# A Patient With Necrobiotic Xanthogranuloma Presenting With an Anterior Mediastinal Mass, Plasma Cell Dyscrasia, and a Lymphoproliferative Disorder

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## Introduction

Necrobiotic xanthogranuloma (NXG) is a rare systemic disease primarily associated with cutaneous plaques; these plaques can manifest anywhere, but most commonly affect the face and periorbital regions. It has a distinct histopathology with extensive necrobiosis and infiltrates of inflammatory cells. Patients with NXG are often found to have paraproteinemia or hematologic disorders, including multiple myeloma or lymphoproliferative diseases. We describe a case of NXG in a patient without characteristic skin lesions, who was diagnosed after a biopsy of an anterior mediastinal mass. This case is also significant because the patient's bone marrow biopsy showed simultaneous lymphoproliferative and plasma cell disorders, which, to our knowledge, have not been reported in previous literature.

## Case Report

A 68-year-old man presented with a history of facial and neck swelling for over 15 years. During that time, he was treated for a possible infectious etiology, had surgery for ptosis, and was periodically monitored. He denied any fevers or chills and had no weight loss. His physical exam showed mild facial and cervical edema but did not reveal any lymphadenopathy or abnormal skin lesions. In 2009, as the edema worsened, a computed tomography (CT) scan of the chest was done, which showed a multilobulated, well-defined mass measuring 2.8 cm × 5.1 cm, primarily in the region of the thymus (Figure 1). There was almost complete obliteration of the right brachiocephalic vein and superior vena cava.

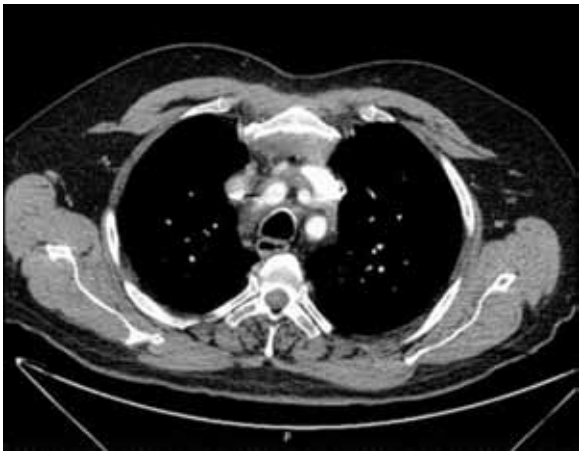

**Figure 1.** Anterior mediastinal mass with almost complete obliteration of the right brachiocephalic vein and superior vena cava.

A biopsy of the mass showed no evidence of malignancy, and gram stains and acid-fast bacilli (AFB) stains were negative for bacteria. The pathology showed soft tissue with necrobiosis; septal panniculitis; granuloma formation, including foamy histiocytes; Touton giant cells; and foreign body giant cell reaction with rare polarizable material consistent with NXG (Figure 2).

NXG has a known association with paraproteinemia and, in some cases, with hematologic malignancies. The patient was referred to the hematology clinic, and his complete blood count showed a mild thrombocytopenia with 115,000 cells/μL (normal, 150,000–450,000 cells/μL), a

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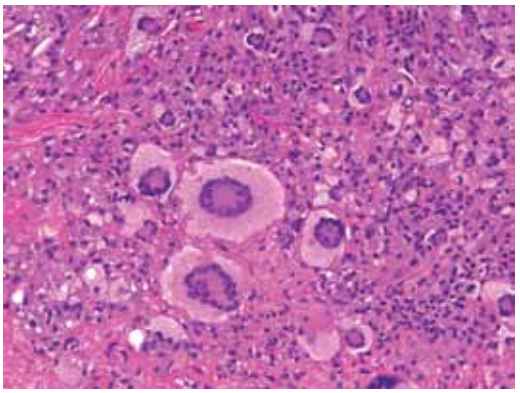

**Figure 2.** The lesion comprises many Touton-type giant cells and foamy histiocytes (200× magnification).

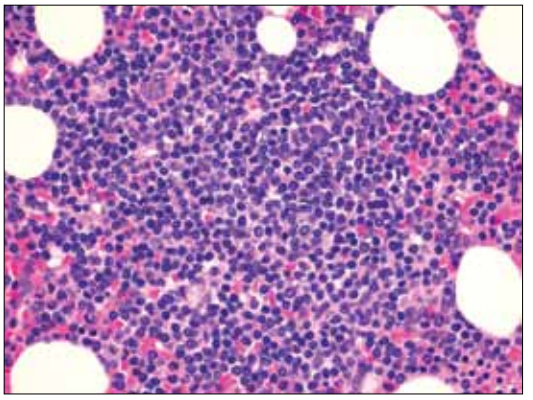

**Figure 3.** An ill-defined lymphoid aggregate composed of many small-to-medium–sized lymphocytes (400× magnification).

white blood cell count of 4,800 cells/μL and a hemoglobin of 15,700 cells/μL. His serum chemistries were significant for an elevated globulin of 3.8 g/dL (normal, 2.3–3.5 g/dL) and a low albumin to globulin ratio of 1.0 (normal, 1.1–2.2). His angiotensin-converting enzyme (ACE) level was 60 (normal, 9–67) and the beta-2 microglobulin was 3.6 mg/L (normal, 0.0–3.0 mg/L). His complement levels showed a C3 of 170 (normal, 88–203) and a C4 of 17 (normal, 13–49), while his C-reactive protein (CRP) was 7.3 mg/L (normal, 0.0–8.0 mg/L). Serum-free light chain analysis was positive for an elevated kappa level of 3.71 mg/dL (normal, 0.33–1.94 mg/dL) with a lambda level of 0.77 mg/dL (normal, 0.57–2.63 mg/dL), resulting in an elevated kappa to lambda ratio of 4.81 (normal, 0.26–1.65). Serum protein electrophoresis was normal, with an albumin of 4.1 g/dL (normal, 3.5–5.0 g/dL), an alpha-1 globulin of 0.4 g/dL (normal, 0.1–0.4 g/dL), an alpha-2 globulin of 0.8 g/dL (normal, 0.5–1.0 g/dL), a beta globulin of 0.8 g/dL (normal, 0.5–1.2 g/dL), and a gamma globulin of 1.3 g/dL (normal, 0.5–1.5 g/dL). Quantitative immunoglobulins were significant for a low IgM of 20 mg/dL (normal, 35–213 mg/dL), a low IgA of 35 mg/dL (normal, 59–292 mg/dL), and an IgG at the upper limit of normal with 1,500 mg/dL (normal, 596–1,584 mg/dL). Immunotyping electrophoresis showed an IgG kappa monoclonal gammopathy.

The patient's bone marrow biopsy was hypercellular with numerous ill-defined lymphoid aggregates composed of small-to-medium–sized lymphocytes, some with irregular nuclear contours (Figure 3). Although an increase in plasma cells was not seen by morphology, kappa and lambda in-situ hybridization revealed a kappa light chain restriction, with a kappa to lambda ratio of approximately 10:1, consistent with a monoclonal plasma cell population (Figure 4). Flow cytometry showed an additional lymphomatous infiltrate, with 4% of the cells co-expressing CD10 and CD19 B cells, and 3-color analysis of this small population showed kappa light chain restriction. Furthermore, polymerase chain reaction (PCR) of the bone marrow was positive for immunoglobulin heavy chain gene arrangement, which supported the flow cytometry findings of a B-cell malignancy.

The patient was thus diagnosed with concomitant lymphoproliferative and plasma cell disorders with associated NXG in an anterior mediastinal mass. Aside from facial and neck swelling, the patient has remained relatively asymptomatic and as such, no further treatment has been initiated. He will continue to be followed for progression of disease or symptoms caused by the anterior mediastinal mass.

## Discussion

NXG is a rare disorder with approximately 120 cases reported in the literature since it was first described in 1980.[1,2] To our knowledge, this is the first case in which NXG presented with an anterior mediastinal mass in a patient with both lymphoproliferative and plasma cell disorders.

The most common presentation of NXG is with firm yellow plaques and nodules occurring anywhere on the body, ranging from 0.3 to 25 cm in diameter. The majority of those with NXG have facial lesions, many of which are periorbital. Some patients have lesions on the trunk or extremities without any facial involvement.[3] The plaques are often violaceous with a yellow or xanthomatous hue, and telengiectasias may be present. The lesions do not usually cause symptoms, but can occasionally cause pruritus, burning, and tenderness.[4] The clinical course of these lesions is usually slowly progressive. However, ulceration,

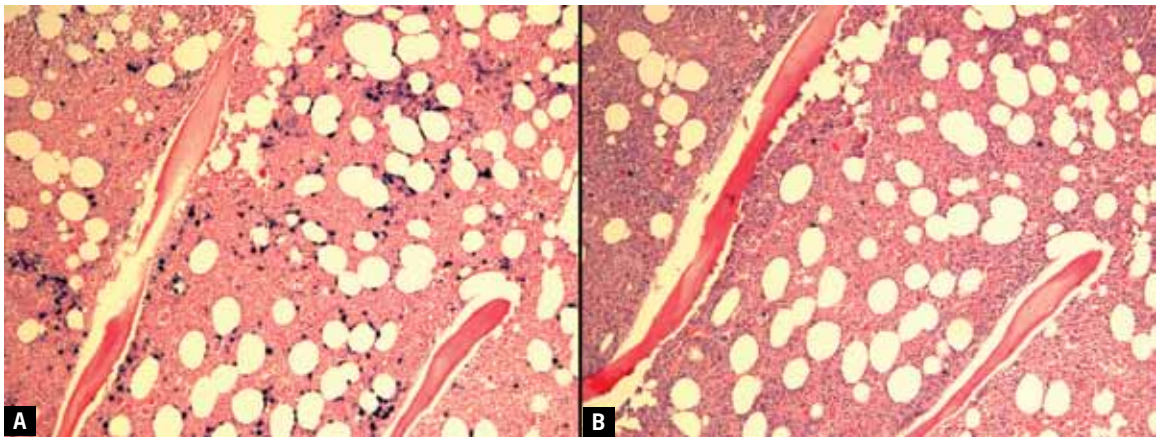


**Figure 4.** Kappa in-situ hybridization (100× magnification) of the bone marrow (A) shows many positive cells, with only rare positive lambda cells (B).

which can be extensive, has been reported in up to 47% of patients. There has also been a case report of severe destructive lesions that required amputation of the leg.[5] Some of these lesions can scar, and in a few cases, lesions developed on preexisting surgical scars.[6]

Ophthalmic complaints are also frequently encountered. In addition to the cutaneous lesions, which can have bilateral or unilateral ocular involvement, other ocular findings include diplopia, scleritis, decreased visual acuity, proptosis, blepharoptosis, and restricted ocular motility.[6] Several years before he was seen in our clinic, our patient had complained of ptosis, for which he had received surgery. No biopsy reports from that operation or imaging results of the orbits are available. However, he has had no other ocular complaints or findings since that time.

Although our literature search did not mention NXG of an anterior mediastinal mass, there have been reported cases of systemic involvement with no evidence of cutaneous disease. The respiratory tract, including the lung, epiglottis, larynx, pharynx, trachea, and bronchus, has been the most frequently reported site.[7,8] There have also been multiple cases of cardiac disease,[9] as well as patients with spleen,[1] lacrimal gland,[10] intracranial,[11] and skeletal muscle[12] involvement. These findings were sometimes not discovered until an autopsy was performed.[4]

A diagnosis of NXG requires characteristic histological findings on a biopsy. Granulomatous inflammation is usually band-like, consisting of inflammatory cells including foamy histiocytes, lymphocytes, Touton giant cells, and foreign body giant cells.[6] Most of the features extend from the middle dermis through the panniculus. The majority of cases exhibit cholesterol clefts within necrobiotic foci; however, this finding can be absent.[13] Biopsies also frequently show nodular lymphocytic or lymphoplasmacytic aggregates.[5] The alternative diagnosis to consider is necrobiosis lipodica (NLD). Both of these diseases have necrobiosis, foreign body giant cells, and lymphoid cells. However, NLD is not commonly associated with paraproteinemia, and Touton giant cells, lymphoid nodules, and cholesterol clefts are more common with NXG.[14]

Monoclonal gammopathy has been reported in up to 80% of patients diagnosed with NXG. IgG kappa gammopathy occurs in 63% of patients; 24% have IgG lambda gammopathy; and 1 case of IgA gammopathy has been reported.[4] In addition to a monoclonal gammopathy, NXG is also associated with other hematologic disorders, including multiple myeloma, plasma cell dyscrasia, and lymphoproliferative disorders. There have been cases of patients diagnosed with NXG who already had a diagnosis of another hematologic disorder. These malignancies have been seen as early as 8 years before the onset of skin lesions and as late as 11 years after the onset.[15,16] As a result of this association, most patients diagnosed with NXG eventually receive bone marrow biopsies. In Spicknall and Mehregan's review in 2009, of the 70 patients with NXG who had bone marrow biopsies, 17 patients (24%) had abnormal plasma cells, 10 patients (14%) had multiple myeloma, and 4 patients (6%) had a lymphoproliferative disorder.[1] The lymphoproliferative diseases included chronic lymphatic leukemia (CLL), Hodgkin lymphoma, 1 case with both CLL and non-Hodgkin lymphoma (NHL), and 1 case in which the bone marrow specimen exhibited a lymphoproliferative picture.[4,17] Our patient's bone marrow had evidence of both a lymphoproliferative and plasma cell disorder, a finding that has not been previously reported in the literature.

The pathogenesis of NXG is not fully understood. One hypothesis is that serum immunoglobulins form a complex with lipids and are deposited in the skin. This then causes a giant cell foreign body reaction, which

results in the NXG lesions.[18] Another proposal is that because the paraproteinemia is so pervasive in this disease, the lesions are a result of the proliferation of macrophages with an affinity for the Fc portion of the excessive immunoglobulins.[16] However, since paraproteinemia is sometimes absent in NXG, it may be more of a secondary finding rather than the actual cause.[19] There has also been research on the possibility that activated monocytes are driven to accumulate lipids, which deposit in the skin and then elicit an inflammatory reaction.[20] Finally, there is now some evidence that there may be an infectious component to this disease, since 6 of 7 patients examined in 1 report were found to have *Borrelia* by focus-floating microscopy of biopsy specimens.[21]

Several different treatment approaches for NXG have been attempted, with varying degrees of success. For patients with skin lesions, surgical excision has been used. In some cases, recurrence is rapid and new lesions are more severe than the original lesions, whereas others have had more favorable responses with extended remission periods.[6,22] Similarly, topical, intralesional, or systemic corticosteroids have resulted in inconsistent results.[13,23] Alkylating agents are frequently used for patients with and without plasma cell disorders, often in conjunction with steroids. Chlorambucil, cyclophosphamide, and melphalan have all been used; some lesions improve, some remain stable, and others improve only to recur.[24-26] Among patients with hematologic malignancies, trials of chemotherapy and stem cell transplant have sometimes resulted in improvement, whereas other cases showed no benefit or eventual recurrence.[15,17,27]

At this time, we have not started any treatment for our patient, since the anterior mediastinal mass is not causing significant symptoms. The patient's lymphoid and plasma cell disorders do not require therapy, and he is reluctant to undergo chemotherapy due to concerns regarding side effects.

## Conclusion

NXG is a rare condition, and available literature consists mostly of case reports and review articles. As a result, many questions pertaining to its pathogenesis and treatment remain. Our case confirms that NXG is a systemic disease that can present without characteristic skin findings. In fact, our patient's diagnosis was delayed for many years, until his symptoms resulted in imaging that showed an anterior mediastinal mass. This case also illustrates the important relationship between NXG and hematologic disorders. Our patient's bone marrow biopsy showed features of both lymphoproliferative and plasma cell disorders. The frequency of paraproteinemias and nodular lymphocytic aggregates suggests that there is a correlation between these disorders and NXG, but there is still not a full understanding of the pathophysiology. Hopefully, as more cases of NXG are discovered, and patients can be followed and continually studied, the role of these relationships in the etiology of NXG will be clarified.

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# Review
## Necrobiotic Xanthogranuloma

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Chen and colleagues describe an interesting case of a 68-year-old man presenting with facial and neck edema and mediastinal mass, with eventual diagnosis of necrobiotic xanthogranuloma (NXG) and associated plasma cell dyscrasias and lymphoproliferative disorder.[1] The rarity of this condition precludes it from being studied on a large scale, but as cases are reported and literature is reviewed, we can hopefully gain a better understanding of its pathophysiology and treatment.

NXG was first described in 1980 by Kossard and Winkelmann; they discussed 8 patients with xanthomatous plaques, noted to have monoclonal gammopathy, which were predominantly immunoglobulin G (IgG) kappa type.[2] Since then, more than 100 patients with this disorder have been described, with approximately 80% associated with a monoclonal gammopathy.

## Clinical Presentation

NXG is associated with slowly progressive, destructive, and infiltrating xanthomatous plaques and cutaneous lesions that can cause significant tissue destruction and systemic involvement. The lesions may ulcerate with areas of indurations consisting of yellow or xanthomatous discoloration.[3,4] The plaques and lesions may involve the trunk and extremities, but more than 80% of patients present with periorbital involvement. Most patients have asymptomatic lesions, but symptoms may include pruritis, paresthesias, burning, and pain. Lesions mostly appear in patients in their 5th to 6th decades of life, with documented cases ranging from 17 to 86 years of age.[5,6]

Physical findings outside of the skin lesions are often unrevealing, but in the case series by Mehregan, more than 20% of patients had hepatomegaly, and almost 20% had splenomegaly.[3] Hematologic involvement may include neutropenia, cryoglobulinemia, hypocomplementemia, and hyperlipidemia.[3] Systemic involvement includes multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and lymphoplasmacytic lymphoma, as well as the lung and heart.[7-12] However, the most common hematologic involvement is a plasma cell dyscrasia monoclonal gammopathy of unknown significance (MGUS), with up to 80% of patients presenting with IgG type with either kappa or lambda light chain. Chen and associates report the first case of concurrent plasma cell dyscrasias and a lymphoproliferative disorder, albeit one of very low involvement.

## Diagnosis and Pathophysiology

A histopathologic review of the lesion is important. Histologically, NXG is characterized by granuloma formation within the subcutaneous and dermal layers, with focal areas of necrobiosis. The granulomas consist of multinucleated giant cells of several types. Cholesterol clefts within the areas of necrobiosis give the foamy appearance that is often seen. Other characteristics and findings are thoroughly described by Chen and Balagula.[1,11] Given the association of NXG with MGUS and hematologic malignancies and disorders,

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serum immunoglobulins, free light chains, and routine complete blood and metabolic counts are necessary. A bone marrow biopsy with immunophenotyping, cytogenetic and molecular studies, and computed tomography (CT) scan of the chest, abdomen, and pelvis may be necessary, depending on physical exam and blood test results.

## Management

Management of NXG has ranged from watch-and-wait methods in asymptomatic patients, to surgery, radiation, plasmapheresis, intralesional corticosteroids, systemic and cytotoxic agents (eg, chlorambucil, melphalan, interferon alpha-2b, cyclophosphamide, methotrexate, hydroxychloroquine, azathioprine, nitrogen mustard), and high-dose steroids in symptomatic patients.[4,5,12] Treatment responses have been variable, with recurrences in many cases. Most recently, the use of lenalidomide (Revlimid, Celgene) with dexamethasone in a patient with NXG and smoldering myeloma showed resolution of lesions after 3 months of treatment, and a durable response with no recurrence at 12 months.[13] My colleagues and I have also reported a complete response to thalidomide (Thalomid, Celgene) and dexamethasone in a patient with NXG and smoldering myeloma (10% bone marrow plasma cells) with extensive skin lesions, who achieved a persistent, complete response 3 years after cessation of treatment.[14] There has been one reported case of autologous stem cell transplant (ASCT) and high-dose melphalan with a durable response.[15] Thalidomide, lenalidomide (immune modulatory drugs), and ASCT are treatment modalities for multiple myeloma, a hematologic malignancy with monoclonal gammopathy, with overall response rates of 80–90% and complete responses of 40–50%.[16] When combined with a steroid, thalidomide, lenalidomide, and bortezomib (Velcade, Millennium Pharmaceuticals) are considered first-line agents in the treatment of patients with multiple myeloma. These agents are becoming more frequently studied in other hematologic disorders as well, including Hodgkin lymphoma, NHL, Waldenström macroglobulinemia, and other lymphoproliferative disorders and leukemias. These drugs may hold promise in maintaining long-term, symptom-free duration while also preserving skin integrity. The length of systemic treatment has yet to be determined. Treatment duration has ranged from 2 to 24 months. In the case series using lenalidomide[13] and thalidomide,[14] the duration of treatment was 3 months versus 24 months, respectively.

## Conclusion

NXG is a rare disorder with slowly progressive, but oftentimes disfiguring, skin lesions. It is frequently associated with hematologic disorders, of which MGUS is most common. Accurate diagnosis of the lesions and further testing is necessary in order to choose appropriate treatment strategies. Although 80% of patients may not need any treatment or may only require topical agents and local procedures, a select group of symptomatic patients with disfiguring skin lesions and/or systemic involvement may require systemic therapy. Novel oral agents like lenalidomide and thalidomide in combination with dexamethasone may prove to be beneficial in these patients. As more cases are reported, we hope to better understand the pathophysiology and treatment of this disorder.

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