Actas Dermosifiliogr. 2017;108(5):400–406

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

REVIEW

Adult Xanthogranulomatous Disease of the Orbit: Clinical Presentations, Evaluation, and Management☆

J.M. Ortiz Salvador,* D. Subiabre Ferrer, A. Pérez Ferriols

Servicio de Dermatología, Hospital General Universitario de Valencia, Valencia, Spain

Received 13 May 2016; accepted 2 December 2016
Available online 1 May 2017

KEYWORDS
Adult xanthogranulomatous disease of the orbit;
Histiocytosis;
Granulomatous inflammatory diseases;
Foam cells;
Touton-type multinucleated giant cells

Abstract Adult xanthogranulomatous disease of the orbit refers to a heterogeneous group of clinical syndromes with differing degrees of systemic involvement and distinct prognoses. The different syndromes all present clinically with progressively enlarging, yellowish lesions of the orbit. Histologically, the lesions are characterized by an inflammatory infiltrate of foam cells and Touton-type multinucleated giant cells. The xanthomatized histiocytes are $CD68^{+}$, $S100^{-}$ and $CD1a^{-}$. There are 4 clinical forms of xanthogranulomatous disease of the orbit: adult xanthogranulomatous disease of the orbit, adult onset asthma and periocular xanthogranuloma, necrobiotic xanthogranuloma, and Erdheim-Chester disease. The treatment of local lesions are treated with systemic corticosteroids and other immunosuppressors. Vemurafenib, tocilizumab, and sirolimus have shown promising results in systemic disease.

PALABRAS CLAVE
Enfermedad xantogranulomatosa orbitaria del adulto;
Histiocitosis;
Enfermedades inflamatorias granulomatosas;

Enfermedad xantogranulomatosa orbitaria del adulto. Formas clínicas, evaluación y manejo

Resumen La enfermedad xantogranulomatosa orbitaria del adulto comprende un grupo heterogéneo de síndromes clínicos con diferentes grados de afectación sistémica y pronóstico variable.

Todas las formas se manifiestan clínicamente como lesiones amarillentas infiltradas orbitarias de crecimiento progresivo. Histológicamente se caracteriza por un infiltrado inflamatorio compuesto fundamentalmente por histiocitos espumosos y células gigantes multinucleadas tipo Touton. Estos histiocitos xantomatizados son CD68+, S100-y CD1a-.

☆ Please cite this article as: Ortiz Salvador JM, Subiabre Ferrer D, Pérez Ferriols A. Enfermedad xantogranulomatosa orbitaria del adulto. Formas clínicas, evaluación y manejo. Actas Dermosifiliogr. 2017;108:400–406.

* Corresponding author.
E-mail address: Josema.ortiz.salvador@gmail.com (J.M. Ortiz Salvador).

Histiocitos espumosos;
Células gigantes multinucleadas tipo Touton

Existen 4 formas clínicas de enfermedad xantogranulomatosa orbitaria del adulto: el xantogranuloma orbitario del adulto, el asma del adulto asociado a xantogranulomas orbitarios, el xantogranuloma necrobiótico y la enfermedad de Erdheim-Chester.

El tratamiento de las lesiones locales se basa fundamentalmente en corticosteroides sistémicos y otros inmunosupresores. En los casos con enfermedad sistémica vemurafenib, tocilizumab y sirolimus ofrecen resultados prometedores.

Introduction

Adult xanthogranulomatous disease of the orbit (AXDO) comprises a heterogeneous group of uncommon diseases that share cutaneous manifestations and histopathology findings.[1,2] AXDO involves various non-Langerhans cell histiocytoses that mainly infiltrate the orbit and ocular adnexa. The disease can also affect other organs, with severe systemic manifestations. As AXDO is uncommon, treatment is controversial, and several approaches have been proposed in the literature, although there are few controlled trials that support them.[3,4]

Depending on clinical characteristics and clinical manifestations, we can distinguish between 4 clinical forms of AXDO: adult-onset xanthogranuloma (AOX), adult-onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX), and Erdheim-Chester disease (ECD).

Etiology and Pathogenesis

The histiocytes that cause AXDO and other histiocytoses are formed in the bone marrow as monocytes. Monocytes can become part of the dendritic cell system or the mononuclear phagocyte system, which is formed by fixed tissue macrophages and by free macrophages. Specifically, AXDO originates from free macrophages in the monocyte-macrophage system,[5] thus explaining the immunohistochemical characteristics of the infiltrate found in this condition, which is composed of cells that are positive for monocyte lineage markers (CD68, factor XIII) and negative for dendritic cell markers (S100, langerin, CD1a).

In AXDO, macrophages present a vacuolated cytoplasm, which gives them a foamy or ''xanthomatized'' appearance.[1]

AXDO is thought to be caused by a stimulating agent that induces proliferation of histiocytes,[2] although the nature of this stimulus is currently unknown. In the case of NBX, most cases are associated with paraproteinemia (generally immunoglobulin [Ig] G).[1,6] Nevertheless, it remains unclear whether the presence of paraproteinemia is a trigger in NBX or an associated cofactor. Several pathophysiological factors have been implicated in ECD. The most relevant is a mutation in the *BRAF* gene in up to 68% of patients.[7,8] Other findings include increased production of interleukin 6[9] and occasional hyperactivity of the mTOR pathway involving mutations in the *NRAS* gene.[10]

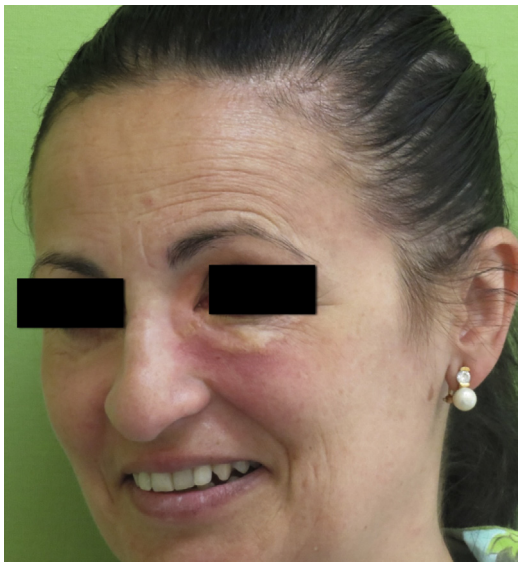

Figure 1 Yellowish periorbital infiltrated plaques in a patient with adult xanthogranuloma of the orbit.

Clinical Presentation

AOX is the most benign form of the disease, although it is more uncommon than AXDO, with barely 10 cases reported in the literature.[1] It manifests as xanthomatous, yellowish infiltrated plaques affecting both orbits (Figure 1). AOX has been reported in patients aged 38 to 79 years.[2] Prognosis of this benign condition is excellent, and no extracutaneous manifestations are observed.[1]

AAPOX is an uncommon form of AXDO. In addition to orbital lesions that are similar to those of AOX, AAPOX is characterized by adult-onset asthma.[11] Diagnosis of lung involvement is by pulmonary function tests, which reveal reversible obstruction of the airways.[11,12] Since the lung parenchyma is not involved, the results of imaging tests are usually negative.[2]

NBX is an aggressive form of AXDO. It progresses with xanthomatous, indurated, yellowish papules (Figure 2) that are locally aggressive.[2,13] The patient tends to develop telangiectasias, ulceration, and fibrosis. The eye is involved in 50% of cases in the form of proptosis, keratitis, or uveitis. The lesions are not limited to the orbit, and the skin may be involved at other sites.[6] Practically 100% of cases of NBX are accompanied by paraproteinemia,[13] which may be associated with monoclonal gammopathy of undetermined