Orbital Pseudotumor

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Introduction

Ophthalmologists in the early 1800s made an interesting observation that several patients with presumed orbital tumors showed spontaneous improvement without any treatment. Until then proptosis was considered as prima facie of orbital neoplasm. Panas coined the term “pseudoplasm” for these puzzling cases. Birchfield in 1930 used the term orbital pseudotumor for such cases ¹,². Improvements in diagnostic techniques as also better understanding of the pathology of orbital pseudotumor helped us to define orbital pseudotumor as a nonspecific idiopathic, benign inflammatory process characterized by polymorphous lymphoid infiltrate with varying degrees of fibrosis. It is also known as idiopathic orbital inflammatory syndrome (IOIS). Pseudotumor orbit accounts for 10% of orbital tumors ³. The peak incidence of the condition is in fourth and fifth decade but it can also occur in children. There is no sex predilection. It is usually unilateral though bilateral involvement is possible in children. Orbital pseudotumor is usually a monophasic illness but it can be recurrent, especially in children. It remains a diagnosis of exclusion, as it is diagnosed after excluding orbital tumors, thyroid eye disease and systemic inflammatory disease. IOIS is characterized by its chronicity, and classified based on anatomic location, or histologic subtype ³,⁴.

Classification/Types

Based on the onset

- Acute
- Subacute
- Chronic

Depending on the target tissues involved

- Diffuse
- Localised
- Anterior orbit
- Posterior orbit
- Extraocular muscles
- Optic nerve
- Lacrimal gland

Histopathological classification

- Classical or Cellular
- Granulomatous
- Eosinophilic
- Vasculitic
- Desmoplastic /Fibrous

Pathogenesis

The cause and pathogenesis still remains to be elucidated. Infections, post infections, autoimmune, genetic, environmental factors have been proposed as causes ¹,⁵,⁶. Successful treatment of the condition with corticosteroids and other immunosuppressive agents suggests an autoimmune mechanism ⁷. It is mediated by both B and T lymphocytes ⁵. The acute form of the disease consists of polymorphous infiltrate while the subacute and chronic forms have increasing fibrovascular stroma ¹.
Clinical features

IOIS can present with varying range of clinical features depending on the orbital structures involved, the degree of inflammation and fibrosis 3,8. The presentation is usually acute with proptosis, diplopia, orbital pain, eyelid swelling, ptosis, chemosis and visual loss 1,5,7. Relapses and remissions with or without treatment are not uncommon.

Pseudotumour with significant desmoplastic change typically present with slowly progressive visual loss, diplopia or proptosis 1. Commonly involved structures include orbital fat, lacrimal gland, extraocular muscles 3, others being, optic nerve, sclera and tenon. Orbital involvement may be focal resulting in pseudotumor variants, myositis, dacryoadenitis, optic perineuritis, periarteritis and scleromeningitis 8. A posterior pattern of pseudotumor presents with symptoms of orbital apex syndrome. Patient has signs of optic nerve dysfunction and ophthalmoplegia. These include diplopia, decreased vision, dyschromatopsia, visual field defects, relative afferent pupillary defect and disc edema.

The diverse forms of orbital pseudotumour have varying clinical picture.

Dacryoadenitis - Pseudotumour of lacrimal gland has typical presentation of dacryoadenitis. The characteristic sign is “S” shaped ptosis with associated superotemporal conjunctival chemosis and congestion 1,9. The lateral rectus muscle being in close proximity is commonly involved resulting in painful ophthalmoparesis and diplopia 1.

Orbital myositis – This condition is a common variant of IOIS presenting with diplopia and pain typically exacerbated on ocular movement 1. There is restriction of ocular movement in the field of action of the affected muscles. Localized conjunctival injection and chemosis are seen at the tendinous insertion of involved muscle 1,10. Medial and superior recti are commonly involved 1,10. The entire muscle including the belly and tendon is enlarged 1,10.

Idiopathic sclerosing orbital inflammation

Idiopathic sclerosing orbital inflammation (ISOI) (Fig. 1) is a rare pathological subgroup of pseudotumor accounting for 5 % to 7.8 % of cases 11. The onset is insidious presenting with diplopia, decreased vision and proptosis 1. ISOI is diagnosed based on the characteristic histological picture of marked fibrosis with sparse mixed chronic inflammatory infiltrate 11. It has a predilection for the posterior superior or lateral orbit especially the lacrimal gland, rich in lymphocytes which play a critical role in causing fibrosis 11. The sclerosing variant is associated with systemic multifocal fibrosclerosis like retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel’s sclerosing thyroiditis and pachymeningitis 1. This form of pseudotumor typically does not respond to steroid therapy.

Paediatric pseudotumor

The clinical features of IOIS are peculiar in children. 6-16 % of cases occur in the first two decades of life 1,6,12. Bilateral involvement is common and is associated with iritis, and optic disc edema 5,8,12. The associated constitutional symptoms in children lead to erroneous diagnosis. Recurrences are common and morbidity is high 1,8. Eosinophilia of peripheral blood and in tissue biopsy is a feature seen in one third of cases 1. In children it is important to exclude orbital cellulitis, dacryoadenitis, rhabdomyosarcoma, retinoblastoma, neuroblastoma, dermoid cyst and hemangioma before diagnosing pseudotumor 1.

Diagnosis

The diagnosis of pseudotumour orbit is usually clinical and confirmed by prompt response to steroids. In order to rule out the systemic conditions mimicking pseudotumor complete physical examination is essential followed by complete hemogram, erythrocyte
sedimentation rate, C-reactive protein level, antinuclear antibody and antineutrophil cytoplasmic antibodies. Histopathological testing is required when the clinical presentation is atypical recurrent or persistent. Imaging is indicated when there is threat to vision or loss of function and in lesions involving the lacrimal gland or the orbital apex.

**Histopathology**

The classical form of orbital pseudotumor is the cellular variety which presents acutely and mimics lymphoid tumors. The cellular infiltrate of orbital pseudotumor tends to be diffuse and multifocal in contrast to lymphoid neoplasm. It consists of hypocellular polymorphous infiltrate composed of mature lymphocytes, plasma cells, macrophages and polymorphonuclear leukocytes. Atypical findings are tissue eosinophilia, granulomatous inflammation, vasculitis and desmoplasia.

Eosinophils are present in paediatric pseudotumor in particular. Eosinophil degranulation contributes to tissue fibrosis. Granulomatous inflammation with multinucleated giant cells and non-caseating granuloma can mimic sarcoidosis. Histological features of true vasculitis limited to the orbit are rarely found and primarily affects small arteries and arterioles. Chronic forms of the disease are characterized by increasing fibrous component. Lymphoid follicles with germinal centers are also observed in the chronic phase. Extraocular muscle, fat and lacrimal gland are replaced with fibrous tissue. The desmoplastic response can ultimately result in dense fibrosis and entrapment of orbital structures and mass effect. Some cases are primarily sclerotic in nature presenting insidiously with no prior acute phase. They have scant cellular infiltrate with dense desmoplastic stroma.

Histopathological diagnosis can be arrived at by fine needle aspiration and cytology (FNAC) or incisional biopsy. FNAC is an useful diagnostic tool in a presumed case of orbital pseudotumor as the condition mimics tumor both clinically and radiologically. Being a simple procedure done under topical anesthesia it saves the patient from the inconvenience of orbital exploration.

**Imaging**

Ultrasonography (USG), computed tomography and magnetic resonance imaging (Fig. 2) are useful diagnostic imaging modalities in pseudotumor orbit. The appearance of pseudotumour in imaging varies depending on whether the involvement is diffuse or localized. Typically there is diffuse enlargement of extraocular muscles inclusive of the tendon in pseudotumour. In USG the lesion has low internal reflectivity (10% to 40%) due to absence of interfaces and sound attenuation is minimal. The borders are well defined when the lesion is localized and poorly defined in diffuse lesions. A “T” sign is seen in associated posterior scleritis due to effusion in Tenon's space. CT demonstrates similar findings which enhances with contrast. Pseudotumour appears hypointense to fat on T1 weighted images and isointense or hypointense to fat on T2 weighted images with marked gadolinium enhancement. MR imaging now provides prognostic significance as well. Lesions that appear hyper intense compared with cerebral cortex on short inversion time inversion-recovery (STIR) images reportedly respond well to corticosteroid therapy whereas lesions that are hypointense or isointense compared with extraocular muscle respond poorly.

**Differential Diagnosis**

The differential diagnosis includes thyroid eye disease, orbital cellulitis, Wegener's granulomatous, lymphoma, leukemia, sarcoidosis, amyloidosis, dermoid cyst. It is of paramount importance to distinguish pseudo-
tumors from true neoplasm of orbit. The therapeutic response to corticosteroids is misleading and provides wrong assurance as some improvement can occur in other diseases. Presence of thyroid lid signs and tendon sparing extraocular muscle enlargement helps in differentiating it from IOIS. Orbital cellulitis is accompanied by signs of systemic toxicity including fever, and leucocytosis with shift to left. A thorough systemic work up will help in differentiating pseudotumor from systemic affections like sarcoidosis, lymphoma, leukemia’s. Rarely orbital affection may be the only sign of the systemic disease. In the absence of systemic disease, histopathology aids in differentiating IOIS from other conditions. Fine needle aspiration biopsy or open biopsy may be performed for this.

Treatment
The spectrum of adjuvant treatment in IOI is broad and evolving. Options include corticosteroids, radiation therapy, non steroidal anti-inflammatory drugs, cytotoxic agents (chlorambucil, cyclophosphamide), corticosteroid sparing immunosuppressants (for example, methotrexate, cyclosporine, azathioprine); intravenous immunoglobulin, plasmapheresis, and the newest class, biologic treatments, which includes anti-tumor necrosis factor alpha (TNF-α).

Oral steroids: The mainstay of therapy is corticosteroid which has diagnostic sensitivity of 78 % due to the prompt response of the condition to steroids. Recurrence rate of 50-60 % has been reported by previous studies with corticosteroids. Dose ranging from 60-100 mg/day is initiated. High dose oral steroid for 2-3 weeks followed by slow tapering is recommended. Effective immunosuppression needs to be in sufficient dose and maintained for the duration of active disease. Intravenous pulse steroids are reserved for patients with rapid progression of symptoms. Failures in corticosteroid treatment may be termed primary, if there is no improvement despite adequate steroid dosage; recalcitrant, if there is breakthrough inflammation during tapering steroid dosage; recurrent, if the pseudotumor recurs after a period of remission. The systemic side effects due to prolonged steroid therapy includes cushingoid symptoms and signs, growth retardation, weight gain, risk of development of gastrointestinal bleeding, and inability to obtain follow-up on steroid therapy.

Intraorbital injection of triamcinolone acetonide 20-40 mg has also been shown to be effective in the treatment of IOIS, with reduced systemic side effects of oral steroids.

Immunosuppressants: Cyclophosphamide 200mg/day is used to treat patients with recurrence on steroid therapy. Cyclosporine 2-5mg/kg and methotrexate 7.5-12.5mg/kg are the steroid sparing drugs used.

Immune modulators: Biological immunomodulators have revolutionized the treatment of autoimmune diseases. Infliximab (chimeric monoclonal antibody), TNF-α blocker at 6 weekly dosage schedule of 3-5 mg/kg has been recently introduced in the treatment armamentarium of IOIS. TNF inhibition is associated with increase in antinuclear antibodies and systemic lupus erythematosus, hence concomitant methotrexate therapy is recommended.

Radiation – Radiotherapy is used to treat patients intolerant or resistant to steroids. Dose ranging form 1500 – 2500 cGy over 10-15 days is appropriate in steroid resistant cases. Average time taken for response to radiotherapy is 3-8 months. Localized mass, presence of lymphoid follicles, absence of eosinophils and initial response to steroids are good prognostic factors for response to radiotherapy.

Complications
Desmoplastic component of pseudotumour results in fibrous entrapment of extraocular muscles resulting in restriction of ocular movements and diplopia. Mass effect caused by both inflammation and desmoplasia causes compressive optic neuropathy and dysfunction of ocular motor nerves. Obstruction of venous drainage results in orbital congestion. IOIS has the tendency to spread intracranially, paranasal sinuses, into infratemporal and pterygopalatine fossa through the major openings in the posterior orbit; optic canal, superior and inferior orbital fissure. Hence in cases with persistent or recurrent or progressive clinical symptoms contrast enhanced computed tomography and magnetic resonance imaging is indicated. In the presence of extraorbital extension, biopsy should be performed to exclude other conditions mimicking ISOI. IOIS causes
open angle glaucoma secondary to raised episcleral pressure. Engorged ciliary processes/ posterior scleritis with choroidal effusions/ relative obstruction of vortex veins with swelling of uvea pushing iris-lens diaphragm are the mechanism put forward for secondary angle closure glaucoma caused by pseudotumor.

**Conclusion**

Orbital pseudotumor comprises a significant proportion of cases of orbital lesions. It should be considered in the differential diagnosis of acute proptosis in adults. Orbital pseudotumor is typically characterized by the rapid development of pain, proptosis, and swelling around the eye and orbit. Ultrasound and computed tomographic (CT) scanning typically shows a diffuse infiltration of the orbit, an inflammation of the eye wall (sclera), and/or T-sign (with the optic nerve). Orbital pseudotumor related orbital masses typically have poorly defined margins. Patients with classic findings of orbital pseudotumor may be treated without a biopsy. These cases typically respond rapidly to steroid therapy (which helps confirm the diagnosis). Atypical cases of orbital pseudotumor usually undergo biopsy which helps establish the diagnosis.

**References**