Adult Orbital Xanthogranulomatous Disease

Review of the Literature

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This article provides an overview of the pathologic features of adult orbital xanthogranulomatous disease, a rare heterogeneous group of disorders that includes 4 clinical syndromes: adult-onset xanthogranuloma, necrobiotic xanthogranuloma, adult-onset asthma and periocular xanthogranuloma, and Erdheim-Chester disease. The diagnosis is made by biopsy of the lesion, demonstrating tissue infiltration by the hallmarks of xanthoma cells and Touton giant cells. The differential diagnosis is broad, including syndromes within the adult xanthogranulomatous disease category as well as other entities involving the eyelid and the orbital tissues. Because of its rarity and sometimes close similarity to other disease entities, it is often misdiagnosed initially. This article focuses on the morphology and immunohistochemical patterns in diagnosis of adult orbital xanthogranulomatous disease with emphasis on adult-onset asthma and periocular xanthogranuloma in particular, its clinical features and associated systemic manifestations in differential diagnosis, as well as the current management strategy.


The so-called adult orbital xanthogranulomatous disease (AOXGD) is a heterogeneous group of syndromes that are rare and poorly understood. Adult orbital xanthogranulomatous disease presents with variable clinical features from which 4 subtypes are subclassified: adult-onset xanthogranuloma (AOX), necrobiotic xanthogranuloma (NBX), Erdheim-Chester disease (ECD), and adult-onset asthma and periocular xanthogranuloma (AAPONX). Histopathologically, each of these entities is characterized by infiltration of “hallmark cells,” especially foamy histiocytes and Touton-type giant cells, both of which are often negative for S100 and CD1a. This infiltration, along with accompanying lymphocytes, can replace the normal lacrimal gland architecture, causing mass effects and loss of tear production. With emphasis on AAPONX in particular, all 4 entities of AOXGD are discussed in term of their clinical and histopathologic features, laboratory and ancillary findings, as well as differential diagnosis and current management plan.

CLINICAL FEATURES

Adult orbital xanthogranulomatous disease is rare and, as a group, it affects patients from 17 to 85 years of age with no significant sex preference (73 male versus 64 female patients). Adult-onset xanthogranuloma is an isolated xanthogranulomatous lesion without significant systemic involvement. It is the least common entity among AOXGDs, and affects patients with ages ranging from 38 to 79 years, with no sex preference. The significance of recognizing this entity is that it is often self-limited and does not require aggressive treatment unlike the other subtypes of AOXGDs, which can sometimes cause significant consequences.

Necrobiotic xanthogranuloma is characterized by the presence of subcutaneous skin lesions that tend to ulcerate and become fibrotic. It often affects adults aged 20 to 85 years, with no significant sex preference (32 males and 40 females). Frequently associated systemic findings include paraproteinemia and multiple myeloma.

Erdheim-Chester disease is an idiopathic condition of lymphohistiocytic infiltration in the orbit as well as internal organs including the heart, lungs, retroperitoneum, bones, and other tissues. The infiltrating elements are xanthogranulomatous with Touton giant cells and are accompanied by regional fibrosis. Like AAPONX, it presents preferentially in males (male to female ratio, 2:1) and affects patients from 17 to 77 years of age. This condition is often fatal, with death due to cardiomyopathy, severe lung disease, or chronic renal failure. In addition, bone involvement is common with frequent critical consequences despite aggressive therapies. Because of its frequent and significant systemic involvement, bilateral diffuse orbital masses should alert the clinician and/or pathologist to the possibility of this serious systemic disease.

Adult-onset asthma and periocular xanthogranuloma is rare, with only 21 reported cases in the literature and a newly diagnosed case at our institution. It often presents with bilateral yellow-orange, elevated, indurated, and non-ulcerated xanthomatous eyelids and/or orbital masses. It typically extends into the anterior orbital fat and sometimes involves the extraocular muscles and/or the lacrimal gland(s). Adult-onset asthma and periocular xanthogranuloma is most often seen in adult patients with ages ranging from 22 to 74 years, with twice as many males affected as females. Most patients experience adult-onset asthma within a few months to a few years after onset of periocular lesions, the underlying mechanism of which is unknown but it points to a poorly understood systemic immunologic derangement with concurrent bronchial and ocular adrenal dysfunction. Asthma has also been reported with some frequency in patients with sinus histiocytosis and massive lymphoadenopathy. Even when asthmatic symptoms are severe enough to require systemic corticosteroids and inhalation therapy, the findings from a chest x-ray may be negative. In addition to...
Adult orbital xanthogranulomatous disease often presents with bilateral yellow-orange, elevated, indurated, and nonulcerated xanthomatous eyelids and/or orbital masses. It can be very extensive and causes significant mass effect that prevents the patient from seeing properly (shown here is a patient with adult-onset asthma and periocular xanthogranuloma).

Figure 1. Adult orbital xanthogranulomatous disease usually contains sheets of mononucleated foamy histiocytes (xanthoma cells) infiltrating the orbiccularis muscles and the anterior orbital fibrous tissue, accompanied by variable numbers of dispersed and/or aggregates of lymphocytes, plasma cells, and Touton giant cells (inset) (hematoxylin-eosin, original magnifications ×40 and ×400 [inset]).

Figure 2. Infiltrating xanthoma cells often have small, round nuclei and abundant clear or vacuolated cytoplasm (hematoxylin-eosin, original magnification ×200). Oil red O staining of frozen sections confirms the lipid content of the xanthoma cells (not shown).

Figure 3. These foamy histiocytes (xanthoma cells) are usually negative for CD21, CD35, CD1a, and S100 (not shown) but are strongly positive for CD68 (not shown) and CD163 (immunoperoxidase, original magnification ×200).

HISTOPATHOLOGIC FEATURES AND LABORATORY FINDINGS

All AOXGD subtypes share common histopathologic features characterized by sheets of mononucleated foamy histiocytes (xanthoma cells) infiltrating the orbiccularis muscles and the orbital tissue, accompanied by variable numbers of dispersed and/or aggregates of lymphocytes, plasma cells, and Touton giant cells (Figure 2). These infiltrating xanthoma cells often have small, round nuclei and abundant clear or vacuolated cytoplasm (Figure 3). Oil red O staining of frozen sections confirms the lipid content of the xanthoma cells. Scattered among these xanthoma cells are Touton giant cells characterized by a ring of nuclei around a central eosinophilic zone that is surrounded by a zone of pallor extending to the periphery of the cell (Figure 2). Lymphoid

asthma, AAPOX is frequently associated with lymphadenopathy (8/20), paraproteinemia (5/14), and rarely with other lymphoproliferative disorders (1/21) or internal organ dysfunction (1/21).

Because the eyelids remain intact and the process does not reach the deep orbital and periorbital connective tissues, visual acuity may not be affected and ocular motility is generally well preserved unless the extraocular muscles are involved. Only rarely are the corneas exposed to the infiltrate, but in rare cases where lacrimal gland involvement causes punctate corneal epitheliopathy, the patient may suffer from a dry eye condition. The eyelid and periocular infiltration can be very extensive and cause significant mass effect that prevents the patient from seeing properly (Figure 1).
follicles are commonly scattered throughout, with variable reactive germinal centers, especially seen in AAPOX. Variable degree of fibrosis is often present but without necrobiosis of collagen except for those patients with NBX. Immunohistochemically, the foamy histiocytes are strongly positive for CD68, CD163 (Figure 4) and factor XIIIa but are usually negative for CD21, CD35, S100, and CD1a (not shown). However, rarely, these foamy histiocytes can be positive for S100 and negative for factor XIIIa, as in rare cases of juvenile xanthogranuloma. Therefore, neither a negative factor XIIIa nor a positive S100 result should preclude the diagnosis of AOXGDs. The lymphoid infiltration has a reactive profile with germinal centers being positive for CD20 and negative for BCL2. The parafollicular T cells are CD3+ and are often predominantly CD8+. There is often no influx of CD4+ T cells.\(^1\),\(^2\),\(^4\),\(^7\)

Immunophenotyping by flow cytometry, serum protein immunoephelophoresis, or even bone marrow biopsy are sometimes performed and periodically repeated to evaluate multiple myeloma, monoclonal gammopathy of undetermined significance, or lymphoma that may be associated with AOXGDs, especially NBX or rarely AAPOX. Because patients with xanthogranulomas can have plasma cell dyscrasias and lymphoproliferative malignancies, especially in the presence of necrobiosis, a thorough baseline systemic evaluation and long-term follow-up are mandatory.\(^2\),\(^5\) As for AAPOX, results of extensive systemic evaluations are often unremarkable except for rare reports of elevated levels of α-high-density cholesterol and/or late onset of M-protein (IgG) production on serum protein immunoephelophoresis, suggesting that the inflammatory infiltrates may have stimulated B cell populations.\(^1\),\(^3\)

ANCILLARY STUDIES

Radiologic studies of patients with AOXGD may reveal evidence of prophysis with an abnormal infiltrative soft tissue mass and increased fat. Associated enlargement of extracocular muscles with possible lacrimal gland involvement is often present, while encasement of the optic nerve, bone destruction, and intracranial extension are not often noted. For AAPOX in particular, computed tomography scanning may reveal preseptal and anterior orbital involvement with occasional posterior tracking along or within the orbital muscles and fat, usually sparing the optic nerve and connective tissues. Facial bones are usually not involved.\(^1\) Magnetic resonance imaging often discloses hypointense signals in the eyelids that extend into the anterior orbital fat.\(^1\) Electron microscopic studies are sometimes used in difficult cases and often show cytoplasmic lipid vacuoles, mitochondria, and phagosomes within the xanthoma cells but no Birbeck granules.\(^1\)

As the mechanisms in the xanthogranulomatous disorders are poorly understood, there is no genetic information currently available to allow targeted mutational analysis. Histopathologic analysis from biopsy combined with associated clinical presentations is now considered the gold standard for diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AOXGD, including AAPOX, is broad and includes entities within the category of AOXGDs as well as other disease entities involving the orbital and periorbital tissues. Although AOXGDs all have similar lymphgranulomatous infiltrates, there are often subtle differences in the amount of lymphoid follicles, the number of Touton giant cells, the extent of fibrosis, and the presence of necrosis. Curiously, these features may vary within the same specimen and change with time and treatment. Therefore, on the basis of histomorphology alone, the AOXGDs are difficult to subclassify and usually require correlation with patterns of systemic involvement.

Specifically, necrobiosis with palisading epithelioid histiocytes is most often seen in NBX, whereas large lymphoid aggregates with reactive germinal centers are often found in cases of AAPOX. Whereas orbit/adnexal xanthogranulomas frequently involve the anterior orbital tissue in AOX, AAPOX, and NBX, in ECD, the lesion is often diffuse and involves mainly the posterior orbital tissue, leading to visual loss.

While most cases could be classified as 1 of the 4 AOXGD syndromes, some cases fall in between. Patients often have varying combinations of periocular xanthogranuloma and other blood dyscrasias including thrombocytopenia, paraproteinemia and/or monoclonal gammopathy of undetermined significance. Among the 4 syndromes, NBX is the most frequently encountered followed by ECD and AAPOX, whereas AOX is the least common subtype of AOXGDs.\(^2\)

In addition, AOXGDs should also be differentiated from other non-Langerhans disorders of histiocytes, including juvenile xanthogranuloma. This tumor usually manifests as a self-limited, corticosteroid-sensitive skin tumor that rarely has systemic manifestations. Infants and young children are mainly affected with head and neck lesions. Many extracutaneous sites, however, have been reported, particularly the eye, where juvenile xanthogranuloma may cause spontaneous hyphema and result in secondary glaucoma and eventual blindness. Approximately one-half of patients with ocular involvement also have skin lesions.\(^8\)

Other entities involving ocular adnexal or orbital tissue that may require distinction from AOXGDs include Langerhans histiocytosis, Rosai-Dorfman disease, inflammatory malignant fibrous histiocytoma, inflammatory myofibroblastic tumor (inflammatory pseudotumor) of the orbits, propofol from Graves disease, multiple myeloma, and lymphoma. Langerhans histiocytosis is a class 1 histiocytosis, a group of idiopathic disorders characterized by the proliferation of specialized bone marrow–derived Langerhans cells and mature eosinophils. Langerhans histiocytosis accounts for less than 1% of all orbital tumors. Although rare, orbital involvement is not uncommon.

Sinus histiocytosis with massive lymphadenopathy or Rosai-Dorfman disease is a rare benign proliferative histiocytic disease of unknown origin. It predominantly affects the lymph nodes. The head and neck region, usually in association with lymph node involvement, represents one of the most common extranodal areas affected. The other common extranodal site is skin. Rarely, there is widespread dissemination with liver, kidney, respiratory organs, orbit, and eyeball involvement. The mean age of onset is 20 years (from birth to 74 years).

Inflammatory pseudotumor of the orbits is a rare disease characterized by inflammation occurring within the orbit that simulates a neoplasm. Patients commonly present with an abrupt onset of diffuse or compartmentalized orbital pain associated with diplopia, restricted range of motion of the eye, and swelling/reddening of the eyelid. Other causes of orbital inflammation must first be excluded before this diagnosis is established.

Graves ophthalmopathy connotes a process clinically char-
characterized by eyelid retraction, proptosis, conjunctival exposure, ocular injection, ocular chemosis, corneal compromise, extracocular muscle infiltration, and fibrosis with the potential for compressive optic neuropathy. It is the most common cause of bilateral, symmetric proptosis in adults. Most patients with ocular Graves disease manifest systemic hyperthyroidism. Up to 80% of patients with systemic hyperthyroidism show some eye signs. Interestingly, ocular findings may occur independently from thyroid dysfunction, and when this happens, it poses a diagnostic challenge. However, the histopathologic features of the malady include an infiltration of the thyroid gland, skin, extracocular muscles, and orbital fat by lymphocytes, macrophages, plasma cells, and mast cells along with mucopolysaccharides, instead of xanthoma cells and Touton giant cells.

When AOXGD presents with monoclonal gammopathy, as in cases of necrobiotic xanthogranuloma or in rare occasions, AAPOX, it needs to be differentiated from multiple myeloma with involvement of the orbit or plasma cytoma of the eye and/or of the orbit. Orbital involvement in both conditions is very rare (with less than 50 cases reported in the literature) with the clinical outcome being significantly worse in multiple myeloma. Fine-needle aspiration offers an opportunity for noninvasive verification of these entities and thus, plays a major role in early diagnosis and management of these patients’ condition.9

Finally, AOXGD should also be differentiated from lymphomas involving the orbit that may arise spontaneously or may be associated with the development of systemic lymphoma. These lesions may cause a painless, unilateral proptosis or may manifest as a salmon patchlike thickening protruding into the conjunctiva. Histopathologically, it may be difficult to differentiate malignant lymphoma from a lymphoid hyperplasia. Lymphomas characteristically show a diffuse monotonous infiltrate of atypical lymphocytes. There is minimal vasculature, no follicles, and no mixture of other cell types such as plasma cells, in contrast with benign lesions such as xanthogranuloma, which tend to show a mixture of cells, increased vascularity, and formation of follicles or germinal centers. The definitive diagnosis often requires fresh tissue and histopathologically often shows monoclonal staining with B-cell predominance. A typical lymphoid hyperplasia will show a mixture of B and T cells and will be polyclonal.

**CURRENT TREATMENT**

Intralesional corticosteroid injection has been successfully used in controlling symptoms and signs of AOX and occasionally NBX with eyelid and orbital involvement. This therapy avoids the use of systemic corticosteroids and cytotoxic agents and is currently accepted for treating these disorders. In addition, this regimen avoids the complexity and expense of plasmapheresis and the significant local morbidity of radiation therapy, both of which are only partially effective.10 The eyelid lesions in NBX can be successfully treated with radiotherapy or systemic prednisolone and chlorambucil unless extensive destruction has occurred. Treatment modalities for ECD are broad, ranging from observation to systemic steroids, radiation therapy, and chemotherapy, including cyclophosphamide, doxorubicin, and vincristine. Interferon-α has also been used to induce reduction in exophthalmos and control of systemic manifestations.11 Retro-orbital irradiation is often not effective. It should be noted that despite treatment, ECD often follows an aggressive course.

Despite surgical debulking, AAPOX often recurs within 6 to 12 months. Although systemic prednisone treatment may cause temporal shrinkage, alone it is usually not successful in causing a long-lasting resolution. Combined prednisone and systemic chemotherapy for paraproteinemia may result in more complete resolution of the xanthogranulomatous eyelid deposits.12,13 Radiotherapy has also been successfully used, but the results are more anecdotal than statistical. Patients without detectable systemic disease at the time ocular adnexal lesions appear should be spared surgical debulking because of possible scarring. In this setting, high doses of systemic corticosteroids and low doses of periocular radiotherapy may be given in the hope of protecting the globe. If this approach fails, systemic corticosteroids and light chemotherapy may be tried.14-16 For patients with monoclonal gammopathy of undetermined significance, follow-up should include serial serum protein immunoelectrophoresis and bone biopsy as needed.

A recent study evaluated the efficacy of methotrexate in the treatment of the periorbital changes in AOX with or without asthma. With follow-up of more than 3 years, methotrexate at a dosage of 10 to 20 mg/wk with folate supplementation and a course of corticosteroids showed promising results in significantly reducing inflammation and ptosis.17

In summary, adult orbital xanthogranulomatous diseases are rare and pose challenges in daily clinical practice. Recognizing their clinical and histopathologic features will facilitate early diagnosis and appropriate therapeutic management.

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**References**