Necrobiotic xanthogranuloma (NXG) is an indolent non–Langerhans cell histiocytosis characterized by yellow xanthomatous plaques that tend to ulcerate. Necrobiotic xanthogranulomas have a predilection for the bilateral periorbital region and often present with consequential ophthalmic findings. Histopathology usually reveals a distinctive pattern of histiocytic xanthogranuloma with hyaline necrobiosis. Necrobiotic xanthogranuloma has been documented to have a close association with paraproteinemia. We report the case of a 76-year-old man with periorbital NXG without development of a monoclonal gammopathy. Clinically, the patient presented with dry eyes and substantial periorbital edema with multiple yellow indurated plaques. He developed the condition 30 years prior to presentation at which time it was initially diagnosed as xanthelasma. He underwent surgical excision of the lesions 10 years prior to the current presentation and biopsy results revealed a diagnosis of NXG. The periorbital lesions recurred several years prior to presentation, prompting annual computed tomography scans to rule out ocular invasion. Periorbital edema and plaques improved during a 6-month regimen of acitretin but returned to baseline just months after discontinuation. 


Necrobiotic xanthogranuloma (NXG) was first described in 1980 by Kossard and Winkelmann1 as a xanthomatosis associated with paraproteinemia. It is an indolent disorder characterized by indurated, yellow to violaceous red papules, plaques, or nodules often presenting with telangiectases and ulceration.2 The lesions have a predilection for the bilateral periorbital region in the majority of documented cases, consequently producing ocular findings such as periocular skin lesions, blepharoptosis, restricted ocular motility, and proptosis.3

Necrobiotic xanthogranuloma is a systemic disease that may involve extracutaneous sites such as the heart, respiratory tract, spleen, kidneys, ovaries, liver, skeletal muscle, and central nervous system.4,6 The most common sites include the respiratory tract and heart, with documented cases of pulmonary and myocardial giant cell granulomas.4 In a 2009 review, Spicknall and Mehregan7 reported an increased frequency of systemic involvement.

The distinctive histopathologic features of NXG consist of large bands of necrosis and a pattern...
of palisading histiocytic granulomas comprised of Touton giant cells, bizarre foreign body giant cells, foam cells, and cholesterol clefts. These histopathologic findings differentiate NXG from other clinical differential diagnoses such as necrobiosis lipoidica.

Necrobiotic xanthogranuloma is associated with paraproteinemia in 80% of documented cases, most commonly as an IgG monoclonal gammopathy. The etiology of this indolent disorder remains unclear despite proposed theories of its pathogenesis. Consequently, treatment proves difficult with no recommended first-line therapy and a tendency for recurrent cutaneous lesions. We report an unusual case of periorbital NXG without development of a monoclonal gammopathy.

Case Report
A 76-year-old man presented with a long-standing history (30 years) of bilateral periorbital NXG. Approximately 30 years prior to the current presentation, the patient presented to a dermatologist with dry eyes and periorbital cutaneous lesions that were originally diagnosed as xanthelasma. He later developed edema of the right periorbital region that progressed to involve the left periorbital region. He underwent surgical excision of the lesions 10 years prior to the current presentation, which showed the lesions were infiltrating into the muscle. At that time, a diagnosis of NXG was made.

The department of plastic surgery at an outside institution evaluated the patient and identified no further treatment options; however, annual computed tomography scans were performed to detect disease progression.

The patient presented for increasing periorbital manifestations of NXG. He denied any other remarkable medical history or any family history of NXG, malignancy, or hematologic disorders. His surgical history was exclusive to the excisional surgery of the periorbital lesions. At the time of presentation he was not taking medications and had no known drug allergies. He denied tobacco use but occasionally consumed alcohol.

On systemic inquiry the patient's only concerns were ocular in nature and included dry, sensitive, and painful eyes. Dermatologic examination revealed substantial periorbital edema with multiple yellow indurated plaques (Figure). There were no additional findings on physical examination.

Extensive hematologic and oncologic investigations revealed the absence of a monoclonal gammopathy. Serum protein electrophoresis was negative for paraproteinemia and quantitative serum immunoglobulin testing was normal. A complete blood cell count, lipid panel, CD4 count, CD8 count, C3, C4, and computed tomography scan did not reveal any abnormalities. A complete metabolic panel identified elevated serum glucose levels...
(162 \text{ mg/dL} \text{ [reference range, 74–118 mg/dL]}),
low serum albumin levels (3.3 \text{ g/dL} \text{ [reference range, 3.5–4.8 g/dL]}),
and low serum calcium levels (8.8 \text{ mg/dL} \text{ [reference range, 8.9–10.3 mg/dL]}).
IgG subclass (SC) proteins were mildly increased
with an IgG SC1 of 950 \text{ mg/dL} \text{ (reference range, 382–929 mg/dL)},
IgG SC3 of 211 \text{ mg/dL} \text{ (reference range, 22–178 mg/dL)},
and IgG SC4 of 292 \text{ mg/dL} \text{ (reference range, 4–86 mg/dL)},
and the plasma IgG was in the upper limit of the reference range with a value of
1591 \text{ mg/dL} \text{ (reference range, 791–1643 mg/dL)}.

After the hematologic and oncologic workup
was completed, intravenous immunoglobulin and
acitretin were recommended to the patient as viable
treatment options to reduce the cutaneous sequelae
of NXG. A 6-month regimen of acitretin markedly
improved cutaneous edema and plaque size.
However, these sequelae returned to baseline just
months after acitretin was discontinued.

Comment
Necrobiotic xanthogranuloma is a distinct granulo-
lomatous disorder with no predilection for sex and
the average age of onset is 54 years.\textsuperscript{2} Consistent
with prior reports, our patient presented with
bilateral periorbital lesions and ophthalmic concerns
of dryness, burning, and sensitivity. Reddy et al\textsuperscript{19}
demonstrated that aggressive forms of periorbital
NXG may involve ocular tissues and result in vision
loss and corneal perforation. On follow-up, our
patient underwent annual computed tomography
scans to rule out further progression.

Eighty percent of patients diagnosed with NXG
have an associated monoclonal gammopathy and
10% develop multiple myeloma.\textsuperscript{2} Our case presents
an unusual variant of NXG due to the absence of a
monoclonal gammopathy. Chang et al\textsuperscript{10}
described a similar case of NXG without a monoclonal
gammopathy and hypothesized that periorbital
involvement, malignancy, and systemic involvement
are the main contributing factors to the morbidity
of NXG.

Our patient had mildly elevated IgG SC1,
IgG SC3, and IgG SC4 levels. The most substan-
tially elevated subclass was IgG SC4. Elevations
of IgG SC4 often are associated with disorders
that are allergic or autoimmune in nature, such as
pemphigus vulgaris, autoimmune pancreatitis,
and inflammatory pseudotumor.\textsuperscript{11} Our patient denied
prior history and lacked manifestations of allergic or
autoimmune disorders. A similar case was reported
in a 67-year-old man with periorbital NXG and
elevated IgG SC4 levels. Singh et al\textsuperscript{12} postulated
that systemic elevation of IgG SC4 can be associated
with NXG of the orbit.

Due to the rarity and uncertain etiology of
NXG, there are no definitive first-line therapies.
There have been encouraging results with intrave-
nous immunoglobulin,\textsuperscript{13} autologous stem cell
transplantation,\textsuperscript{14} lenalidomide,\textsuperscript{15} melphalan
with prednisolone,\textsuperscript{16} and chlorambucil with low-dose
corticosteroids.\textsuperscript{11} In 2007, Ho et al\textsuperscript{17} identified that
CD20 and CD25 were both strongly expressed in
tissue specimens of NXG, indicating the possible
effectiveness of rituximab and denileukin difti-
tox, which target CD20 and CD25, respectively.
It is unclear how these data pertain to patients
without paraproteinemia because the treatment
often is directed at the monoclonal gammopathy.
These uncertainties are concerning because of
the undesirable and often toxic side effects
associated with these therapies. Psoralen plus
UVA therapy was described as an alternative to
cytotoxic drugs and immunosuppressive agents in
1 patient without paraproteinemia.\textsuperscript{18}

Bullock et al\textsuperscript{19} proposed that NXG arises from a
foreign body giant cell reaction resulting from circu-
lating immune complexes precipitating in periortibital
tissues. Although the relationship between the cuta-
neous manifestations and a monoclonal gammopathy
remains poorly understood, cases of NXG without
paraproteinemia challenge this theory. Our case
supports the theory that there is no correlation
between the histopathologic findings of NXG and
the extent of the monoclonal gammopathy.

Conclusion
The etiology and pathogenesis of NXG remain
elusive. We strive to attain a more sophisticated
understanding of NXG to identify efficacious treat-
ment options. Our case highlights the ambiguous
association between the cutaneous lesions of NXG
and a monoclonal gammopathy.

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