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Viewpoint

Orbital inflammation: Biopsy first

Ilse Mombaerts, MD, PhD[a,*], *Geoffrey E. Rose, DSc, FRCOphth*[b], *James A. Garrity, MD*[c]

[a] *Department of Ophthalmology, University Hospitals Leuven, Leuven, Belgium*
[b] *Adnexal Service, Moorfields Eye Hospital and Institute of Ophthalmology, London, UK*
[c] *Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota, USA*

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ABSTRACT

Orbital inflammation is a response of the immune system and not a diagnosis in itself. Exposing the underlying disease introduces a labyrynthine challenge owing to the broad array of possible causes ranging from infectious, structural, autoimmune, idiopathic to neoplastic origin. In this regard, and despite its unkown etiology, idiopathic orbital inflammation (IOI) intrinsically is a genuine diagnostic entity. Where clinical and radiological findings of an orbital inflammatory mass are inconclusive, pathological examination of the tissue biopsy—obtained by minimally invasive approach and local anesthesia—is advocated to work towards a diagnosis in a most timely and effective manner. A corticosteroid response can be observed in most orbital disorders with lymphocytic components, including IOI, and, accordingly, constitutes a paradoxical and weak tool to identify the diagnosis in orbital inflammation.

1. Introduction

Orbital inflammation accounts for about 60% of patients referred to an orbital specialist center, most being thyroid orbitopathy.[43] Twenty percent of nonthyroid orbital masses are accompanied by inflammation, of which most are idiopathic.[4] Idiopathic orbital inflammation (IOI) is better known as pseudotumor, a term coined in 1905 by Birch-Hirschfeld—the son of a pathologist—at a time when surgical exploration and histopathological analysis were the only diagnostic options for a presumed orbital tumor.[5,14] In 1985, Leone and colleagues proposed that the response to a short course of high-dose systemic glucocorticoids (termed a "corticosteroid trial") was diagnostic evidence for IOI and that this obviated the need for tissue biopsy.[23] Since then, a corticosteroid-responsive orbital inflammation has become virtually synonymous with IOI. Subsequent insights from pathological and genetic research have, however, led to the differentiation of IOI from lymphoma and lymphoid hyperplasia, and, more recently, to the recognition of a new fibro-

* Corresponding author: Ilse Mombaerts, MD, PhD, Department of Ophthalmology, University Hospitals Leuven, Kapucijnenvoer 33, 3000 Leuven, Belgium.
E-mail address: ilse.mombaerts@uzleuven.be (I. Mombaerts).
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inflammatory disorder, immunoglobulin G4-related disease (IgG4-RD). The current concept of IOI encompasses nonspecific inflammation of the lacrimal gland (dacryoadenitis), extraocular muscle (myositis), or orbital adipose tissue from an unidentifiable cause.

2. The deception of a "corticosteroid trial"

Corticosteroids influence many aspects of the immune response. They switch off inflammatory genes that have been activated during the chronic inflammatory process and, at higher doses, upregulate anti-inflammatory proteins and postgenomic effects.[2] By altering lymphocyte recirculation, they also induce lymphocytopenia after a single large dose, although the white count returns to normal within 24 hours.[2] Furthermore, corticosteroids induce apoptosis in lymphocytic lesions, causing the misleading phenomenon of clinical improvement following high-dose corticosteroid treatment in both benign and malignant disease.[33] Orbital inflammation can be the presenting face for a vast array of injurious agents—either primary inflammation or secondarily induced by other lesions—and both will commonly show a corticosteroid response (Table 1).[27] The erroneous diagnosis of IOI based on a corticosteroid trial has been reported in many cases such as orbital B- and T-cell lymphomas, metastatic disease, epithelial lesions of the lacrimal gland, fungal infections, granulomatosis with polyangiitis (GPA), and sarcoidosis.[1,19,24,35,47] The diagnostic power of the corticosteroid trial is further lowered by the corticosteroid unresponsiveness found in 21% of patients with biopsy-confirmed idiopathic dacryoadenitis and 45% of patients with sclerosing IOI.[31,48]

A corticosteroid trial should not be confused with tentative administration for therapeutic reasons, this being particularly beneficial in severe idiopathic orbital myositis and sightsaving in IOI lesions associated with optic neuropathy. In such cases, a clinically adequate response is not diagnostic, and vigilance for other diseases remains required during follow-up. A therapeutic course of corticosteroids should be high dose and prolonged to prevent recurrent activity of IOI. We feel that a course should consist of oral methylprednisolone 60 mg/d (or its equivalent) for 2 weeks, followed by 40 mg/d for 2 weeks, 20 mg/d for 2 weeks, and thereafter gradually tapered by 5 mg/d every week.

3. Diagnostic pathway in orbital inflammation

Three diagnostic phases need to be considered in a patient with orbital inflammation: examination, investigation, and tissue sampling (Fig. 1).

3.1. *Clinical phenomena suggestive of etiology*

The clinical features of acute inflammation as defined in the Celsus tetrad:*rubor* (redness), *calor* (heat), *dolor* (pain), and *tumor* (swelling) vary depending on location in the orbit, amount of inflammation or fibrosis, and etiology. Pain, for

Table 1 – Classification for possible causes of orbital inflammation