Necrobiotic Xanthogranuloma

A Review of 17 Cases With Emphasis on Clinical and Pathologic Correlation

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Objective: To identify correlations between clinical presentation, specific histopathologic findings, and subsequent disease course in patients with necrobiotic xanthogranuloma (NXG).

Design: Retrospective review of medical records and histopathologic examination of fixed tissue samples.

Setting: Tertiary care medical center.


Main Outcome Measures: Description and distribution of clinical lesions, presence of monoclonal gammopathy, multiple myeloma, and correlation with microscopic patterns of skin lesions.

Results: Eleven patients (65%) showed involvement of the periorbital area, and the trunk was affected in 8 patients (47%). Twelve patients (71%) had a monoclonal gammopathy; of these, 3 (18%) had multiple myeloma. Histopathologic examination of 12 patients showed findings consistent with NXG, including a bandlike pattern of necrobiotic granulomatous inflammation, atypical giant cells, cholesterol clefts, and plasma cells. No correlations were identified between clinical presentation and specific histopathologic findings. Although most patients had a serum monoclonal gammopathy, staining with antibodies to CD3, CD20, κ light chains, and λ light chains showed polytypic lymphocytes and plasma cells in all cases.

Conclusions: The association between NXG and paraproteinemia is well documented and corroborated by this study. However, the skin lesions in NXG represent reactive inflammation and are not associated with the presence of monoclonal plasma cells or multiple myeloma.

Arch Dermatol. 2009;145(3):279-284
between clinical presentation, specific histopathologic findings, and subsequent disease course of NXG. We also sought to determine whether the inflammatory cells of NXG lesions were polytypic or monotypic and whether this correlated with the presence or absence of a monoclonal gammopathy.

**METHODS**

This study was approved by the Mayo Clinic Institutional Review Board. Seventeen patients with a history of NXG were identified from the dermatology records in the Mayo Clinic archives. One patient had been included in a previous NXG study. Clinical data, including age, sex, clinical presentation, treatment, and outcome, were abstracted from electronic and paper medical records. Histopathologic examination was performed on tissues fixed in neutral, buffered formalin and embedded in paraffin. Hematoxylin-eosin–stained slides were available for secondary review in 12 cases, although all 17 patients had documented pathologic findings consistent with NXG based on slides previously reviewed by Mayo Clinic dermatopathologists. Paraffin-embedded tissue blocks from 11 cases were cut and stained with antibodies against the following antigens: CD3, CD20, IgG4, and GLUT1.

IgG4 is the least common of the IgG subclasses, typically comprising 6% of total IgG. Elevated serum IgG4 levels are associated with allergic and autoimmune disorders such as autoimmune pancreatitis, inflammatory pseudotumor, and pemphigus vulgaris. An intense cytoplasmic staining pattern is seen in IgG4-positive plasma cells. GLUT1 is a ubiquitous membrane glucose transporter. It is activated by hypoxia-sensing cellular pathways and may sustain cellular metabolism via glycolysis when hypoxia occurs. GLUT1 may be upregulated in anoxic environments; when upregulated, it has a strong membrane staining pattern.

**RESULTS**

Nine of the 17 patients were men. The mean age at diagnosis was 52 years (range, 26-82 years). The mean age at disease onset was 49 years (range, 21-79 years). Eleven patients (65%) had periorbital involvement (Figure 1), and the trunk was the second most commonly affected site (8 patients [47%]). Sixteen patients (94%) were affected at more than 1 site. Ten patients (59%) reported dermatologic symptoms such as itching, burning, tenderness, and pain. Ulceration of lesions was observed in 8 patients (47%), and the lower extremities were affected in 4 patients (24%) (Figure 2).

Extracutaneous manifestations of disease were observed in 3 different patients with mastoid involvement, pulmonary lesions, and facial nerve palsy attributable to local invasion. Bilateral blindness developed in 1 patient, ptosis was observed in 1 patient, and 3 patients had partial visual occlusion due to NXG lesions. Other systemic findings included splenomegaly, hypertension, and hyperlipidemia (3 patients each), melanoma (1 patient), and cirrhosis and esophageal varices (1 patient).

Twelve patients (71%) had a serum monoclonal gammopathy (k gammopathy in 8 [47%] and $\lambda$ gammopathy in 4 [24%]), and 3 (18%) had multiple myeloma. Nine patients (53%) had plasmacytosis or a plasma cell proliferative disorder on bone marrow examination. One patient had both multiple myeloma and type 1 cryoglobulinemia.

The mean time from the first appearance of NXG lesions to the development of hematologic disorders was 2.4 years.

Follow-up data on treatment and response were available for 13 patients (mean follow-up time, 3 years). Chemotherapy was the most commonly administered treatment, used most often in combination with oral corticosteroids. Chemotherapy alone accounted for the improvement of 2 patients. Four patients received chlorambucil with prednisone; 2 achieved an excellent response, and 2 showed no improvement. One patient had a partial response to melphalan and prednisone. One patient underwent pulse dexamethasone treatment cycles for 1 year and showed marked improvement in skin lesions. Another patient was treated with prednisone and thalidomide for 3 years and achieved remission of skin lesions for 2 years.

Radiotherapy (15-24 Gy) was administered to 2 patients. One patient had ocular involvement, and radiotherapy resulted in partial improvement of the lesions. The lesions ultimately recurred and were excised surgically. No further recurrence has been documented to date. The other patient was treated unsuccessfully with chlorambucil and prednisone for lesions of the parotid gland and left lung; radiotherapy resulted in complete clearance of lesions.
other patients were treated with intralesional corticosteroids and topical immunomodulators but showed no response. Four patients died during the follow-up period; of these, 2 had multiple myeloma and presumably died of complications of the disease. Overall, we observed no associations between clinical characteristics, presentation of disease, and response to treatment.

Histopathologic findings for all 17 patients were reviewed by a dermatopathologist at our institution at the time of initial diagnosis. The cutaneous biopsies from 12 patients were reexamined for this study and showed findings consistent with NXG (Table). Almost all showed necrobiosis, and 10 cases (83%) showed a prominent, bandlike pattern of granulomatous inflammation alternating with inflammatory cells (Figure 3). Two cases showed sarcoidlike granulomatous inflammation (Figure 4). Foamy histiocytes were the main feature in 2 patients, and both patients were younger than 40. Ten cases (83%) contained atypical giant cells with multiple nuclei clustered at one end of the cell (“polarized” nuclei; Figure 5). Touton giant cells and asteroid bodies were present in some cases. All cases showed nodular lymphocytic or lymphoplasmacytic aggregates. Six cases showed increased numbers of plasma cells, and 3 contained dense plasma cell aggregates. We observed no correlations between clinical presentation and specific histopathologic findings such as atypical giant cells, necrobiosis, or plasma cells.

Immunohistochemistry was performed in 11 cases. All cases showed a polyclonal, reactive pattern when stained with antibodies to CD3, CD20, κ light chains, and λ light chains (Figure 6). One case had numerous IgG4-positive plasma cells, 4 cases showed only focal IgG4 staining, and 6 cases were completely negative. The GLUT1 staining pattern was scattered and focal in cells surrounding necrotic areas in 6 cases (55%). It was not upregulated in any case (Figure 7).

Necrobiotic xanthogranuloma is a chronic, progressive, multiorgan disease of unknown cause. Given the rarity

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Anatomic Site</th>
<th>Cholesterol Clefts</th>
<th>Atypical Giant Cells</th>
<th>Plasma Cell Grade</th>
<th>Nodular Lymphocytes</th>
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</table>

a The predominance of surrounding plasma cells was graded using the following scale: 1, scattered or few plasma cells; 2, moderate to numerous plasma cells; and 3, dense aggregates of plasma cells.
of NXG, no controlled therapeutic trials have been conducted to date; thus, prognostic factors have not been well established and no first-line therapy is recommended.7 Evaluation of therapeutic outcomes is extremely difficult because multiple treatments are used. In this study, we found the combination of low-dose corticosteroids and chlorambucil to be most effective. Of note, 2 patients with multiple myeloma showed improvement of their skin lesions after undergoing autologous peripheral stem cell transplantation followed by either chemotheray or corticosteroid treatment.

The clinical findings in this patient series were similar to those described in previous reports. Men and women were affected relatively equally, and the periorbital area was the most frequently involved site (11 [65%]). Ulceration of lesions was common (8 patients [47%]) and tended to be extensive and aggressive. Extracutaneous involvement by NXG has been reported in previous studies.9,12-18 In the present study, mastoid and pulmonary involvement by NXG was observed.

The association between NXG and hematologic disorders is well documented,2,5,6,19 and our study findings also support this association. Hematologic disorders may emerge before or after the onset of skin lesions (8 years before onset to at least 11 years after onset). For this reason, patients with NXG require lifelong follow-up care.2

The granulomatous inflammation in NXG skin lesions usually affects all layers of the dermis and often extends into the panniculus. The most obvious histopathologic features are large zones of necrobiosis surrounded by well-formed, palisading lymphohistiocytic granulomas. The necrobiotic areas are composed of altered collagen bundles that alternate with sheets of histiocytes and associated inflammatory cells to create a bandlike arrangement.1,3 Cholesterol clefts in the areas of necrobiosis are characteristic of NXG and are a helpful clue when considering the differential diagnosis.20 Granulomas typically include numerous giant cells, many of which have atypical histologic features such as polarized nuclei, massive size, or a large number of nuclei. Granulomas viewed under polarized light do not show foreign bodies.3 Fat droplets have been observed in the cytoplasm of histiocytic foam cells, and Touton cells can be highlighted with Oil red O and Sudan IV stains. A small amount of mucin deposition may be observed with Alcian blue stain, and Giemsa staining shows decreased or absent elastic fibers. Asteroid bodies and other nonspecific inclusions may also be present within giant cells.1,21 Immunohistochemical examination has shown that the histiocytes in NXG are CD68 positive and
CD1a negative, with no Birbeck granules, which corresponds to a non–Langerhans cell histiocytosis.1

This study also confirmed the microscopic similarities between necrobiosis lipoidica diabetorum (NLD) and NXG. These entities share a number of histologic features, including extensive hyaline necrobiosis, foreign-body giant cells, and lymphoid nodules.20 Clinically, NLD usually is not associated with a serum paraprotein. Atypical giant cells and Touton giant cells are more common in NXG, whereas NLD usually has broader bands of lipid deposition.20 Lymphoid nodules, usually composed of B cells, are 4 times more common in NXG.20 Cholesterol clefts also appear to be much more common in NXG.22 A review of 331 cases of NLD from a 50-year period identified only 3 cases with cholesterol clefts, and all were associated with severe diabetes mellitus.20

Aside from NLD, the differential diagnosis of NXG includes granuloma annulare, foreign-body granuloma, juvenile xanthogranuloma, rheumatoid nodules, amyloidosis, xanthoma disseminatum, and Erdheim-Chester disease.2 Erdheim-Chester disease is an idiopathic histiocytic disorder that most often affects the lungs, skeletal system, and central nervous system. Xanthomatous skin lesions also are commonly seen. As with NXG, the histiocytes of Erdheim-Chester disease are CD68 positive and CD1a negative, with no Birbeck granules. Although no histologic pattern is specific for NXG, the combination of typical clinical and pathologic findings allows definitive diagnosis of this disease.

There are several hypotheses regarding the pathophysiologic features of NXG. One theory suggests that the serum monoclonal protein may functionally resemble a lipoprotein; thus, it may bind to lipoprotein receptors on monocytes and induce xanthoma formation.1,23 Alternatively, paraproteinemia together with serum immunoglobulins may be deposited in the skin, eliciting a granulomatous response or foreign-body giant cell reaction.21 If this were true, a monocytic staining pattern would be expected. However, our study showed a polytypic staining pattern in the inflammatory cells of all 11 NXG skin biopsy specimens. In addition, the number of IgG4 plasma cells was not increased, which suggests that immune complex deposition is an unlikely instigating cause of skin lesions. A third hypothesis suggests that ischemia may cause necrobiosis.4 Our study examined expression of GLUT1, an indicator of tissue hypoxia. Despite the presence of necrobiosis in all 11 cases, GLUT1 was not upregulated in any patient. A recent report by Zelger et al14 suggests that NXG may be an infectious disease caused by spirochetal microorganisms, as 6 of 7 patients studied showed Borrelia species on focus-floating microscopic examination. No other studies have detected the presence of spirochetes in biopsy specimens from patients with NXG. Additional studies need to be done to determine whether these organisms are causative of NXG or merely passive bystanders.

Because NXG is such a rare disease, this study presented several challenges. Although we had a relatively large number of patients with NXG, the power of the study was limited by the low disease incidence. Our institution is a large referral center, so an inherent case selection bias was present. The retrospective nature of the study restricted us from drawing firm conclusions about the correlation of clinical and pathologic findings. Although the clinical characteristics of NXG are well documented, the potential immunologic mechanisms and pathogenesis of the disease are still poorly understood.

In conclusion, the etiology of NXG continues to be evasive. We did not show an appreciable correlation between clinical presentation and histopathologic findings. All skin biopsy specimens were consistent with a reactive phenomenon, despite a serum monoclonal protein in most cases. Furthermore, the histopathologic findings of NXG lesions appear to be a poor predictor of a serum monoclonal protein. No correlation between histopathologic findings and disease course or extent of disease was identified. More studies are needed to investigate the significance of the serum monoclonal gammopathy in patients with NXG.

Accepted for Publication: August 22, 2008.
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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wood, Wagner, Abbott, and Gibson. Acquisition of data: Wagner, Abbott, and Gibson. Analysis and interpretation of data: Wood, Wagner, and Gibson. Critical revision of the manuscript for important intellectual content: Wood, Wagner, and Gibson. Administrative, technical, and material support: Gibson. Study supervision: Wood, Abbott, and Gibson.

Financial Disclosure: None reported.

REFERENCES

Mount Tsukuba and the Origin of Tacrolimus

The historic, sacred mountain of Mount Tsukuba is situated approximately 60 km northeast of Tokyo in the central-eastern region of the Japanese archipelago. Rising 877 m above sea level, it comprises 2 distinct peaks: Nantai-san on the western side and Nyotai-san on the eastern side, both of which overlook the vast expanse of the Kanto plain. Part of the Tsukuba Quasi-National Park, Mount Tsukuba is a unique home to both cool and warm temperate plant communities, including deciduous and evergreen forests of Japanese beech, mizunara, and red oak, as well as 65 species of ferns. Several plants, including Tsukuba-kinnonso (Ajuga yesoensis var. tsukubana) and Tsukuba-torikabuto (Aconitum japonicum ssp. maritimum), were first discovered there.

Along with Mount Fuji, Mount Tsukuba is regarded as Nihon Hyakumeizan, one of the celebrated mountains in Japan. It is mentioned in Man'yōshū, the oldest anthology of Japanese poetic verse, as well as in the poetic verses of the revered 17th century haiku master, Matsuo Bashō. Despite its modest size, the mountainside of Mount Tsukuba is abundant with flora and fauna, in contrast to the barren landscape of Mount Fuji. Indeed, as folk legend explains, a god named Miyamori-Mikoto had once asked the 2 mountains for a place to spend the night. Smitten with pride because of its size and grandeur, Mount Fuji refused the request. However, when the deity approached Mount Tsukuba, he was warmly welcomed and treated with hospitality. Ever since then, Mount Tsukuba has been blessed with rich vegetation, while Mount Fuji has remained a cold and barren mountain.

Mount Tsukuba is also a place of spiritual worship. At the foot of the mountain lies a more than 1-century-old Shinto shrine, dedicated to a male divinity, Izanagi-no-Mikoto, and a female divinity, Izanami-no-Mikoto. According to the earliest recordings of Japanese mythology, the 2 deities wed and created the islands of Japan as well as other gods that presided over the newly formed land. The twin peaks of Mount Tsukuba are said to represent the male and female deities; they are worshipped as husband and wife, and couples visit the shrine to pray for happiness and marital bliss.

Importantly, tacrolimus has its origins in Mount Tsukuba. Tacrolimus was discovered during screening for immunosuppressive activity in compounds isolated from the fermentation broths of Streptomyces tsukubaensis, a bacteria found in the soil at the base of Mount Tsukuba. It was found to have strong immunosuppressive activity in vivo and prevented the activation of T lymphocytes in response to antigenic stimulation in vitro. Originally designated FK-506, it was later given the generic name of tacrolimus, derived from the words Mount Tsukuba, the site of its discovery; macrolide, its chemical classification; and immune suppressant, its primary effect in humans.

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