Clinical Features and Treatment Outcomes of Patients With Necrobiotic Xanthogranuloma Associated With Monoclonal Gammopathies

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Abstract

Necrobiotic xanthogranuloma is a rare chronic granulomatous disorder of the skin associated with a monoclonal gammopathy. We report the findings from a single tertiary medical center retrospective study describing the clinical features of 35 patients with necrobiotic xanthogranuloma and monoclonal gammopathy and their subsequent disease course and response to treatment.

Introduction: Necrobiotic xanthogranuloma (NXG) is a rare chronic granulomatous disorder of the skin associated with a monoclonal gammopathy. **Patients and Methods:** The present report describes the findings from a single tertiary medical center retrospective study, including the clinical features of 35 patients with NXG and monoclonal gammopathy from 2000 to 2015 and their subsequent disease course and treatment response. The median age at diagnosis was 56 years (range, 26-88 years). **Results:** Most patients had a plasma cell dyscrasia consisting of monoclonal gammopathy of undetermined significance in 28 patients and smoldering multiple myeloma in 5 patients; the remaining 2 patients had chronic lymphocytic leukemia. An IgG isotype of monoclonal gammopathy was present in almost all the patients (97%). The most common site of cutaneous involvement of NXG was periorbital (66%). The treatments were heterogeneous and included excision, intralesional injection, radiotherapy, and systemic chemotherapy. The median follow-up period was 46 months (range, 4 to 234 months). The median overall survival had not been reached at the analysis, and 80% of the patients were still alive. Eight patients (23%) had disease progression to multiple myeloma at a median of 67 months (range, 21 to 107 months), demonstrating that although the clinical course is generally indolent, malignant transformation is not uncommon. At the last follow-up visit, 80% had signs of either clinical improvement or stable skin disease. **Conclusion:** Cutaneous objective responses can be achieved with treatment of lymphoplasmacytic malignancies.

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Introduction

Necrobiotic xanthogranuloma (NXG) is a rare skin disorder characterized by slowly progressive granulomas within the subcutaneous and dermal layers of the skin with focal areas of necrobiosis.[1,2] They can appear as yellowish to red-orange or violaceous plaques, nodules, or papules, with areas of ulceration, telangiectasia, or atrophy (Figure 1). These lesions are associated with giant cells (Touton type), cholesterol clefts, and foam cells, which are necessary to confirm the diagnosis.[1]

The association between NXG and hematologic disorders with monoclonal gammopathy was first described by Kossard and Winkelmann.[3] The most commonly described association has been with plasma cell dyscrasias, such as monoclonal gammopathy of undetermined significance (MGUS),[4] smoldering multiple myeloma (SMM),[5] and multiple myeloma (MM).[6] Other reported associations include non-Hodgkin lymphoma, chronic lymphocytic leukemia

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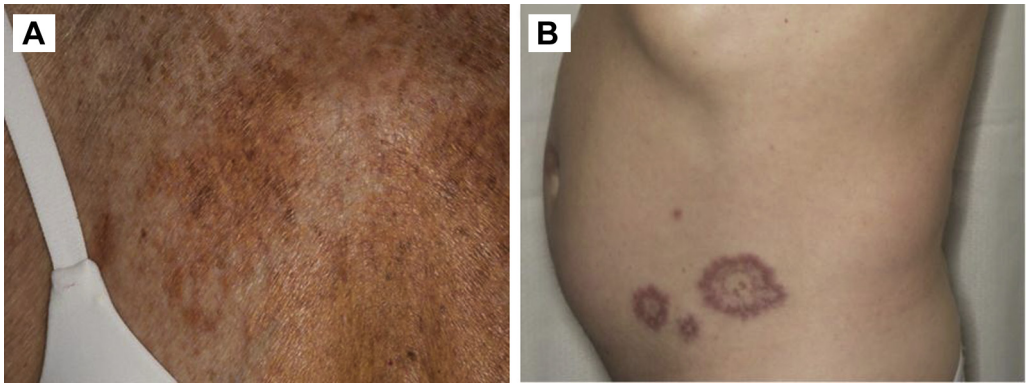
Figure 1 Yellowish to Brown, Raised Plaque Lesions Consistent With Necrobiotic Xanthogranuloma on (A) the Chest of a Patient and (B) the Abdominal Flank of a Patient



(CLL),[7] Hodgkin lymphoma,[8] and lymphoplasmacytic lymphoma.[9] Various treatment modalities have been used, and variable dermatologic responses have been observed with immunomodulatory drugs (IMiDs)[10] and proteasome inhibitors (PIs), immunosuppressive agents, alkylating agents, corticosteroids, and high-dose chemotherapy followed by autologous stem cell transplantation.[11] Such strategies have been used in addition to local therapy, including local steroid injections or carbon dioxide laser treatment.[9] Given its rarity, no consensus guidelines have been published on the optimal management of this condition. The lack of consensus has been reflected by the heterogeneity of the treatment regimens used by physicians whose treatment decisions must largely be based on limited data from case reports and anecdotal evidence. In the present report, we describe the largest single-center experience on the presentation, natural history, and treatment outcomes of patients with NXG associated with monoclonal gammopathy.

Patients and Methods

The Mayo Clinic's data discovery and query database was searched to identify patients with a histologic diagnosis of NXG from January 1, 2000 to December 31, 2014. The electronic medical records of the individual patients identified were reviewed. Patients were included if they met the following criteria: (1) the presence of NXG skin lesions confirmed by histopathologic examination; and (2) the documented presence of a monoclonal gammopathy detected by protein electrophoresis and/or immunofixation in either serum or urine. The Mayo Clinic institutional review board approved the present study, in accordance with federal regulations and the Declaration of Helsinki.

For the patients included in the present study, the following data were collected: patient demographics and characteristics, location of the NXG lesions, and the hematologic characteristics. The sites of skin involvement were those documented by the physician from the patient's history and physical examination and any lesions identified on the cross-sectional imaging studies. The laboratory parameters collected included the complete blood cell counts, erythrocyte sedimentation rate, C-reactive protein, total complement activity (CH50), C3, C4, cryoglobulins, lipid panel, and β_2-microglobulin, when available.

We collected data on the treatments used to manage the NXG lesions in our patient population and analyzed both their dermatologic responses and the hematologic outcomes. The response to therapy was evaluated by reviewing each patient's medical record and assessing the response in the skin lesions. A clinical response was defined as a decrease in the size or number of NXG lesions, and progression was defined as an increase in the size or number of the NXG lesions. Clinical benefit was defined as the percentage of patients with either a decrease or no change in the size or number of the NXG lesions. Statistical analysis was performed using the SAS biostatistical software JMP, version 10.0.1 (SAS Institute Inc., Cary, NC). Survival and follow-up analysis was done using the forward and reverse Kaplan-Meier method, respectively.

Results

Patient Demographics

A total of 35 patients with NXG and coexistent paraproteinemia were included in the present study. The monoclonal gammopathy was MGUS in 28 patients (80%), SMM in 5 (14%), and CLL in 2 patients (6%). The clinical and histopathologic characteristics of these 35 patients are listed in Table 1. Of these patients, 17 were men (49%). The median age at diagnosis was 56 years (range, 26-88 years). Of the 35 patients in our study cohort, 34 (97%) had an IgG isotype of the monoclonal gammopathy. In 25 of 32 patients in this cohort (78%), monoclonal gammopathy testing was initiated only after an initial histopathologic diagnosis of NXG (accurate dates of monoclonal gammopathy testing in the remaining 3 patients was not available).

Anatomic Location of Lesions

The anatomic distribution of the NXG lesions is also listed in Table 1. The most common site for NXG involvement was the periorbital region (n = 23; 66%). NXG lesions were present at the site of a scar, from either a previous NXG excision or an unrelated surgical scar, in 8 patients (24%). These included scars after appendectomy, thyroidectomy, and splenectomy, as well as smaller incisions for shoulder arthroscopy in 1 patient. Extracutaneous NXG lesions were reported in 6 patients (17%), including 4 with