ARCHIVOS DE LA SOCIEDAD ESPAÑOLA DE OFTALMOLOGÍA

www.elsevier.es/oftalmologia

Review

Orbital inflammatory disease☆

R. Rachwani-Anil[a,*], F. Zamorano-Martín[b], C. Rocha-de-Lossada[c,d,e], M. García-Lorente[b], C. Pérez-Casaseca[b], C. Hernando-Ayala[b], S. Ortiz-Pérez[d]

[a] Departamento de Oftalmología, Hospital Norte de Málaga, Antequera, Málaga, Spain
[b] Departamento de Oftalmología, Hospital Regional Universitario-Hospital Civil, Málaga, Spain
[c] Qvision: Departamento de Oftalmología, Hospital Vithas Virgen del Mar, Almería, Spain
[d] Departamento de Oftalmología, Hospital Virgen de las Nieves, Granada, Spain
[e] Departamento de Oftalmología, Ceuta Medical Center, Ceuta, Spain

ARTICLE INFO

Article history:
Received 23 March 2021
Accepted 17 May 2021
Available online 3 February 2022

Keywords:
Orbital pseudotumour
Orbital inflammation
Myositis
Orbitopathy
Orbit

ABSTRACT

Orbital inflammatory disease (OID), commonly known as orbital pseudotumour, is an inflammatory disease of unknown cause. It has different forms of presentation and different degrees of severity. Its variable nature is the main cause for this disease to be misdiagnosed and misclassified. The prognosis of OID depends on the tissues affected and the histology. OID usually responds favourably to systemic steroid treatment. However, empiric steroids may mask other underlying diseases that respond well to this treatment as well, namely, IgG4-related disease or lymphoproliferative disorders. This fact has led to controversy among various authors as some recommend performing a biopsy in most of the cases, whereas others defend that this procedure should only be performed if the patient has not responded to empiric steroid treatment. Although steroids have been the mainstream treatment of OID, the side effects, relapse rates and lack of response in some cases have resulted in them being replaced by immunosuppressive and immunomodulator therapies that currently stand as a key steroid-sparing treatment option, in addition to radiotherapy and surgery. The aim of this review is to update the evidence on the diagnosis and treatment of OID.

☆ Please cite this article as: Rachwani-Anil R, Zamorano-Martín F, Rocha-de-Lossada C, García-Lorente M, Pérez-Casaseca C, Hernando-Ayala C, et al. Enfermedad inflamatoria orbitaria idiopática. Arch Soc Esp Oftalmol. 2022;97:89–99.

* *Corresponding author.*
E-mail address: rahul.medum@gmail.com (R. Rachwani-Anil).

Enfermedad inflamatoria orbitaria idiopática

Palabras clave:
Pseudotumor orbitario
Inflamación orbitaria
Miositis
Orbitopatía
Órbita

RESUMEN

La enfermedad inflamatoria orbitaria idiopática (EIOI), comúnmente conocida como pseudotumor orbitario, es una enfermedad inflamatoria de etiología desconocida. Sus síntomas pueden ser muy variables tanto en intensidad, gravedad, formas de presentación o gravedad. Esta heterogeneidad ha condicionado que sea una entidad difícil de definir y clasificar. El pronóstico de la EIOI depende de su localización, presentación e histología. La EIOI suele responder favorablemente a los corticoides sistémicos, sin embargo, este hecho puede hacer que la entidad sea confundida con otras enfermedades que también tienen buena respuesta a corticoides, como la enfermedad relacionada con la IgG4 y las enfermedades linfoproliferativas. Esta controversia ha alzado una polémica entre autores que defienden la realización de biopsia previa al tratamiento en la mayoría de los casos, frente a otros que afirman que la biopsia debe indicarse en lesiones que no responden adecuadamente al tratamiento médico empírico. Si bien los corticoides se sitúan como los protagonistas de la EIOI, los efectos secundarios, las tasas de recidivas y la falta de respuesta de algunos subtipos han permitido el paso a agentes inmunosupresores e inmunomoduladores que ocupan un escalón fundamental en la terapia combinada o ahorradora de corticoides, junto con la radioterapia y la cirugía. El objetivo de esta revisión es actualizar la evidencia sobre el diagnóstico y tratamiento de la EIOI.

Introduction

The terms non-specific orbital inflammation and orbital pseudotumour were coined in 1905 by Birch-Hirschfeld to define non-granulomatous orbital inflammatory diseases of unknown etiology and spontaneous recovery.[1] In an attempt to categorise orbital inflammations, the concept of idiopathic orbital inflammatory disease (IOID) emerged and is the most accepted term today.[2] They are defined as benign, non-infectious, space-occupying inflammatory lesions of unknown cause. Their diagnosis, therefore, is one of exclusion after ruling out orbital tumours and inflammatory masses of known cause.[3]

IOID is the third most common orbital pathology after thyroid orbitopathy and lymphoproliferative diseases[4] and accounts for 6-16% of all orbital lesions.[5] It has a wide age range of presentation between five and 75 years, although it is more frequent in adults of average age between 30–60 years[5], while myositic involvement is more frequent in women.[6] It is usually unilateral, being bilateral in 8–20% of cases.[6] It is less common in pediatric patients, with bilateral involvement being more frequent in these cases and presenting with constitutional signs and symptoms.[5]

The recurrence rate in the pediatric age group can be as high as 76%, regardless of bilateral or unilateral involvement. The overall recurrence rate of IOID after resolution can vary between 33–58%.[7]

Etiology and pathogenesis

The exact etiology of this disease is not known although a possible autoimmune, genetic, virological and environmental trigger has been suggested.[8]

It is sometimes associated with immunological diseases such as Crohn's disease, lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, ankylosing spondylitis, Behçet's disease and juvenile idiopathic arthritis.[9] Enghelberg et al.[10] described an association with autoimmune diseases and atopy in up to 38% in a study of 260 patients vs. 10% reported by Mombaerts[3] and 84% in a study of 25 patients by Yuen and Rubin.[11]

Molecular mimicry, where an antigen shares similar structures with its own antigens, may explain some cases of acute conditions.[12] Orbital myositis has been linked to certain infectious conditions that may act as triggers such as viral infections, streptococcal infections, Lyme disease or varicella zoster virus.[12,13]

There are some drugs such as bisphosphonates[14] that can cause IOID. Ortiz et al.[15] described two patients with IOID of pharmacological cause, one after injection of hyaluronidase in the context of peribulbar anaesthesia, and the other from a patient with Paget's syndrome under treatment with intravenous zoledronic acid.

On the basis of a questionnaire, Bijlsma et al.[16] proposed a number of possible risk factors in 103 patients with IOID. In addition to those already mentioned, they described female sex, young age, low socioeconomic status, high body mass index and the presence of a pre-existing immune disease unrelated to the pathogenesis of IOID.

There are several theories about the etiology of inflammation. Elevated levels of inflammatory cytokines such as interleukins, interferon (IFN), tumour necrosis factor (TNF) in histopathological samples from patients with IOID and increased expression of CD20 and CD25 have been described.[12] The latter are phosphoproteins of the cell wall of B cells in the case of CD20, and T cells in the case of CD25, and their expression is increased in inflammatory or neoplastic processes.[12]

Table 1 – IOID classification[16].

Presentation	Histopathology	Location
Acute	Classic	Fuzzy
Subacute	Granulomatous	Apical
Chronicle	Sclerosant	Optic nerve Extrinsic ocular muscles (myositis)
	Non-specific	Lacrimal gland (dacryoadenitis) Sclera

Classification and histology

There are several classifications of IOID in the literature.[3,16] These will be important in making a correct diagnosis and therefore more targeted treatment. They can be distinguished according to presentation (acute, subacute or chronic), histopathology (classical, granulomatous, sclerosing or non-specific), and predominant location of inflammation (diffuse, apical, involving the extraocular muscles [EOM], optic nerve, lacrimal gland or sclera) (Table 1).

The most common presentation is acute and involves the lacrimal gland (dacryoadenitis), accounting for almost half of the cases, followed by myositis, with the medial rectus muscle being the most affected.[12]

Depending on the onset, a distinction is made between acute forms, with symptoms lasting less than a week, subacute forms with symptoms lasting between a week and a month, and chronic forms lasting more than a month.[17]

Histologically, the classical subtype is characterised by its similarity with a chronic inflammatory infiltrate comprising mature small lymphocytes, mostly T cells, plasma cells, neutrophils, eosinophils, and occasionally histiocytes and macrophages. Histological specimens usually have a mixed T-cell (80%) and B-cell (20%) infiltrate.[18] Macroscopically, classic IOID tissue resembles a consistent, rubbery, pinkish-yellow lesion.[3]

The presence of granulomatous inflammation is rare. It is characterised by an infiltration of histiocytes and often well-demarcated non-caseating granulomas, without being associated with granulomatous diseases or systemic vasculitis.[19]

The sclerosing subtype is characterised by a replacement of normal orbital tissue by a dense, fibrous tissue with immature collagen tangles and little inflammatory infiltrate. Previously thought to be a chronic form of IOID, this infiltrate is now thought to be a specific and distinct entity, which may even be related to IgG4-related disease (ER-IgG4).[20]

The most commonly used classification is based on anatomical location.[16] Diffuse IOID is characterised by an orbital mass of variable extent and poorly demarcated, blurring the orbital structures. It may extend from the orbital apex towards the posterior margin of the globe, or adapt in its progression to the fascial planes, the globe or the orbital bones.[16] The apical subtype is characterised by an abrupt onset predominantly in the orbital apex, due to the possible involvement of the optic nerve. This form has a guarded

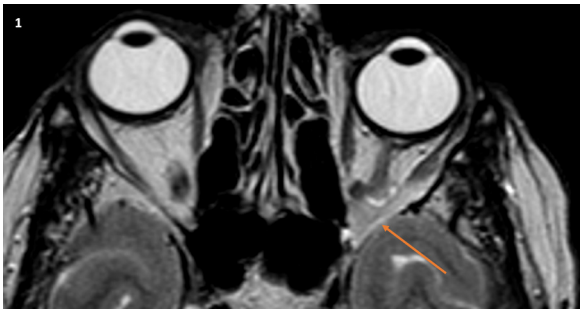

Fig. 1 – IOID of apical subtype. Note the infiltration affecting the orbital apex.

prognosis in relation to the final visual acuity (VA) (Fig. 1).[16] Tolosa-Hunt syndrome has been considered as a form of IOID of the orbital apex characterised by an extension of inflammation into the cavernous sinus through the superior orbital fissure.[12] Involvement of the extrinsic ocular muscles (EOMs), commonly myositis, is characterised by relatively diffuse thickening of one or more EOMs (with or without involvement of the muscle attachment tendons), with discrete extension of the inflammatory process into the surrounding fat, so that the outline of the muscle is discretely "blurred" (Fig. 2a,b).[16] Optic nerve involvement usually occurs in the form of perineuritis, in this subtype there is thickening and enhancement of the optic nerve sheath with possible extension into the surrounding fat.[21] Lacrimal gland involvement (dacryoadenitis) produces a diffuse enlargement of the lacrimal gland respecting its shape, which may also be accompanied by inflammation of adjacent tissue (Fig. 3a,b).[16] Scleral involvement appears in forms of sclerotenonitis and periscleritis or scleritis, characterised by thickening of the uveoscleral tunic, which may be accompanied by edema in Tenon's space.[16] Finally, non-specific forms do not meet the criteria of any other section.[16]

The role of ER-IgG4 in relation to different inflammatory conditions, including orbital inflammation, has been the subject of numerous lines of research in recent years, and it is considered that a large proportion of the IOIDs diagnosed years ago now correspond to ER-IgG4. In this regard, Enghelberg et al.[10] described a high prevalence of ER-IgG4 (up to 33%) among 260 biopsy-diagnosed patients with IOID. Furthermore, this group observed that up to 90% of the ER-IgG4s had accompanying fibrosis, suggesting an overlap with the sclerosing variant of IOID[10]. Sclerosing IOID is an insidious, persistent, progressive process refractory to conventional IOID[22] treatment. The median age of presentation is the fifth decade.[23]

Bijlsma et al.[16] introduced a concept of combined classification of IOID according to radiological and histopathological findings. Their rationale was based on the heterogeneity of symptoms and signs of IOID. Classification systems based on histopathology alone were found to have moderate content validity and the ability to distinguish between different categories of the classification. Localisation-based classifications also showed moderate content validity, but good distinctiveness between categories. In contrast, a combined classification comprising histopathology and location ensures good reliability, feasibility and face validity. The most frequent forms

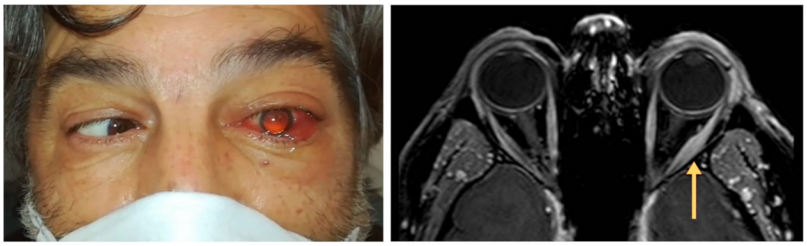

Fig. 2 – IOID-myositis. Involvement of the lateral rectus muscle of the left eye.

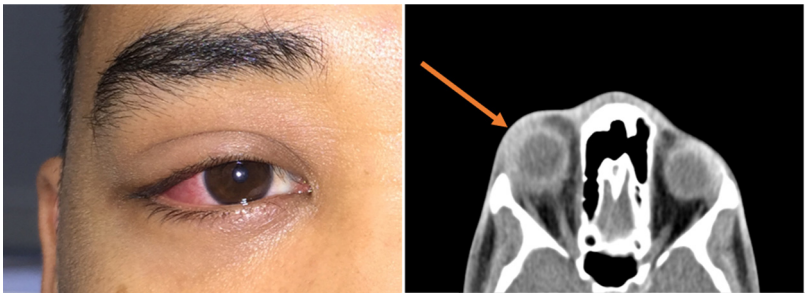

Fig. 3 – IOID-dacryoadenitis. Note the typical "italic S" ptosis sign. Involvement of the lacrimal gland of the right orbit.

observed were classic-diffuse, classic-myositis and classic-dacryoadenitis. Limitations of the study include the inclusion of patients from older studies that today could be diagnosed as lymphomas or, especially, ER-IgG4-related disease.

Eshraghi et al.[17] classified IOID into nine groups according to radiological and histopathological findings. The conclusion of their study is the definition of a new group, multiple tissue involvement, and the characterisation of fatty involvement into acute or fibrosing. They observed a worse prognosis and response to treatment in the multi-tissue involvement group.

Signs and symptoms

The characteristics of acute inflammation include the Celsus tetrad: flushing, warmth, pain and tumour. These will vary depending on the location of the inflammation in the orbit, the degree of inflammatory response, the presence of fibrosis and its etiology.[24]

Acute forms usually present with proptosis, limitation of extraocular movements and pain. They may also present with visual acuity (VA) loss, usually due to optic neuropathy. Subacute forms usually have a less explicit presentation with diffuse pain and variable myositis, with infrequent VA loss. Chronic forms usually present primarily with proptosis.[25]

If the inflammatory process involves the anteriormost structures of the orbit, external inflammatory signs such as palpebral erythema, conjunctival hyperemia and chemosis, and greater or lesser degree of diplopia and pain with EOMs are common in some cases. If the process compromises the more posterior areas of the orbit, pain, diplopia and proptosis to a variable degree usually predominate[25]. There are forms of localised involvement in the apex that manifest almost exclusively with pain, sometimes accompanied by loss of vision. The Tolosa-Hunt syndrome is characterised by hemicranial periorbital pain, paralysis of the III, IV or VI pair, and decreased vision due to optic nerve involvement. It is important to emphasise that other causal lesions, i.e. infectious pathology, tumours or sarcoidosis[12] must have been excluded. Bilateral presentation is more frequent in the pediatric age group.[12]

Dacryoadenitis is the most common subtype of IOID, accounting for approximately 50% of all cases. It usually presents with a painful, localised mass in the outer portion of the upper eyelid, producing a predominantly lateral ptosis (with an italic S-shape). It may be bilateral. Some patients who were initially classified as IOID were later diagnosed as ER-IgG4 due to high levels of this immunoglobulin. This entity may involve the periorbital soft tissues, optic nerve and branches of the trigeminal nerve.[12]

Orbital myositis may be acute, subacute or recurrent and may involve one or multiple EOMs. The most commonly involved are the medial rectus, followed by the superior, lateral and inferior rectus. It usually affects young patients in the third or fourth decade of life with a greater predisposition in women.[17]

The most frequent signs and symptoms of sclerosing IOIDs are pain, proptosis, edema, hyperemia and diplopia[10]. Enghelberg et al.[10] described VA worse than 20/40 in 42% of cases with this entity. Up to 42% of cases in the series included in this author's review[10] were associated with autoimmune diseases, including ER-IgG4, sarcoidosis, hemochromatosis, hyperthyroidism, diabetes mellitus and autoimmune diseases, as well as elevated acute phase reactants and ANA and ANCA markers. Yuen et al.[11] also described the association with Behçet's disease, rheumatoid arthritis, juvenile idiopathic arthritis and Crohn's disease. In addition, up to 15% were associated with neoplastic processes[10], such as myofibroblastic tumours of the pelvis and kidney, mesothelioma, pituitary macroadenoma, bilateral renal oncocytoma and breast cancer.

Diagnosis

The diagnosis of IOID is one of exclusion. It is based on ruling out other diseases causing similar clinical pictures by means of clinical history and physical examination, and supplementary examinations (laboratory, imaging and histopathological studies).

Medical history and physical examination

The diagnostic orientation of any patient with orbital symptoms should always begin with a complete history and examination.

Concernng anamnesis, it is important to take into account the sex and age of the patients as certain diseases have a preference for presentation based on these data. Toxic habits such as smoking are related to thyroid-related ophthalmopathy and a multitude of neoplasms. The presence of diagnosed systemic diseases or symptoms that may be a clue to certain autoimmune diseases are essential, such as rhinosinusal symptoms in cases of granulomatosis with polyangiitis, or skin or joint manifestations, which are common in several autoimmune diseases. It should be borne in mind that many systemic diseases can have an orbital inflammation as their first manifestation.

The ophthalmological examination should be complete and structured, including an external inspection for masses and inflammatory signs, VA, colour vision, and even campimetry if optic nerve involvement is suspected. It is also important to examine the classic palpebral and orbital measurements, namely palpebral aperture, elevator muscle function and exophthalmometry, to name the most important ones. We must also perform an examination of ocular motility, both extrinsic and intrinsic. Sometimes we can find alterations in facial sensitivity due to alterations in the branches of the trigeminal nerve that pass through the orbit. Thus, a decrease in sensitivity in the central frontal area will inform us of a possible involvement of the supratrochlear nerve, or an alteration at cheek level could indicate an involvement of the floor of the orbit through which the infraorbital nerve passes. At the ocular level, slit-lamp examination of the ocular surface, intraocular pressure and fundus is important. It is also important to rule out the presence of papillary oedema, retinal exudates or chorioretinal folds.

A complete examination will give us a lot of information to guide further supplementary examinations.

Laboratory studies

Once the picture has been established, laboratory tests can be ordered in a targeted manner, as there are certain markers that support the diagnosis of some diseases.[24] Thus, a thyroid profile including thyroid stimulating hormone (TSH), thyroid hormone levels and quantification of antithyroid antibodies will be basic to rule out thyroid orbitopathy. Antinuclear antibodies (ANA), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be nonspecifically elevated in systemic inflammation or autoimmune orbital disease.[24] A hepatopancreatic profile provides an indication of pancreatic dysfunction and can rule out autoimmune pancreatitis associated with ER-IgG4. IgG4 titres are not always elevated in this disease. This finding is only one of the diagnostic criteria and can help to monitor the disease.[24] ER-IgG4 may show imaging changes in the thyroid gland, pancreas, aorta, retroperitoneum, lungs, mediastinum, pituitary and others. Elevated angiotensin enzyme, lysozyme or calcium may be indicative of sarcoidosis. Chest X-ray may show hilar lymphadenopathy. Cytoplasmic antineutrophil cytoplasmic antibodies (ANCA) and basic urine profile could point to granulomatosis with polyangiitis, and imaging tests would show pulmonary and/or sinus involvement. Paraproteinaemia and lytic bone lesions would point to histiocytosis. It is important to rule out tuberculosis involvement to avoid possible worsening by corticosteroids, as well as serological tests to rule out syphilis (VDRL and RPR) and Lyme[24].

Despite all these data, the serological study is of limited value in many cases for the diagnosis of orbital inflammation, as we sometimes find non-specific results.[26] For example, the positive predictive value of angiotensin-converting enzyme or lysozyme in sarcoidosis, or serum IgG4 titres for ER-IgG4 orbitopathy, are too low to rely solely on these data.[26] Furthermore, C-ANCA in GPA and anti-RO or anti-LA in Sjögren's syndrome are undetectable in a large proportion of patients presenting with disease confined to the orbit.[27]

Imaging studies

Imaging tests will not show pathognomonic signs of IOID, but will be essential to localise the compromised tissue and to make a differential diagnosis with other orbital pathologies (Table 2).

On computed tomography (CT) we can find increased enhancement in the affected tissues after contrast administration, increased orbital fatty infiltration and rule out bone erosion[28]. T1-weighted magnetic resonance imaging (MRI) findings usually show areas that are hypointense with respect to fat and isointense with respect to muscle; in T2, areas of inflammation are isointense or slightly hyperintense with respect to fat, unlike hematomas or lesions suggestive of malignancy, which are more hyperintense[12]. In MRI with gadolinium contrast, enhancement is variable depending on the inflammatory phase. In acute phases, the enhancement is marked. In the chronic and sclerosing phase, the enhancement is mild or moderate.[12]

Lymphoproliferative diseases may show similar findings. Diffusion MRI (DWI-MRI) is the most reliable technique to distinguish cellulitis and lymphoproliferative diseases from inflammatory lesions and is based on the apparent diffusion coefficient[29]. Lymphomas show increased density, given the increased cellularity, while inflammatory processes show lower density and a higher apparent diffusion coefficient.[29]

Dynamic contrast-enhanced MRI makes it possible to distinguish the contrast uptake and washout curves for a given tissue, allowing more vascularised tissues to be assessed and thus distinguishing IOLS from lymphomas.[23]

Orbital ultrasound (B-Scan) is less commonly used in the diagnosis of these conditions, due to its limitations of less

Table 2 – Radiological findings according to anatomical involvement[12].

Myositis	Unilateral thickening of the MEO with myotendinous involvement, with a fusiform appearance on CT and MRI.
Dacryoadenitis	Diffuse lacrimal gland growth with poorly defined margins. Rule out lymphoma by DWI-MRI and definitely by biopsy.
Periscleritis	Heterogeneous thickening of the sclera and/or uvea associated with edema towards Tenon's space, showing the ring sign.
Perineuritis	MRI shows the donut sign on coronal slices, showing circumferential enhancement around the optic nerve sheath, and the rail sign on axial slices. Optic neuritis usually shows enhancement of the optic nerve, not the sheath.

CT, computed tomography; MRI, magnetic resonance imaging; EOM, extraocular muscles; DWI-MRI, diffusion MRI.

penetration and definition of the tissues in addition to being more dependent on the explorer. It can offer signs of inflammatory involvement when the condition is anterior, and helps to rule out ocular complications such as retinal detachment or choroidal detachment.[30]

Histopathological study

Except for orbital biopsies of the most anterior zone, with more direct access, biopsy of intraconical lesions or those affecting the most posterior portions of the orbit, carry significant risks of complications, some of them irreversible.[25] This fact has encouraged the increasing use of corticosteroid therapy without an established etiological diagnosis. However, it seems more reasonable to try to establish such a diagnosis before treating, although always assessing the pros and cons of each action, as will be discussed below.

Open biopsy is usually preferred to fine needle aspiration (FNA) because the latter could not be representative as it may not yield sufficient tissue, in addition to involving a blind intraorbital procedure with its associated risks and not allowing for a debulking procedure, which in many cases is beneficial. However, in cases of lymphoma or metastases, or situations where open surgery is contraindicated, FNA may be indicated and sufficient. In any case, the following criteria should be followed to obtain a quality biopsy in cases of orbital inflammation, following the NAILS mnemonic rule[31]:

- N: no prior corticosteroids, which may mask the clinical presentation, alter the cellularity of the biopsy and thus compromise histopathological analysis.
- A: atraumatic. Preoperative intralesional anaesthetic injection and cauterisation of the lesion should be avoided. It is advisable to grasp the lesion only once with atraumatic forceps or serrated forceps, as this may increase the risk of bleeding and visualisation of the surgical field.
- I: intralesional specimen. The biopsy should be obtained from several areas of the lesion, as an inconclusive result may be due to biopsying only areas of the periphery.
- L: Large biopsies. Samples should have a minimum volume of $6 \times 6 \times 6$ mm to be representative and reduce artifacts. This will allow good pathological processing of the tissue, as well as aiding cytoreductive treatment in some cases.
- S: saline storage. To allow flow cytometry. Formalin is normally sufficient for histopathology, immunohistochemistry, immunophenotyping and molecular genetic studies.

Advances in diagnostic techniques: molecular diagnostics and immunohistochemistry

Rosenbaum et al.[32] designed a diagnostic algorithm based on genetic analysis of RNA samples in an attempt to increase the diagnostic accuracy of the cause of IOID. They found that, using such an algorithm, they obtained higher diagnostic accuracy of the possible etiology of IOID, in their case in up to 76% of cases, compared to histopathological analysis of the specimen by expert pathologists, achieving a diagnostic accuracy of 49% to 58%. In addition, they described that sometimes patients primarily diagnosed with IOID may represent limited forms of GPA, hence molecular diagnostics can help to better understand inflammatory orbital diseases.

Numerous studies have documented imbalances of certain inflammatory cytokines in IOID. Wladis et al.[33] described elevated levels of interleukin (IL)-2, IL-8, IL-10, IL-12, interferon (IFN)-γ and tumour necrosis factor (TNF)- αin histopathological samples of IOID, inferring a pivotal role of T-helper 1 cells in the pathogenesis of IOID. Another immunohistochemical study has documented a remarkable expression of CD20 and CD25 in IOID, proposing rituximab (RTX), which would bind to CD20 receptors, and denileukin diftitox (ONTAK), which would bind to CD25, as possible beneficial treatments in the management of IOID.[34]

Recently, gene expression profiling methods have been used to investigate the phenotypic variability of IOID. Up-regulation of immunoglobulins, CXCR4, YKL-40, CXCL9, the SLAM family 8, IL-7 receptor and down-regulation of alcohol dehydrogenase 1B, perilipin 1, adiponectin, leptin receptor and C1Q have been documented in patients with IOID by gene expression array methods.[33] Genotypic analyses will help to define the phenotypic variability observed between cases of IOID, thereby aiding in more targeted treatment.[12]

Diagnostic management

Currently, authors do not agree on how to conduct the initial management of the patient. Glass et al.[24] recommend performing a corticosteroid response test, as IOID can be diagnosed clinically, thus avoiding surgical risks, while Mombaerts et al.[31] advocate initial biopsy prior to such treatment, claiming the potential diagnostic error and modification of tissue cellularity that empirical corticosteroid treatment would entail.

Glass et al.[24] justify the recommendation of corticosteroids as first-line diagnosis and treatment through a review of large studies of orbital biopsies. They found that more than 80% of patients with non-tumour and non-infectious pathology in the Shields[5] (1,264 patients) and Newcastle[35] (162 patients) groups were idiopathic orbital disease. This incidence could be overestimated, as ER-IgG4 was not ruled out; however, later studies recategorised these cases and they represented less than 5% of idiopathic inflammation.[24,36] Because biopsy has always been reserved for atypical or non-responsive cases, the results may be biased towards atypical cases. For example, thyroid orbitopathy is rarely biopsied by clinical diagnosis and by supplementary laboratory and imaging tests. This is why most orbital inflammations that are biopsied are classified as idiopathic, precisely because they do not allow the determination of a more selective treatment regimen. An exhaustive clinical study of the patient with the help of the supplementary tests described above would enable a correct differential diagnosis.

Corticosteroids are inexpensive, accessible drugs and are the first line of treatment for a large number of orbital inflammatory diseases due to the scarcity of specific targeted therapies, and have the advantage that they can resolve most systemic inflammatory diseases, thus avoiding the patient having to undergo a biopsy which, even in expert hands, could cause significant morbidity including loss of vision, diplopia or ptosis to name a few. This risk is higher if the lesion is located in the orbital apex or around the optic nerve. Rapid response allows patients to be classified into good responders, who can be monitored and avoid biopsy, and non-responders or atypical responders, who may require biopsy and a switch to corticosteroid-sparing treatment.[24]

Mombaerts et al.[31] argue that the anachronistic practice of performing a diagnostic trial with corticosteroids should be abandoned as their favourable response would be anticipated by any lesion surrounded by inflammatory cells, including some malignant neoplasms. Histopathological confirmation is crucial, as IOID remains a diagnosis of exclusion. IOID is a diagnosis that should be differentiated from orbital inflammation produced as an immune system response to other causes such as infection, structural damage, autoimmune, or neoplastic. The designation of any orbital inflammation that responds well to empirical corticosteroid treatment as IOID would, according to these authors, be erroneous.

Orbital inflammation is usually limited to the orbit, and therefore serological and systemic studies usually have a low predictive value. When clinical and radiological findings are inconclusive, the search for the causative agent of inflammation should be accompanied by tissue biopsy performed by minimally invasive techniques and pathological findings should be interpreted in the context of clinical, imaging and serological findings. IgG4 plasma cell positivity should not be misinterpreted as synonymous with ER-IGg4, as it occurs in several other diseases. Moreover, this new entity further supports the performance of a biopsy.[31]

Misdiagnosis of IOID, based on a good response to corticosteroids, has been described in many cases of B- and T-cell lymphomas, metastatic disease, lacrimal gland epithelial lesions, fungal infections, GPA and sarcoidosis.[37] The diagnostic power of corticosteroid response is even lower if we add the fact that up to 21% of patients with idiopathic dacryoadenitis and 45% with sclerosing IOID do not respond adequately to this treatment.[38] It is also described that, as mentioned above, corticosteroid treatment may mask and defer the etiological diagnosis, which is especially important in cases of severe lesions that may compromise vision. In these cases, the search for an aetiological diagnosis is of great importance, even after a first positive response to corticosteroid treatment.[21]

In routine practice, the tendency is to initiate corticosteroid treatment prior to performing a biopsy, especially when the location is in the orbital apex or optic nerve, due to the high risk of visual loss as a post-surgical complication, or in primary myositis because it is usually correctly characterised in most cases by examination and neuroimaging.[3] The exception to the above is when there are undefined or atypical radiological and clinical findings, such as a neoplasia history.[21] Some authors add that biopsy should not be indicated in cases where surgery would be contraindicated.[39]

In their study of 60 patients with dacryoadenitis and inflammatory signs, Luemsamran et al.[40] observed that 61.7% had a specific histopathology and 38% had a related systemic disease, therefore it is always recommended to biopsy when there is isolated inflammation of the lacrimal gland.[40] Furthermore, the results of different studies have shown that chronic dacryoadenitis followed by lymphoproliferative lesions were the most frequent histopathological findings in lacrimal gland biopsy.[5]

Diagnostic consensus on IOID using a Delphi method

In order to establish a diagnostic algorithm for IOID, a group of 35 experts belonging to the Orbit society participated in an *online* trial and scored, on a five-point scale, a number of items as diagnostic criteria based on the literature and their personal experience.[41] The conclusions they reached were as follows:

- The management of non-myositis IOID should be based on clinical, MRI or CT, some laboratory tests and biopsy.
- Management of myocytic IEOI should be based on MRI, CT, some laboratory tests and response to corticosteroid treatment.

This algorithm has special considerations.[41] It is only valid for acute phases. Clinical, radiological or pathological findings may be altered if the patient has already received corticosteroid treatment or surgery. The finding of non-specific orbital inflammation is not sufficient to establish a diagnosis of IOID, and when histopathology is not diagnostic, biopsy of other sites should be considered.

Differential diagnosis

The recognition of ER-IgG4 as a diagnostic alternative to IOID has recently been questioned. Pathological differentiation is based on the absolute or relative number of IgG4-positive

plasma cells.[42] Positive staining is common in several orbital inflammatory lesions other than ER-IgG4. There is increasing evidence that there is an increase of IgG4-positive plasma cells in IOID, GPA, sarcoidosis, zonal marginal lymphoma, lymphoid hyperplasia and adult xanthogranuloma.[42]

Goto et al.[43] established diagnostic criteria for orbital ER-IgG4, highlighting imaging tests demonstrating (1) enlargement of the lacrimal gland, trigeminal nerve or extraocular muscles, as well as hypertrophic lesions or masses in various ophthalmic tissues; (2) histopathological analysis demonstrating lymphocytic and plasmacytic infiltrates, but not necessarily fibrosis, plus an IgG4+/IgG ratio greater than 40% or a minimum of 50 IgG4+ cells per field; (3) serum IgG4 greater than 135 mg/dL. The diagnosis is definite when all three criteria are met, probable when the first and second criteria are met, and possible when the first and third criteria are met. Sjörgen's syndrome, sarcoidosis, GPA, thyroid orbitopathy, IOID, bacterial or fungal dacryoadenitis or orbital cellulitis, and mucosa-associated lymphoma (MALT) must be excluded for definitive diagnosis.

Orbital and systemic diseases that may present with similar signs and symptoms include orbital cellulitis, thyroid orbitopathy, vascular lesions such as lymphangioma, and neoplastic processes such as lymphoma, metastases or rhabdomyosarcoma. Other more serious diseases, such as metastases of rhabdomyosarcoma or Ewing's sarcoma, chronic recurrent multifocal osteomyelitis and SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) have been described as causing secondary orbital inflammation.[12]

Bilateral involvement should be a red flag as it can cause serious morbidity with severe, chronic, progressive disease that commonly manifests with proptosis, restriction of the EOMs and pain.[29] There is growing evidence that sclerosing IOID may be a subtype of IgG4, and this should be suspected if there is systemic or bilateral involvement.[12]

In pediatric patients, the differential diagnosis includes orbital cellulitis, orbital trauma with retained foreign body, ruptured dermoid cyst, lymphangioma, neuroblastoma, Langerhans cell histiocytosis, and malignancies such as rhabdomyosarcoma, leukaemia, neuroblastoma and metastatic retinoblastoma.[12]

Treatment

Currently available therapeutic agents are:

Corticosteroids

Systemic corticosteroids are the first line of treatment for IOID.[12,22] Initially, up to 75% of patients show significant improvement in signs and symptoms.[44] The dose used is usually 1 mg/kg/day of prednisone with a slow, progressive tapering schedule over six to eight weeks. Intraorbital triamcinolone has also been described as an effective treatment in some cases.[12]

Mombaerts et al.[44] observed that 78% of patients initially responded to corticosteroids. However, up to 52% showed relapses after response or down-regulation. Corticosteroids alone are usually not sufficient in sclerosing IOID, and treatment with immunomodulators alone or in combination with corticosteroids is necessary in about half of the cases.[11]

External radiotherapy

It is used as an adjuvant or alternative treatment to corticosteroids when symptoms reappear during the downward regimen, when corticosteroids are ineffective or contraindicated. This treatment reduces steroid dependence with complete cessation of steroids in up to 50% of patients and dose reduction in up to 25% of cases. The dose is usually 1000–3000 cGy over two to three weeks on a fractionated basis. The success rate ranges from 50–70%.

Side effects include dry eye, keratitis, cataract, retinopathy, optic neuropathy and periocular dermatitis.[45] The radiotoxic effect starts from the beginning of treatment. An acute phase with release of proinflammatory cytokines is distinguished, followed by activation of other mediators leading to tissue fibrosis. The exaggerated and uncontrolled activation of these cytokines constitutes the basic pathophysiology of radiotherapy toxicity.[46] In addition, radiation affects tissues in the pathway to the target tissue. In this respect, the lens of the eye is the structure most sensitive to the effects of radiation, and a single dose of 2 Gy has been shown to induce cataract formation.[46] The radiotoxic effect that leads to cataract formation occurs in the germinative zone of the anterior aspect of the lens, causing the DNA of the proliferative cells to be affected, as well as the migration of the remains of the crystalline fibres that accumulate in the subcapsular region.[46] Dry eye syndrome occurs due to involvement of the main and accessory lacrimal glands. On the other hand, epiphora is usually a consequence of tear duct obstruction. Conjunctival involvement ranges from squamous metaplasia and keratinisation to atrophy and necrosis.[46]

Antimetabolites

- Metrotexate: is a folic acid antagonist that inhibits dihydrofolate reductase in the synthesis of folic acid, which is an enzyme required for DNA and RNA synthesis, resulting in inhibition of cells with high proliferative capacity and thus suppressing B and T-cell function.[12] Although available studies have shown good results, these are series of few patients, such as that of Rosenbaum et al.[47] who described an improvement in four out of seven patients, so the evidence is sparse.
- Azathioprine: is a purine analogue that interferes with DNA synthesis and inhibits the proliferation of cells with high proliferative capacity, especially cells of the immune system. Rootman et al.[48] observed successful treatment in combination with corticosteroids.
- Mycophenolate mofetil: has a mechanism of action similar to azathioprine and inhibits purine synthesis, preventing B and T cell replication. Side effects include gastrointestinal discomfort and immunosuppression. Hatton et al. reported good results in three of four patients who had been refractory to corticosteroids.[49]

Calcineurin inhibitors

- Cyclosporin A: is an immunomodulatory agent that inhibits Il-1 and IL-2, decreasing T-lymphocyte activation. It has serious side effects such as renal dysfunction, hypertension, hepatotoxicity, and hematological and dermatological malignancies. Some cases of IOID have shown remission with cyclosporine.[50] Gumus et al.[51] stabilised a patient with idiopathic myositis and scleritis with topical cyclosporine A and topical dexamethasone, which was instituted due to the side effects of systemic cyclosporine A and topical dexamethasone in the patient.

Alkylating agents

- Cyclophosphamide: is an alkylating agent that damages proliferating cells by cross-linking DNA and RNA. Side effects include myelosuppression, gastrointestinal distress, haemorrhagic cystitis and induction of secondary neoplasms.[12]
- Chlorambucil: has side effects similar to cyclophosphamide.[12]

Lymphocyte inhibitors

- Rituximab: is a mouse and human chimeric monoclonal antibody against CD20 lymphocytes, a phosphoprotein of the B-cell cell wall. Side effects include pulmonary toxicity, intestinal obstruction, cardiotoxicity and immunosuppression. There are some published cases of improvement of symptoms such as oedema and diplopia in patients with IOID.[52] Savino et al. described successful treatment in three patients with intraorbital rituximab injections.[53]
- Daclizumab: is a humanised monoclonal antibody directed against IL-2 (CD 25) T-cell receptors. It has been used initially for liver transplant rejection and in multiple sclerosis, but there is currently little clinical experience. A case of orbital myositis with good evolution and one year of follow-up after treatment with this drughas been published.[54]

TNFαinhibitors

- Infliximab: is a chimeric monoclonal antibody against TNFα. Its side effects include reactivation of latent tuberculosis, erythema, headache, hypotension, lupus-like reaction, risk of lymphoma, among others. It has a synergistic effect with methotrexate. A favourable response has been described in several patients with chronic and refractory IOID previously treated with corticosteroids and radiotherapy. The dose is 3–5 mg/kg intravenous at weeks 0, 2, 6 and every four to eight weeks until the desired effect is achieved. Good results in recalcitrant myositis have been reported in seven patients with response in all.[55]
- Adalimumab: is a humanised IgG1 monoclonal antibody against TNFα. The risk of developing autoantibodies and allergic reactions is lower than with Infliximab. Good results have been reported in relapsed pediatric cases.[56]

Surgery

Surgery can be performed in focal masses, in some cases of anterior/diffuse IOID and dacryoadenitis. A large biopsy or cytoreduction of the orbital lobe of the lacrimal gland has been effective in up to 80% of patients with idiopathic dacryoadenitis as initial therapy. Less than 10% required anti-inflammatory treatment after the procedure.[12] This cytoreduction procedure has not been associated with the development of dry eye as the palpebral lobe is left intact.[57]

Other alternative treatments under study include intravenous immunoglobulins and plasmapheresis that act by neutralising or filtering out the autoantibodies. These treatments would be considered in recalcitrant cases.[58]

Therefore, corticosteroids remain the mainstay of treatment despite the high recurrence rate of up to 50% and the poor response to treatment in some subtypes and in sclerosing IOID. There is no consensus on treatment protocols in corticosteroid-resistant cases, being managed with immunosuppressants or immunomodulators, or combined therapy with corticosteroids.[59]

Conclusions

IOID is a diagnostic and therapeutic challenge in ophthalmology. It can involve several orbital structures, with various clinical presentations and in addition imaging tests are variable and overlapping with those of other diseases. Since it represents a diagnosis of exclusion, other diseases affecting the orbit must be ruled out. Management must be individualised in each case, in general it is recommended to obtain an orbital biopsy before starting a therapeutic trial with corticosteroids, which could mask and delay the diagnosis, except in cases where the biopsy involves a high risk of complications (lesions in the orbital apex), and in cases where the clinical/neuroimaging diagnosis is evident (primary myositis). There is a wide range of therapeutic options based primarily on corticosteroids, including alternatives for refractory cases such as external radiotherapy, immunosuppression/immunomodulation, lymphocyte inhibitors, TNFα inhibitors and decompressive resection surgery.

Funding

None.

Conflict of interest

No conflict of interest is declared.

REFERENCES

1. Kitei D, DiMario FJ. Childhood orbital pseudotumor: case report and literature review. J Child Neurol. 2008;23:425e430.
2. Grove AS, Weber AL. Orbital pseudotumor - historical origin and modern relevance. Ophthal Plast Reconstr Surg. 2013;29:341–6.

3. Mombaerts I, Goldschmeding R, Schlingemann RO, Koornneef L. What is orbital pseudotumor? Surv Ophthalmol. 1996;41:66–78.
4. Rootman J. Why "orbital pseudotumour" is no longer a useful concept. Br J Ophthalmol. 1998;82:339–40.
5. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery Lecture, part 1. Ophthalmology. 2004;111, 997e1008.
6. Mendenhall WM, Lessner AM. Orbital pseudotumor. Am J Clin Oncol. 2010;33:304e306.
7. Kennerdell JS, Dresner SC. The nonspecific orbital inflammatory syndromes. Surv Ophthalmol. 1984;29:93e103.
8. Jacobs D, Galetta S. Diagnosis and management of orbital pseudotumor. Curr Opin Ophthalmol. 2002;13:347e351.
9. Rocha Cabrera P, Abreu Reyes JA, Fernández Ramos J, Losada Castillo MJ, Delgado Frías E, Lozano López V, et al. Sarcoidosis. Debut as orbital pseudotumour. Arch Soc Esp Oftalmol. 2015;90:578–81.
10. Enghelberg M, Go J, Adika A, Sánchez-González MA, Georgescu D, Kay M. Non-specific orbital inflammation and sclerosing variant. Vis Pan-Am. 2017;16:103–9.
11. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: ocular mechanisms and clinicopathology. Ophthalmol Clin N Am. 2002;15, 121e126.
12. Yeşiltaş YS, Gündüz AK. Idiopathic orbital inflammation: review of literature and new advances. Middle East Afr J Ophthalmol. 2018;25:71–80.
13. Kawasaki A, Borruat FX. An unusual presentation of herpes zoster ophthalmicus: orbital myositis preceding vesicular eruption. Am J Ophthalmol. 2003;136:574–5.
14. Sharma NS, Ooi JL, Masselos K, Hooper MJ, Francis IC. Zoledronic acid infusion and orbital inflammatory disease. N Engl J Med. 2008;359:1410–1.
15. Ortiz-Perez S, Fernandez E, Molina JJ, Sánchez-Dalmau B, Navarro M, Correger X, et al. Two cases of drug-induced obital inflammatory disease. Orbit. 2011;30:37–9.
16. Bijlsma WR. Doctoral thesis: progress in etiology, diagnosis, and treatment of idiopathic orbital inflammatory diseases. Universiteit Utrecht; 2011.
17. Eshraghi B, Sonbolestan SA, Abtahi MA, Mirmohammadsadeghi A. Clinical characteristics, histopathology, and treatment outcomes in adult and pediatric patients with nonspecific orbital inflammation. J Curr Ophthalmol. 2019;31:327–34.
18. Enghelberg M, Go J, Adika A, Sánchez-González MA, Georgescu D, Kay M. Non-specific orbital inflammation and sclerosing variant. Vis Pan-Am. 2017;16:103–9.
19. Mombaerts I, Schlingemann RO, Goldschmeding R, Koornneef L. Idiopathic granulomatous orbital inflammation. Ophthalmology. 1996;103:2135–41.
20. Lokdarshi G, Pushker N, Bajaj MS. Sclerosing lesions of the orbit: a review. Middle East Afr J Ophthalmol. 2015;22:447–51.
21. Pemberton JD, Fay A. Idiopathic sclerosing orbital inflammation: a review of demographics, clinical presentation, imaging, pathology, treatment, and outcome. Ophthal Plast Reconstr Surg. 2012;28:79–83.
22. Dagi Glass LR, Freitag SK. Orbital inflammation: corticosteroids first. Surv Ophthalmol. 2016;61:670–3.
23. Moreiras JV, Prada MC. Patología orbitaria. Barcelona: Edika Med; 2000. p. 155–220.
24. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4related disease. Ann Rheum Dis. 2015;74, 14e8.
25. Parkin B, Chew JB, White VA, Garcia-Briones G, Chhanabhai M, Rootman J. Lymphocytic infiltration and enlargement of the lacrimal glands: a new subtype of primary Sjögren's syndrome? Ophthalmology. 2005;112, 20407.
26. Gordon LK. Diagnostic dilemmas in orbital inflammatory disease. Ocul Immunol Inflamm. 2003;11:3–15.
27. Sepahdari AR, Aakalu VK, Setabutr P, Shiehmorteza M, Naheedy JH, Mafee MF, et al. Indeterminate orbital masses: Restricted diffusion at MR imaging with echo-planar diffusion-weighted imaging predicts malignancy. Radiology. 2010;256:554–64.
28. Morales Pérez JM, Cano Rodríguez A, Sobrino Guijarro B, Martínez Moya M, Encinas Tobajas VM. Dynamic magnetic resonance imaging in the diagnosis of tumors and pseudotumors of the musculoskeletal system. Radiologia. 2012;54:38–49.
29. Platnick J, Crum AV, Soohoo S, Cedeño PA, Johnson MH. The globe: infection, inflammation, and systemic disease. Semin Ultrasound CT MR. 2011;32:38–50.
30. Mombaerts I, Rose GE, Garrity JA. Orbital inflammation: biopsy first. Surv Ophthalmol. 2016;61:664–9.
31. Rosenbaum JT, Choi D, Wilson DJ, Grossniklaus HE, Sibley CH, Harrington CA, et al. Molecular diagnosis of orbital inflammatory disease. Exp Mol Pathol. 2015;98:225–9.
32. Wladis EJ, Iglesias BV, Gosselin EJ. Characterization of the molecular biologic milieu of idiopathicorbital inflammation. Ophthalmic Plast Reconstr Surg. 2011;27:251–4.
33. Chevez-Barrios P, Jorgensen JL, Silkiss RZ, Esmaeli B. Receptor expression in orbital inflammatory syndromes and implications for targeted therapy. Tissue Antigens. 2007;70:105–9.
34. Ting DSJ, Perez-Lopez M, Chew NJ, Clarke L, Dickinson AJ, Neoh C. A 10-year review of orbital biopsy: the Newcastle Eye Centre Study. Eye (Lond). 2015;29:1162–6.
35. Andrew NH, Sladden N, Kearney DJ, Selva D. An analysis of IgG4-relateddisease (IgG4-RD) among idiopathic orbital inflammations and benignlymphoid hyperplasias using two consensus-based diagnostic criteria forIgG4-RD. Br J Ophthalmol. 2015;99:376–81.
36. Sullivan TJ, Whitehead K, Williamson R, Grimes D, Schlect D, Brown I, et al. Lymphoproliferative disease of the ocular adnexa: a clinical and pathologic study with statistical analysis of 69 patients. Ophthal Plast Reconstr Surg. 2005;21:177e88.
37. Mombaerts I, Schlingemann RO, Goldschmeding R, Koornneef L. Are systemic corticosteroids useful in the management of orbital pseudotumors? Ophthalmology. 1995;103, 521e8.
38. Zborowska B, Ghabrial R, Selva D, McCluskey P. Idiopathic orbital inflammation with extraorbital extension: case series and review. Eye (Lond). 2006;20:107e113.
39. Young SM, Chan AS, Jajeh IA, Shen S, Seah LL, Choo CT, et al. Clinical features and treatment outcomes of orbital inflammatory disease in Singapore: a 10-year clinicopathologic review. Ophthal Plast Reconstr Surg. 2017;33:182e188.
40. Luemsamran P, Rootman J, White VA, Nassiri N, Heran MKS. The role of biopsy in lacrimal gland inflammation: a clinicopathologic study. Orbit. 2017;36:411–8.
41. Mombaerts I, Bilyk JR, Rose GE, McNab AA, Fay A, Dolman PJ, et al. Consensus on diagnostic criteria of idiopathic orbital inflammation using a modified Delphi approach. JAMA Ophthalmol. 2017;135:769.
42. Deschamps R, Deschamps L, Depaz R, Coffin-Pichonnet S, Belange G, Jacomet PV, et al. High prevalence of IgG4-related lymphoplasmacytic infiltrative disorder in 25 patients with orbital inflammation: a retrospective case series. Br J Ophthalmol. 2013;97:999–1004.
43. Goto H, Takahira M, Azumi A, Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4- related ophthalmic disease. Jpn J Ophthalmol. 2015;59:1 –7.

44. Mombaerts I, Schlingemann RO, Goldschmeding R, Koornneef L. Are systemic corticosteroids useful in the management of orbital pseudotumors? Ophthalmology. 1996;103:521–8.
45. Prabhu RS, Kandula S, Liebman L, Wojno TH, Hayek B, Hall WA, et al. Association of clinical response and long-term outcome among patients with biopsied orbital pseudotumor receiving modern radiation therapy. Int J Radiat Oncol Biol Phys. 2013;85:643–9.
46. González García JL, Santos Silva D, Abreu Perdomo FA, Melgares Ramos MÁ, Valdivia Bregado YT. Complicaciones tardías de la radioterapia ocular / Late complications of the ocular radiotherapy. Rev Cubana Oftalmol. 2016;29:141–7.
47. Smith JR, Rosenbaum JT. A role for methotrexate in the management of non-infectious orbital inflammatory disease. Br J Ophthalmol. 2001;85:1220–4.
48. Rootman J, McCarthy M, White V, Harris G, Kennerdell J. Idiopathic sclerosing inflammation of the orbit. A distinct clinicopathologic entity. Ophthalmology. 1994;101:570–84.
49. Hatton MP, Rubin PA, Foster CS. Successful treatment of idiopathic orbital inflammation with mycophenolate mofetil. Am J Ophthalmol. 2005;140:916–8.
50. Zacharopoulos IP, Papadaki T, Manor RS, Briscoe D. Treatment of idiopathic orbital inflammatory disease with cyclosporine-A: a case presentation. Semin Ophthalmol. 2009;24:260–1.
51. Gumus K, Mirza GE, Cavanagh HD, Karakucuk S. Topical cyclosporine A as a steroid-sparing agent in steroid-dependent idiopathic ocular myositis with scleritis: a case report and review of the literature. Eye Contact Lens. 2009;35:275–8.
52. Ibrahim I, Barton A, Ibrahim A, Ho P. Idiopathic orbital inflammation successfully treated using rituximab in a patient with rheumatoid arthritis. J Rheumatol. 2012;39:1485–6.
53. Savino G, Battendieri R, Siniscalco A, Mandarà E, Mulè A, Petrone G, et al. Intraorbital injection of rituximab in idiopathic orbital inflammatory syndrome: case reports. Rheumatol Int. 2015;35:183–8.
54. Garcia-Pous M, Hernández-Garfella ML, Díaz-Llopis M. Treatment of chronic orbital myositis with daclizumab. Can J Ophthalmol. 2007;42:156–7.
55. Garrity JA, Coleman AW, Matteson EL, Eggenberger ER, Waitzman DM. Treatment of recalcitrant idiopathic orbital inflammation (chronic orbital myositis) with infliximab. Am J Ophthalmol. 2004;138:925–30.
56. Adams AB, Kazim M, Lehman TJ. Treatment of orbital myositis with adalimumab (Humira). J Rheumatol. 2005;32:1374–5.
57. Mombaerts I, Cameron JD, Chanlalit W, Garrity JA. Surgical debulking for idiopathic dacryoadenitis: a diagnosis and a cure. Ophthalmology. 2014;121:603–9.
58. Symon Z, Schneebaum N, Eyal A, Tal S, Rozen N, Shoenfeld Y, et al. Successful intravenous immunoglobulin therapy for resistant inflammatory pseudotumor of the orbit. Thyroid. 2005;15:398–9.
59. Ronquillo Y, Patel BC. Nonspecific Orbital Inflammation (NSOI). Treasure Island (FL): StatPearls Publishing; 2020.