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# Orbital Inflammatory Pseudotumors: Etiology, Differential Diagnosis, and Management

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**Abstract** Orbital inflammation is typically an idiopathic process that occasionally may be identified with a specific local or systemic disease as the causative agent. Orbital inflammatory pseudotumor (also known as *idiopathic orbital inflammation syndrome*, *orbital pseudotumor*, *nonspecific orbital inflammation*, and *orbital inflammatory syndrome*) is defined as an idiopathic tumor-like inflammation consisting of a pleomorphic cellular response and a fibrovascular tissue reaction. Various rheumatologic disorders are associated with orbital inflammation and must be ruled out in cases of orbital inflammatory pseudotumor, including Wegener's granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis. The mainstay of therapy is corticosteroid therapy, although there is an increasing trend toward use of antimetabolites, alkylating agents, cytotoxic agents, and other immunosuppressive agents.

**Keywords** Orbital pseudotumor · Autoimmune disease · Infliximab

## Introduction

Since the first description of orbital inflammatory pseudotumors (OIPs) in 1905, our understanding of this idiopathic disorder has remained complicated by the wide spectrum of clinical and histologic presentations of the disease [1, 2]. The typical presentation is an acute onset of pain typified by a deep, boring orbital ache and headache, with rapid progression occurring over hours to a few days. Patients may have proptosis, lid swelling, chemosis, and limited motility with tenderness to palpation. Clinical findings and complaints include double vision, pain on movement of the eyes, light sensitivity, and (less commonly) vision loss. OIPs can affect patients of all ages without gender or racial predilection. Symptoms are classically unilateral, although children are more likely to present with bilateral disease, and their symptoms more likely to be associated with uveitis, disc edema, and eosinophilia [1, 3].

The subclassification of OIP is based on the specific anatomic target, but it also can be stratified based on pathological findings. The process can primarily affect the lacrimal gland (dacryoadenitis), one or more extraocular muscles (myositis), the sclera (scleritis), posterior tenons (tenonitis), intraocular uvea (uveitis), optic nerve sheath (optic neuritis), or the superior orbital fissure and cavernous sinus (Tolosa-Hunt syndrome), or the process may diffusely involve the orbital fatty tissues. Typical histopathology is characterized by a pleomorphic cellular infiltrate consisting of lymphocytes, plasma cells, macrophages, polymorphonuclear cells, and eosinophils with variable degrees of reactive fibrosis. The histologic findings vary widely, however, and include predominantly lymphoid, granulomatous, sclerosing, eosinophilic, or vasculitic inflammation.

## Etiology

The pathogenesis and etiology of OIPs are currently unknown. Infectious processes such as upper respiratory

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infections and viral illness can be temporally linked to the onset of OIPs. Alshaikh et al. [4] reported a third case of orbital myositis presenting after culture-positive streptococcal pharyngitis, and the current author has seen two pediatric cases of orbital myositis presenting within 1 month of culture-proven streptococcal pharyngitis. The immunopathogenic effect of streptococcal infection has been seen in a variety of systemic complications, including rheumatic fever, glomerulonephritis, reactive arthritis, pediatric autoimmune central nervous system disorders, uveitis, erythema nodosum, tenosynovitis, and polymyalgia [4–7]. Lyme disease and herpes varicella zoster, two infections known to have several autoimmune sequelae, also have been implicated in the development of orbital myositis [8–11].

The association of certain rheumatologic disorders, such as Wegener's granulomatosis, sarcoid, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis, indicates that OIP is an autoimmune disease. In a study by Sobrin et al. [12], 21 of 27 patients treated with infliximab for ocular inflammation had coincidental systemic rheumatologic disease, including ankylosing spondylitis, Behçet's syndrome, reactive arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, relapsing polychondritis, Crohn's disease, psoriasis, and mucus membrane pemphigoid. In another review by Garrity et al. [13], six of seven patients had comorbid conditions of Crohn's disease, psoriasis, discoid lupus, Behçet's syndrome, diabetes, and primary hypothyroidism. Typical work-up for orbital inflammation should include a hematologic work-up with complete blood cell count, electrolytes, thyroid function studies, sedimentation rate, antinuclear antibodies, antineutrophil cytoplasmic antibodies, angiotensin-converting enzyme level, rapid plasma reagin test, and rheumatoid factor.

Although a direct correlation with systemic disease cannot be made with OIP, the rapid response of inflammation to corticosteroids and other immunosuppressive agents supports this theory. Atabay et al. [14] found one or more serum autoantibodies reactive with porcine eye muscle membrane antigens in all eight patients with nonspecific orbital inflammation. Only antibodies against a 55-kD protein were statistically significant, however, with 62.5% of OIP patients positive, compared with 16% of healthy controls. However, antibodies to this protein also have been reported in patients with thyroid-associated eye disease [14].

## Differential Diagnosis

OIP is an inflammatory disorder that represents a diagnosis of exclusion. Prompt response to systemic corticosteroids helps confirm the diagnosis, but inflammation associated with other orbital processes also may improve with this therapy. Orbital and systemic diseases that mimic OIP include orbital cellulitis, thyroid eye disease, sarcoid, lymphoma, lymphangioma, metastatic carcinoma, uveal melanoma, and ruptured dermoid cyst. These often can be distinguished based on radiographic characteristics on CT and MRI along with clinical examination. The most common orbital processes that can present with the same clinical picture as OIP are orbital cellulitis and thyroid eye disease. Biopsy is indicated if the etiology of a discrete orbital lesion is still in question, especially if the response to medical therapy is incomplete.

Orbital cellulitis is most commonly associated with sinusitis, eyelid or facial infections, or trauma with or without orbital foreign body. In more than 90% of cases, orbital cellulitis occurs as a secondary extension of acute or chronic bacterial sinusitis. Clinical findings include fever, elevated white blood cell count, proptosis, chemosis, ptosis, and restriction of motility. Adults commonly present with multibacterial infections, whereas children more often have single-organism infection. History along with imaging of the orbit and sinuses helps distinguish this entity from OIP. Treatment consists of initial broad-spectrum intravenous antibiotic coverage with possible surgical drainage of the sinuses if there is no response or progression once the patient is receiving therapy.

Thyroid eye disease (also known as *thyroid associated orbitopathy*, *Graves' disease*, *Graves' ophthalmopathy*, *dysthyroid ophthalmopathy*, *thyroid orbitopathy*, and other terms) is an autoimmune inflammatory disorder that is most commonly associated with hyperthyroidism. It is the most common cause of unilateral and bilateral proptosis. Thyroid eye disease can present with diffuse orbital fat inflammation but commonly will have evidence of extraocular muscle enlargement confined to the muscle bellies, which is in contrast to idiopathic myositis, which will have thickening involving the tendon and belly of a muscle. It usually has an insidious onset with progressive findings of dry eye, eyelid retraction, lid lag, proptosis, restrictive ophthalmoplegia, and compressive optic neuropathy.

## Management

### Corticosteroids

Systemic corticosteroids, the mainstay of therapy, typically yield a dramatic improvement in all symptoms and findings. Initial doses are typically 1 mg/kg of prednisone, with rapid response and abrupt resolution of the associated pain. The use of steroids can be tapered slowly as soon as clinical response is complete and should be customized to the individual's clinical response to taper over weeks to months. Side effects

include insomnia, mood swings, hyperglycemia, dyspepsia, weight gain, cushingoid facies, and hypertension. These tend to improve as the dose is tapered but may be very distressing to patients when treatment is prolonged.

In a study by Yuen and Rubin [15] that reviewed the treatment of 65 OIP patients, 69% were treated with steroids alone, 12% with steroids and subsequent radiation therapy, 9% with steroids and NSAIDs, 2% with radiation therapy and NSAIDs, 3% with NSAIDs alone, and 2% with surgery alone. A total of 63% of these patients had complete treatment success. Of the treatment failures, 58% had recurrent inflammation after discontinuing initial therapy, 38% had poor response to therapy with recalcitrant inflammation, and 4% (one patient with sclerosing OIP) required exenteration. Steroid dependence and intolerance occurred in 33% and 13%, respectively, of the treatment failures and in 12% and 2%, respectively, of the treatment successes. Although corticosteroids and NSAIDs are highly useful and effective, the adverse effects have led to a broadening of therapeutic agents to include a variety of immune-modulating agents.

## Radiotherapy

Radiation therapy is commonly used as second-line therapy for OIP that responds incompletely to corticosteroids, and may be used as first-line therapy in patients in whom corticosteroids are contraindicated. Low-dose radiation therapy at doses of 1,500 to 2,000 centiGray units administered over 10 days is used. Success rates vary from 50% to 75%, depending on the author [16–19].

## Cyclosporine-A

Cyclosporine-A (CsA) is an immunosuppressant agent that suppresses the lymphocyte-mediated responses. Its effect is related to the inhibition of T-cell activation via interference with the production of interleukin-1 and interleukin-2. Renal function must be monitored, as low-dose CsA is associated with kidney dysfunction and hypertension during the first year of therapy and can lead to permanent renal damage in high doses, with levels greater than 300 to 350 ng/mL [20, 21]. Other complications include gingival hyperplasia, hirsutism, tremor, and hypercholesterolemia. Although CsA has been implicated in the occurrence of secondary malignancies (eg, squamous cell carcinoma of the skin, lymphoma), large studies have been reassuring in indicating that there is no statistically significant increased risk [22•].

Several cases have shown efficacy of the drug in cases of uncontrolled OIP [20, 21, 23–25]. Zacharopoulos et al. [20] treated a patient with OIP with CsA, 4 mg/kg per day, with dramatic response within 6 weeks of therapy. After 18 months of treatment, the patient was able to stop all medications and remained symptom free for 5 years. Gumus et al. [26•] were able to use topical 0.05% CsA (Restasis, Allergan, Irvine, CA) to treat and stabilize a patient with idiopathic orbital myositis and scleritis. The patient was a 35-year-old woman with a 5-year history of recurrent symptoms and negative systemic work-up who had been treated with systemic corticosteroids and oral CsA. She suffered weight gain and acne from the steroids and hirsutism and tremor from the CsA. She was then placed on topical CsA 0.05% eyedrops (Restasis) along with dexamethasone 0.1% eyedrops, with complete resolution of symptoms and no recurrences during a 6-month period of treatment. This is the first report of recalcitrant OIP responding to topical CsA and offers this as a potential immune-modulating therapy (IMT) without the typical systemic side effects.

## Methotrexate

Methotrexate inhibits dihydrofolate reductase, an enzyme needed for the synthesis of DNA and RNA, resulting in the suppression of rapidly dividing cells, suppressing both B-cell and T-cell function. Adverse effects most commonly include dyspepsia, fatigue, hair loss, headache, arthralgias, and elevated liver enzymes. Liver enzymes should be monitored while the patient is receiving therapy, and adjunctive folate supplements should be administered with restriction of alcohol intake to prevent these adverse effects.

A study by Smith and Rosenbaum [27] treated seven patients with OIP and seven patients with orbital inflammation of other origin with methotrexate as a steroid-sparing drug. The initial dose of methotrexate was 7.5 mg/wk orally, increased to 15 mg/wk up to 25 mg/wk, depending on clinical response and side effects. Four of the seven OIP patients demonstrated clinical benefit, one patient showed no response, and two patients did not complete a 4-month trial for undisclosed reasons. Shah et al. [28] reported similar findings, with five of six patients with OIP showing clinical benefit with the use of methotrexate.

## Infliximab

An increasing body of information supports the use of infliximab as a steroid-sparing therapy for recalcitrant OIP. Infliximab is a chimeric monoclonal antibody acting against tumor necrosis factor–$\alpha$ that has been approved for use in treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, and ulcerative colitis. Data regarding infliximab in OIP have used 3- to 5-mg/kg loading doses at weeks 0, 2, and 6, with subsequent therapy administered every 4 to 8 weeks, depending on symptoms, which is in line with the approved dosage for Crohn's disease and rheumatoid arthritis.

A total of 42 OIP patients have been reported to have good response to infliximab in various cases of recalcitrant inflammation despite a combination of corticosteroids, chemotherapeutic agents, and/or radiation therapy [12, 13, 29, 30•, 31–33]. Only one patient was reported to have an adverse reaction to infliximab—a lupus-like reaction with fatigue, photosensitivity, and a positive antinuclear antibody titer, which led to discontinuation of the medication after good response to seven infusions [12]. Most cases (25 of 42) required sustained infusions of infliximab to control inflammation. Sobrin et al. [12] stabilized 10 patients with a finite course of infliximab who were maintained with standard IMT, 1 patient who did not tolerate infliximab, and 3 patients with scleritis who experienced remission of symptoms without the need for further therapy during follow-up periods of 4, 6, and 17 months, respectively. Garrity et al. [13] had a patient with myositis stop all medications after 1 year of treatment, including oral prednisone, intravenous methylprednisolone, cyclophosphamide, radiation, and finally methotrexate with infliximab.

Of note, the studies by Sobrin et al. [12] and Garrity et al. [13] included patients who had comorbid rheumatologic diseases, but only the OIP patients without systemic disease were able to discontinue all therapies [12, 13]. Osborne et al. [29] stabilized a woman with myositis after using only three infusions of infliximab and continuing on IMT at 11-month follow-up. Sahlin et al. [30•] reported a case of sclerosing OIP that stabilized after six infusions of infliximab and continued methotrexate therapy for a follow-up of 3 months. Neither of these patients was found to have rheumatologic disease.

### Other Therapeutic Agents

There are many case reports as well as mentions of other therapeutic agents being used in recalcitrant OIP, including—but not limited to—mycophenolate mofetil, interferon-A, tacrolimus, rituximab, cyclophosphamide, chlorambucil, leflunimide, and azathioprine. There is no consensus on treatment protocol, and more data are needed to determine the most appropriate medication, dose, and treatment duration of all these drugs, which are currently initiated by ophthalmologists and rheumatologists with experience in using them to treat ocular inflammatory disease.

## Conclusions

OIP represents a diagnostic and often therapeutic challenge for rheumatologists and ophthalmologists alike. Although it commonly presents with acute ocular findings consistent with inflammation and responds well to corticosteroids, it is a diagnosis of exclusion that is associated with many rheumatologic disorders. Complete and detailed medical history, relevant serologic tests, and imaging studies are important to exclude causative systemic disorders; however, it is not uncommon for a diagnosis such as thyroid disease to present 6 to 12 months after the orbital process has started. The mainstay of therapy is corticosteroids, but rapid response is not a reliable diagnostic test for identifying OIP. When patients have recurrence during or after corticosteroid taper, suspicion must increase that there is an underlying systemic disease. Biopsy is indicated in refractory cases or when the disease course is otherwise unusual. A range of other therapeutic modalities can be used when patients have recalcitrant disease, and new immunosuppressive medications used by rheumatologists and transplant physicians may offer additional options in the future.

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