely—leukemia. The average age at onset is 58 ± 15 years. Skin manifestations include indurated papules or nodules, which may coalesce into large plaques. Lesions may be asymptomatic or pruritic. The distribution typically involves the trunk, extremities, and periorbital region. Lesions are the result of active inflammation as opposed to the presence of monoclonal plasma cells or monoclonal immunoglobulin. The pathogenesis of NXG is thought to involve an interaction between monoclonal immunoglobulin and lipoproteins, which produces immune complexes, and a characteristic inflammatory pattern involving elevated interleukin (IL)-15; IL-15 promotes macrophage phagocytic activity and secretion of proinflammatory cytokines. Skin-resident macrophages, which have phagocyted the immune complexes, accumulate cholesterol. There is no standard approach to management. Commonly used treatments include systemic corticosteroids, immunomodulatory drugs, high-dose IVIG, alkylating agents, cladribine, antimetabolites, and tumor necrosis factor (TNF)-α inhibitors. Although, historically, treatment has been targeted at an underlying hematologic condition, a recent multicenter cohort found that IVIG had the best treatment response (9 of 9 patients).

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