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Tumor Discovery

CASE SERIES

Inflammatory disease of the orbit: A case series

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Abstract

Inflammatory orbital pseudotumors are a heterogeneous group of diseases characterized by their sensitivity to corticosteroid treatment regardless of the underlying etiology. Histological examination is generally performed following a lack of response to steroids, progressive neurological involvement, or suspicion of malignancy on radiological imaging. Herein, we report three clinical cases presented to our internal medicine department. The first case underscores the need for enucleation of the orbit due to the aggressiveness of orbital pseudotumors. This first case revealed Takayasu disease in a 39-year-old patient. Following the failure of corticosteroid therapy, favorable progression was achieved with adalimumab. Our second case concerns a 49-year-old woman presenting with exophthalmos, demonstrating rapid improvement in both clinical and biological parameters on corticosteroid administration. However, despite clinical amelioration, the partial radiological persistence of the orbital tumor prompted a positron emission tomography scan, revealing intense metabolic activity in the orbit despite the absence of clinical symptoms. Given the impracticability of biopsy, treatment with anti-CD20 was proposed, yielding a favorable radiological response. The third case describes an inflammatory orbital pseudotumor revealed by hemolytic anemia, with improved clinical and biological parameters observed over a 6-month period.

Keywords: Inflammatory disease of the orbit; Orbital inflammatory syndrome; Orbital pseudotumor; Vasculitis; Hemolytic anemia

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1. Introduction

Inflammatory disease of the orbit (IDO) is a disease that affects all elements of the orbit and its appendages. It was first described by Gleason[1] and subsequently elaborated by other researchers.[2]

IDO affects individuals across all age groups, representing up to 6% of orbital disorders and frequently necessitating orbital biopsy procedures.[3] Its differential diagnosis encompasses a variety of disorders, including tumors, infections, congenital deformities, trauma, and systemic or local inflammatory diseases.[4] Several systemic inflammatory disorders are associated with IDO, including giant cell arteritis, Churg-Strauss syndrome, Erdheim-Chester disease, histiocytosis X, autoimmune thyroid disease, sarcoidosis, granulomatosis with polyangiitis, Crohn's disease, systemic lupus erythematosus, and other connective tissue diseases.[5]

Congenital lesions, particularly lymphangiomas and dermoid cysts, may exhibit sporadic symptoms that resemble IDO or develop an inflammatory component.[6] In addition, the extra-scleral expansion of primary eye tumors, such as malignant melanomas, can trigger a subsequent orbital inflammatory response.[7]

Inflammatory elements can present in both primary and metastatic tumors within the orbit, with rhabdomyosarcoma notably exhibiting features resembling an inflammatory disorder. Patients with IDO should undergo thorough evaluation for secondary infectious disorders stemming from bacteria, viruses, fungi, and parasites, as these infections can precipitate severe inflammatory diseases.[8]

The diagnosis of IDO relies on clinical and paraclinical assessments. Despite the aggressiveness observed in certain cases, IDO typically remains a benign condition, although it can pose a threat to orbital function and may lead to oculomotor dysfunction. Histologically, IDO is characterized by chronic inflammation without obvious local cause. In this case series, we presented the clinical, radiological, and evolutionary profiles of three clinical cases of IDO.

2. Case presentation

2.1. Case 1

A 38-year-old woman with a history of pelvic fracture was admitted to the internal medicine department for management of an evolving orbital mass over the past year.

On clinical examination, the patient presented with a painful exophthalmos on the right eye accompanied by inflammatory characteristics, chemosis, periorbital edema, lacrimation, and visual acuity of 4/10. In addition, ocular hypertonia with blurred papillary edges in the temporal region of the eye was noted. The cardiovascular examination also revealed a decreased right radial pulse and a supraclavicular murmur.

Orbital magnetic resonance imaging (MRI) revealed an extra conical intra-orbital lesion process involving the superior rectus and external rectus muscles, in contact with the lacrimal gland, with mass effect and responsible for a grade II exophthalmos, demonstrating hypointensity on both T1 and T2 imaging, with homogeneous and diffuse enhancement (Figure 1A).

A thoracic-abdominal-pelvic scan revealed bilateral lobar retractile parenchymal micronodules, with some exhibiting a budded tree morphology. In addition, diffuse inflammatory thickenings of the aorta and the right common carotid artery (Figure 1B) were observed, along with extensive stenosis of the superior mesenteric artery >15 mm and stenosis of the left renal artery, accompanied by asymmetry of kidney size of 8.5 cm on the left and 11.5 cm on the right.

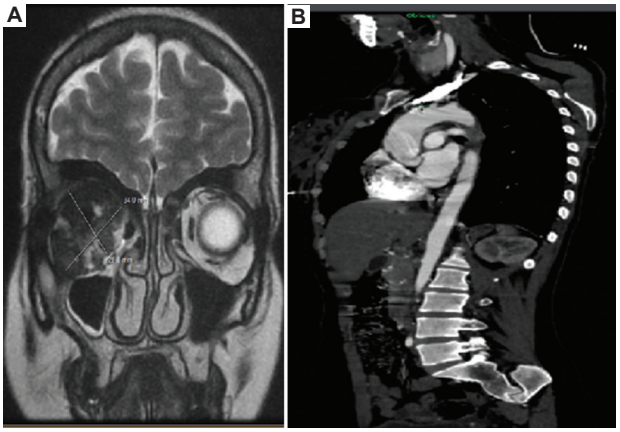


Figure 1. Imaging results of Case 1. (A) Coronal section in T2 sequence, revealing a T2-hyposignal right orbital intra- and extra-cone infiltrate. The infiltrate appears poorly defined and not centered on a particular organ, with weak enhancement after causal contrast, indicative of grade II exophthalmos. (B) Diffuse aortitis indicative of Takayasu disease.

The biological analysis revealed an inflammatory syndrome, while thyroid function tests were within normal limits. Liver and kidney function evaluations showed no abnormalities. Serological test for hepatitis, human immunodeficiency virus, syphilis, cytomegalovirus, toxoplasmosis, and rubella yielded negative results. Levels of angiotensin-converting enzyme and IgG4 were within normal ranges. The lipid profile was within acceptable parameters. *Mycobacterium tuberculosis* (MB) was identified in bronchoscopy through genetic analysis, with the presence of MB also confirmed in the pleural fluid. Subsequently, the patient was initiated on anti-tuberculosis medications (isoniazid, rifampicin, pyrazinamide, and ethambutol for the initial 2 months, followed by a continuation regimen of rifampicin and isoniazid for the subsequent 4 months).

A cardiac ultrasound revealed no abnormalities, with a good systolic ejection fraction.

Following multiple biopsies, the external orbitotomy revealed fat tissue interspersed with numerous vessels featuring congestive walls. Lymphocytic cellularity without atypia was observed, indicative of chronic and fibrous inflammatory remodeling without granulomatous lesions.

A bolus of corticosteroid therapy, administered under antibiotic cover, transiently reduced local inflammatory signals and improved clinical symptoms.

The progression was marked by the rapid resolution of superinfection in the orbit, alongside continued clinical progression of the orbital mass and persistence of the apoplexy syndrome, requiring analgesic treatment.

The ophthalmologists opted for enucleation, accompanied by several muscle and conjunctival biopsies,

due to the unique characteristics of the intraorbital tumor, which exhibited a solid and adherent consistency reminiscent of cartilage. The sole concern was to eliminate an underlying neoplastic process.

The final histological examination confirmed the pseudotumor nature of the inflammatory process. It revealed the presence of lymphoid cells and scattered T-phenotype cells expressing CD3 alongside CD20 expression by numerous well-defined nodules lacking expansive characteristics. In addition, a KI-67 proliferation index of 10% was noted, particularly accentuated in the clear germinal centers, along with vascular lesions. Furthermore, polyclonal rearrangement of the heavy and light kappa chains of immunoglobulins was observed, definitively ruling out the hypothesis of hemopathy or a solid tumor.

It was concluded that the patient had Takayasu disease, as evidenced by a pseudo-orbital tumor in conjunction with pulmonary tuberculosis. The diagnosis was based on the fulfillment of four diagnostic criteria: age, decreased right brachial pulse, supraclavicular murmur, and radiological lesions consistent with diffuse thickenings of the aorta and common carotid artery, as well as stenosis of the superior mesenteric and left renal arteries. Following successful anti-tuberculosis treatment, the patient was commenced on infliximab therapy. Subsequently, there was a resolution of clinical complaints and normalization of inflammatory signals after 1 month of treatment. At the 6-month follow-up, a positron emission tomography (PET) scan revealed a slight residual hypermetabolism localized to the orbital mass, with no hypermetabolism elsewhere.

2.2. Case 2

A 49-year-old woman, mother of four children, with a history of hysterectomy for a benign pelvic mass 4 years ago, presented with a capricious, non-painful orbital mass evolving over 2 years. Clinical examination revealed an irreducible, painful, and non-pulsatile axial exophthalmos, which did not worsen in the forward-leaning position or with the Valsalva maneuver. Visual acuity was 8/10, with no oculomotor abnormalities. Scans and MRI revealed a process of right ocular lesion, extended to the posterior pole with invasion of the optic nerve and involvement of the superior and external rectus muscle (Figure 2A-C).

Biological analysis showed evidence of an inflammatory syndrome, along with negative serologies (serology hepatitis, human immunodeficiency virus, syphilis, and toxoplasmosis). Intradermal tuberculin test and MB sputum test results were negative. Anti-neutropohil cytoplasmic antibodies test was negative, while levels of angiotensin-converting enzyme were within normal limits. Renal and hepatic functions were normal, as were the

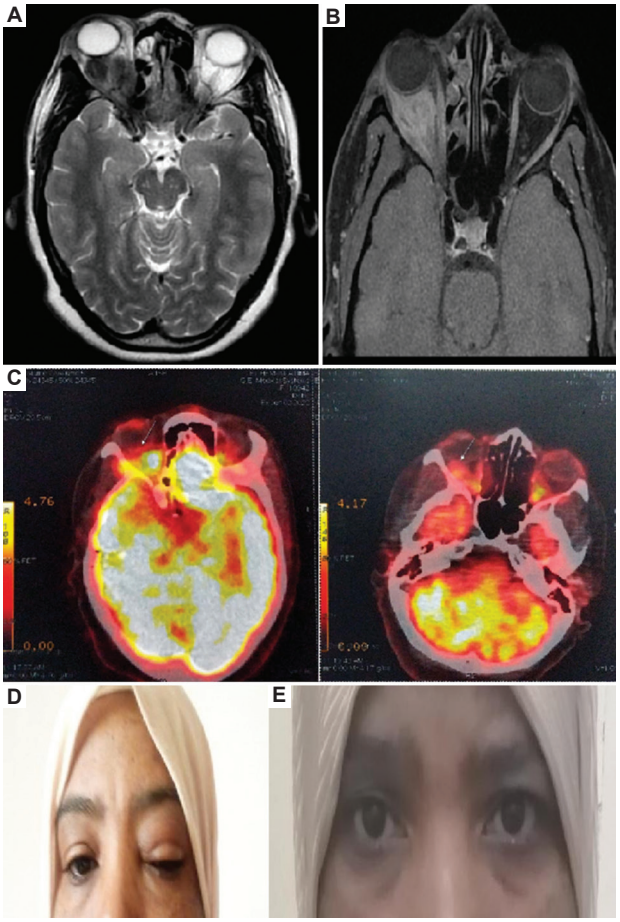


Figure 2. Medical examinations of Case 2. (A) Magnetic resonance imaging of the orbit. (B) Axial and coronal section in T2 sequence, demonstrating a T2-hyposignal, poorly defined right orbital intraconal infiltrate, not centered on a particular organ, and exhibiting weak enhancement after contrast administration, consistent with grade I exophthalmos. (C) Positron emission tomography scan obtained after 1 month of CD20 monoclonal antibodies (rituximab) treatment, demonstrating regression of metabolic activity. External photographs of the patient, captured before (D) and after (E) treatment.

results of the IgG4 assay. A salivary gland biopsy yielded normal findings, with a focus score of 0.

The diagnosis of idiopathic orbital pseudotumor was established based on clinical and radiological criteria. The patient was initially treated with bolus corticosteroids followed by oral corticosteroids at a dosage of 1 mg/kg/day, resulting in favorable clinical progression. Notably, there was a complete resolution of exophthalmos and restoration of visual acuity to 10/10 within the 1st week of treatment (Figure 2C and E). A follow-up imaging study conducted after 3 months of treatment demonstrated a 50% improvement in the inflammatory process (Figure 2D). However, a PET scan revealed persistent disease activity in the right orbital mass, prompting a therapeutic switch to weekly

CD20 monoclonal antibodies (rituximab 375 mg/m^2). A subsequent PET scan after 1 month of rituximab therapy demonstrated a decrease in metabolic activity (Figure 2D). A radiological follow-up was planned after 6 months of treatment, with maintenance therapy using rituximab.

2.3. Case 3

A 58-year-old man with a history of bilateral cataracts for 1 year presented with an alteration in his general condition. General examination revealed an anemic syndrome, splenomegaly with a 6 cm costal margin, hepatomegaly, a solid, and non-pulsatile left orbital tumor (Figure 3A), accompanied by conjunctival jaundice. Orbital MRI revealed a well-defined oval lesion formation in the left palpebral region with regular hyposignal contours on T1 and T2 sequences, without extension into the end orbit (Figure 3C). In addition, scans indicated hepatosplenomegaly measuring 24 cm, with the spleen also measuring 24 cm.

Biological findings revealed profound anemia, characterized by a hemoglobin level of 4 g/dl. In addition, leukopenia was observed with a leukocyte count of 2264/mm^3, along with lymphopenia (lymphocyte count at 765/mm^3) and thrombocytopenia (platelet count at 9000/mm^3). A regenerative reticulocyte count was noted, along with a positive indirect Coombs test. The phospho-calcium balance was within normal limits. Inflammatory markers showed a positive polyclonal profile on protein electrophoresis, with a C-reactive protein level of 85 mg/L. Renal function tests yielded normal results, as did the thyroid test. Furthermore, serological tests indicated a history of successfully treated chronic hepatitis B with an undetectable viral load. Serological tests for hepatitis C, human immunodeficiency virus, syphilis, and toxoplasmosis returned negative results. In addition, the tuberculosis screening was negative.

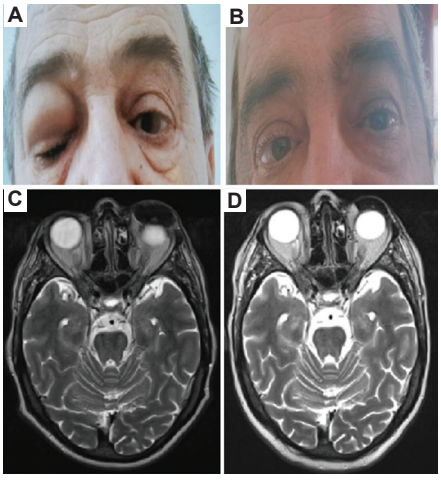


Figure 3. Clinical presentations of Case 3. (A) External photograph of the patient displaying exophthalmos, which developed over 3 months along with hemolytic anemia and tumor syndrome. (B) Complete clinical improvement observed. (C) Axial scan revealing a well-defined oval-shaped lesion in the left upper palpebral region, exhibiting hypo T1 and T2 signals with mild contrast enhancement. (D) Treatment with corticosteroids resulted in partial regression of the left upper palpebral mass, as observed in the hyposignal T2, with slight enhancement after contrast administration in the axial sequence.

The bone marrow biopsy revealed high cellularity indicative of a regenerating marrow. However, immunohistochemistry results (CD20, CD3, CD34, CD15, CD68, and CD30) were inconclusive, failing to definitely rule out a tumoral origin. Subsequently, the patient was initiated on corticosteroid therapy at a dose of 1 mg/kg/day. Based on the remarkable clinical improvement observed (Figure 3B), including weight regain, alleviation of asthenia, and resolution of the orbital mass, a diagnosis of inflammatory orbital pseudotumor with associated hemolytic anemia was established. Notably, normalization of abnormal blood counts and resolution of the inflammatory syndrome were observed as early as 3 weeks into treatment. Follow-up imaging at 2 months revealed partial remission of the condition (Figure 3D), while scans at 6 months indicated complete resolution of hepatomegaly and splenomegaly. Although a palpebral biopsy was proposed, the patient was lost to follow-up.

3. Discussion

Inflammatory diseases of the orbit remain poorly defined in terms of etiology and pathogenesis. Various factors such as infection, immune response, post-traumatic conditions, or molecular mimicry have been proposed as potential causes.[1] The administration of steroids and immunosuppressants is often considered favorable, given the observed increase in inflammation cytokines.

It is important to note the potential diagnostic challenges posed by persistent and progressive tumors resistant to corticosteroid treatment, as observed in Case 1. Such cases raise concerns regarding the presence of an underlying aggressive neoplastic pathology.[9] Bilateralization of the inflammatory process, occurring in 8 – 20% of cases,[10] and exaggerated edema and incoercible periorbital inflammation, led to exenteration. To the best of our knowledge, Case 1 represents the first case of an orbital pseudotumor revealing Takayasu vasculitis of the large trunk.

However, Case 2 illustrates the favorable (essentially clinical) evolution of idiopathic pseudo-orbital tumors, as observed in 70% of cases under corticosteroid treatment.[11] Nonetheless, the persistence of radiological abnormalities required additional therapeutic measurements. The management strategies for refractory cases remain undefined. However, the etiological investigation should

always be thorough to eliminate any plausible association with systemic or other diseases.

Fine-needle aspiration biopsies are used in cases of suspected metastases, although larger fragments are preferred for lymphoma studies, limiting the applicability of this method. Histology remains the gold standard in paraclinical explorations. However, its indications remain limited to cases with progressive neurological deficits, lack of response to steroids, or persistent imaging abnormalities.

In Case 2, the ophthalmologists refrained from performing an orbital tumor biopsy due to its close relationship with the optic nerve.

Furthermore, to the best of our knowledge, the association between hemolytic anemia and an inflammatory orbital pseudotumor has been described in only one case.[12] The clinical and radiological response to corticosteroid therapy after 6 months was favorable.

In general, imaging modalities (PET scan and MRI) reveal different types of involvement, encompassing structures such as lacrimal glands, oculomotor muscles, optic nerve, sclera, episclera, Tenon's capsule, uvea, and orbital fat. In addition, extensions into intracranial structures through the cavernous sinus and the middle cranial fossa represent the two most common locations. This distinction aids in categorizing the disease as localized or diffuse. Our three cases reflect the different involvement of the orbital structures.

Mombaerts cases reflect the different ins used to describe the different histological forms of IDO.[13] The classic form is characterized by polymorphic inflammation and a polymorphic infiltrate comprising lymphocytes, plasma cells, macrophages, eosinophils, and neutrophils. Multinucleated giant cells with foreign bodies are infrequently observed.

The sclerosing form is characterized by extensive fibrosis and a paucity of inflammatory cells, while the granulomatous form is characterized by the presence of histiocytes and multinucleated cells, suggestive of a sarcoid reaction. The final form presents as small-vessel vasculitis. Classical and sclerotic forms are the most prevalent. This classification holds prognostic significance, with classical forms generally exhibiting a better prognosis than sclerotic forms. However, research by Swamy *et al.*[14] demonstrated a recurrence rate of 0.3 per patient-year in classical forms versus 0.15 per patient-year in sclerotic forms. In the classic form, T-lymphocytes outnumber B-lymphocytes, with helper T-lymphocytes surpassing suppressor T-lymphocytes.[15] The proportion of fibrovascular stroma increases in both subacute and chronic forms, leading to fibrosis formation that fixes muscle structures by destroying fatty tissue. The inflammatory infiltrate is believed to stem from local fat necrosis of the ischemic type.[16] In cases of resistance or recurrence, a repeat anatomopathological examination is warranted, as certain forms may transition to lymphoma.[17]

The therapeutic approaches for IDO are diverse and well-documented in published series. Steroids are the mainstay of treatment, offering an excellent response. However, despite the success of low-dose radiation therapy in managing recurrent myositis and optic nerve decompression, documented recurrences underscore its limitations. Calcineurin inhibitors such as cyclosporine or tacrolimus have demonstrated efficacy, with cyclosporine emerging as a viable option for corticosteroid-intolerant diabetic patients. Antimetabolites (cyclophosphamide, azathioprine, and methotrexate) have proven effective in several published series, although requiring regular biological monitoring to monitor side effects.[18] Monoclonal antibodies have also shown promise. Infliximab, when used alone or in combination with methotrexate, yielded favorable results.[19] Rituximab, administered either intravenous weekly at a dosage of 375 mg/m^2 or at 1000 mg on days 0 and 15, has exhibited efficacy in refractory cases unresponsive to steroids, radiosurgery, or conventional treatments, resulting in positive clinical responses.[20] While tocilizumab has demonstrated effectiveness in the treatment of systemic juvenile idiopathic arthritis and rheumatoid arthritis, its use in IDO lacks published evidence.[21]

4. Conclusion

Inflammatory diseases of the orbit are a highly heterogeneous group requiring meticulous clinical examination and thorough investigation to guide therapeutic management. Knowledge of the physiopathology is paramount in effectively utilizing the available therapeutic options. Despite the generally benign nature of the lesions, they pose a significant threat to the functional prognosis of the orbit. This complexity underscores the need for further experimental work to refine global management protocols, particularly considering the variability in histological lesions such as sclerosis, fibrosis, inflammation, myositis, and granuloma.

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Conflict of interest

The authors declare that they have no competing interest.

Author contributions

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Ethics approval and consent to participate

Informed consent was obtained from participants.

Consent for publication

Publication consent was obtained from the patients included in the study.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

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