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Review Article

Non specific orbital inflammatory disease – A review article

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ABSTRACT

Non Specific Orbital Inflammatory Disease (NSOID) is a benign, noninfective inflammatory condition of the orbit which does not have any identifiable local or systemic causes. Orbital pseudotumor was first described in 1903 by Gleason. The clinical diagnosis is one of exclusion with evaluation directed to exclude neoplasms, infections and systemic disorders. IOI is diagnosed by clinical history and evaluation to rule out other causes of orbital disease. Orbital pseudotumor is the third most common orbital disease following Graves ophthalmopathy and lymphoproliferative disease.

1. Introduction

Non Specific Orbital Inflammatory Disease (NSOID) also known as Orbital Pseudotumor or Idiopathic Orbital Inflammation (IOI) is a noninfective inflammatory condition of the orbit which is benign in nature and does not have any specific recognizable cause locally or systemically. Any part of the orbit can be affected and it forms approximately 9-11% of all mass lesions of the orbit.[1] Gleason described orbital pseudotumor for the first time in 1903,[2] following whom it was distinguished as a specific clinicopathological entity by Birch-Hirschfeld in 1905.[3] It is a diagnosis of exclusion after ruling out other conditions like neoplasms, systemic disorders and infections.[4] Orbital Magnetic Resonance Imaging (MRI) is the single most important diagnostic test. Also serological studies and incisional biopsy can be necessary to exclude a systemic cause.[5] After graves ophthalmopathy and lymphoproliferative disease, IOI is the third most common orbital disease.[6]

2. Classification

There is no universally accepted classification for IOI. Based on the orbital site which is involved, IOI can be classified into different types including anterior, diffuse, apical or posterior, myositis, and dacryoadenitis. Other rare IOI types include periscleritis, perineuritis, and focal mass.[7]

2.1. Clinical presentation

Patients with IOI often present with acute symptoms, though symptoms can also be subacute or chronic. IOI is usually unilateral, but bilateral disease can also occur in 8% - 20%.[7,8] Unilateral periorbital pain with remarkable response to corticosteroid therapy is the hallmark of clinical presentation of IOI.[9] IOI is usually seen in the fifth decade and there is no sex predilection except in myositis which is more common in females.[10] Anterior IOI usually involves the conjunctiva, eyelids, neural, and adjacent muscular structures. Patients most commonly present with acute onset of pain with deep boring headache and periorbital swelling. Patients can also present with limited ocular motility and conjunctival chemosis. Rarely, proptosis, uveitis, papillitis

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and exudative retinal detachment can also be seen.[11]

Patients with diffuse IOI present with almost the same features of anterior IOI. Although, the presentation of diffuse IOI is more severe. Furthermore, proptosis is seen more frequently with the diffuse variant compared to anterior IOI.[4]

Apical or posterior IOI is associated with a poorer visual outcome, even though it is less common.[7] It is the most severe form. Clinically, apical IOI presents with orbital pain, restricted eye movements, visual loss and minimal proptosis.[12] Inflammatory lesions of the orbital apex may extend intracranially through superior orbital fissure, optic canal and inferior orbital fissure. The cavernous sinus and the middle cranial fossa are the two most common locations for intracranial involvement.[13]

Myositis involves single or multiple extraocular muscles (EOMs) along with their tendons.[14] Clinically, it presents with unilateral orbital or periorbital pain which gets exaggerated with eye movements, acute or subacute diplopia, ocular motility restriction, proptosis, eyelid swelling and conjunctival injection at the site of tendon insertion.[15] The most frequently involved muscle is the medial rectus followed by the superior, lateral and inferior rectus muscles.[16] Isolated levator palpebrae muscle involvement has also been seldom reported.[17] Radiologically, there is tendon enlargement along with muscle belly involvement giving a tubular configuration, in contrast to Graves ophthalmopathy in which tendon is spared.[18]

Dacryoadenitis is the most commonly encountered subtype of IOI, accounting for approximately 50% of all IOIs.[7,18] The typical acute presentation of dacryoadenitis includes a painful, firm, erythematous mass with edema in the lateral upper eyelid, and S-shaped ptosis sometimes associated with dry eye. In 20% of patients, both lacrimal glands are affected, either simultaneously or sequentially.[7]

Periscleritis refers to inflammation involving the sclera, uvea or Tenon's capsule. A patient with periscleritis may present with diminution of vision, orbital pain, exophthalmos, eyelid edema and associated uveitis.[19]

Optic perineuritis, also known as perioptic neuritis, is a very rare idiopathic orbital inflammatory disease, in which optic nerve sheath is involved from globe to optic canal, instead of the optic nerve axons as in optic neuritis or optic neuropathy. Optic perineuritis usually presents with pain, swollen optic disc and visual field defects involving arcuate and paracentral areas. Optic perineuritis usually responds well to systemic corticosteroids unlike the other entities in the differential diagnosis.[20] Radiologically it is seen as mass lesion surrounding the optic nerve sheath and infiltration into the surrounding orbital fat.

IOI can also present as a localized inflammatory mass in the orbit. The clinical features may vary according to the location and extent of the mass, with symptoms due to mass effect and inflammation or infiltration, which may include proptosis, disturbance in eye movement, compression of optic nerve and inflammatory signs including edema and hyperemia.

Microscopically, IOI shows features of chronic polymorphous inflammatory infiltrate, consisting of mature T lymphocytes, neutrophils, plasma cells and occasionally histiocytes and macrophages. The infiltrate is localized in lymphoid follicles. Stromal changes are seen as edema, proliferative fibrosis and sclerosis, whereas vascular changes as perivasculitis or angiocentric lymphoid cuffing.[5]

2.2. *Differential diagnosis*

Subclassifications of IOI	Differential Diagnosis
Anterior IOI	Orbital trauma with retained foreign body, orbital cellulitis, ruptured dermoid cyst
Diffuse IOI	Lymphoma, Wegener's granulomatosis
Apical IOI	Tolosa-Hunt syndrome, lymphoma, glioma, metastatic lesions
Myositis	Thyroid orbitopathy, vasculitis, metastatic lesions, lymphoma, carotid-cavernous fistula, IgG4-ROD (Immunoglobulin G4-Related Ophthalmic Disease), orbital cellulitis, Wegener's granulomatosis, intramuscular tumor.
Dacryoadenitis	Lymphoma, sarcoidosis, Wegener's granulomatosis, epithelial neoplasm, IgG4-ROD.
Periscleritis	Endophthalmitis, posterior scleritis
Perineuritis	Optic neuritis, optic neuropathy, optic nerve sheath meningioma, optic nerve glioma, increased intracranial pressure.
Focal mass	Lymphoma, metastatic lesions, solitary fibrous tumor.

Investigations include complete blood count, kidney and liver function tests, urine analysis, ECG, X-ray chest, abdominal ultrasound, and thyroid function tests, collagen profile, Venereal Disease Research Laboratory (VDRL) and Anti-Neutrophil Cytoplasmic Autoantibody (ANCA), X-ray skull, Orbital Magnetic Resonance Imaging (MRI).

The necessity for orbital biopsy in the management of IOI is debatable. Typical cases of IOI respond to systemic corticosteroids without the need for orbital biopsy. Myositis and apical IOI are usually managed with systemic corticosteroids initially because of the risks related to surgical intervention. Orbital biopsy has been kept as the last resort for the cases that do not respond to the usual treatment, or show recurrence or progression with corticosteroid treatment.[5]

3. Treatment

IOI may sometimes resolve even without any treatment.

In others, systemic corticosteroids are considered as the first line therapy and approximately 80% of people respond with half of the patients showing relapse. Corticosteroids act by both anti-inflammatory and immunosuppressive effects. Inhibition of phospholipase A2 and cycloxygenase pathways gives anti-inflammatory effects, whereas the inhibition of IL and IFN synthesis, inhibition of major histocompatibility antigen expression and cytotoxic effect on T lymphocytes provide immunosuppressive effects. The usual regimen is 1 mg/kg/day of prednisolone as a starting dose and slowly tapered in 6-8 weeks. It has also been found out that Intraorbital triamcinolone acetonide injection could be an effective treatment for IOI.[21] Systemic side effects of long term systemic corticosteroids include hyperglycemia, hypertension, weight gain, growth retardation, cushingoid features, osteoporosis, avascular bone necrosis and adrenal suppression, whereas glaucoma, cataract and herpetic corneal infection are ocular side effects.[22]

Nonsteroidal anti-inflammatory drugs (NSAIDs) act by their anti-inflammatory effects by inhibiting cyclooxygenase pathway of prostaglandin synthesis. In mild cases of IOI, oral NSAIDs can be given as they have lesser side effects as compared to systemic corticosteroids. The side effects being increased risk of gastrointestinal ulcers and bleeds, myocardial infarction and kidney disease.[23]

External beam radiotherapy (EBRT) is usually given along with or as an adjuvant to steroids. EBRT is indicated when the symptoms reappear during tapering of steroids or when they are not effective or contraindicated. EBRT helps in reducing the dosage of corticosteroids and also corticosteroid dependence, and thus ultimately leading to discontinuation of corticosteroid therapy. Usual dosage is 1000 – 3000 Gy given over 2-3 weeks.[24] Ocular side effects include dry eye, keratitis, cataract, conjunctival erythema, increased or decreased lacrimation and photophobia, optic neuropathy, periocular dermatitis etc.[25]

3.1. Anti metabolites

Methotrexate: Methotrexate is a folic acid antagonist that acts by inhibiting dihydrofolate reductase which is the enzyme required for folic acid synthesis. This leads to inhibition of rapidly proliferating cells which includes suppression of both B and T lymphocyte function. Side effects include fatigue, hair loss, neutropenia, GI disturbances and hepatotoxicity. Supplemention of folate, alcohol restriction and parenteral administration of methotrexate can lessen these side effects.

Azathioprine: Azathioprine is a purine analog, which acts by interfering with DNA synthesis and thus inhibiting rapidly proliferating cells, especially B and T lymphocytes. It was found in some studies that azathioprine has been useful in conjunction with systemic corticosteroids. Side effects are bone marrow suppression, nausea, vomiting and malignancy.[26]

Mycophenolate mofetil: Mycophenolate mofetil is an antimetabolite. It acts by inhibiting purine synthesis B-cell and T-cell proliferation. Initial dose is 500 mg and gradually increased to target dose of 1.5 – 3g daily.[27] Associated side effects include nausea, vomiting, rash, myalgia, headache and immunosuppresion.

3.2. T-Cell/calcineurin inhibitors

Cyclosporine-A: Cyclosporine-A (CsA) provides an immunomodulatory effect by inhibiting IL-1 and IL-2, thus decreasing the activation of lymphocytes. Several studies have shown the efficacy of cyclosporine A in cases of uncontrolled IOI.[9] CsA in low dose is associated with kidney damage and hypertension so renal function should be monitored. Other complications include gum hyperplasia, hirsutism, tremor, and hypercholesterolemia.

3.3. Alkylating agents

Cyclophosphamide: Cyclophosphamide is an alkylating agent. It acts by cross linking DNA and thus damaging proliferating cells.[28]

Chlorambucil: It is also an alkylating agent and acts by alkylating and cross linking DNA during all phases of cell cycle.

3.4. Lymphocyte Inhibitors

Rituximab (B-lymphocyte inhibitor): Rituximab is a chimeric mouse-human monoclonal antibody against CD20, which is a cell-surface phosphoprotein on B-cells. It is also associated with side effects such as lung toxicity, intestinal obstruction, cardiac toxicity and immunosuppression. Savino et al. reported that 3 patients with IOI were treated successfully with intraorbital injections of 10 mg rituximab once a week for 1 month, among whom two patients required 2 months of rituximab and one required 1 month of rituximab treatment at 17.6 months' follow-up.[29]

Daclizumab (T-lymphocyte inhibitor): Daclizumab is a humanized monoclonal antibody directed against IL-2 receptors (CD25) on T cells.

3.5. Tumor Necrosis Factor-α (TNF-α) Inhibitors

Infliximab: Infliximab is a chimeric monoclonal antibody that acts against TNF-α. According to previous studies, infliximab has been reported to have a positive response in patients with chronic and refractory IOI previously treated with corticosteroids, chemotherapy and radiotherapy. The usual dosage is 3-5 mg/kg IV at 0, 2, 6, weeks followed by every 4-8 weeks thereafter until remission is achieved. A report states that in a study conducted on 7 patients with chronic and recalcitrant orbital myositis, favorable response was achieved in all patients with infliximab therapy.[30]

Documented side effects are rash, headache, hypotension, reactivation of latent TB, lupus like reactions, elevation of antinuclear autoantibodies and risk of lymphoma.

Adalimumab: Adalimumab is a fully humanized IgG1 monoclonal antibody which targets TNF-α. There is less risk of developing autoantibodies and allergic reactions as adalimumab is fully humanized. Side effects are similar to those seen with infliximab.

3.6. Surgery

Surgical resection may be used in persistent focal mass type IOI, in some anterior/diffuse IOI cases, and in dacryoadenitis.[8]

In a confirmed case of IOI with painful blind eye, or which is completely refractory to all treatments, orbital exenteration can be considered.[31]

4. Case Report

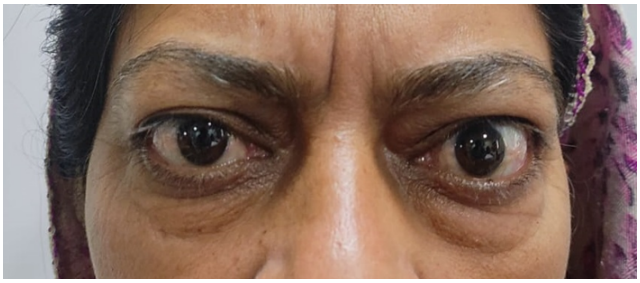

Fig. 1: 40/F, who was a r/o Faridkot presented with c/o protrusion and redness of both eyes for the past 1 month. It was insiduous in onset, not associated with pain or diminution of vision, discharge, diplopia. No history of DM, hypertension, trauma, malignancy or any ocular surgery. Not on any regular medication.

On general examination, she was fully conscious and cooperative. She was well oriented to time, place and person and had given consent.

5. On Examination

BCVA was 6/6 (OU) for D/V and N6 (OU) for N/V with + 1.25 D sphere. IOP was 18 mm Hg (OD) and 19.5 mm Hg (OS) with GAT. EOM were all normal. She was having an erect head posture, but the facial symmetry was not maintained because of the proptosis which was axial and more on Left side than Right. It was not reducible. There was no retraction or lagophthalmos of upper lid. Bells phenomenon was normal. Exophthalmometry findings revealed 2.1 cm OD and 3.2 cm OS.

Fundus examination of both eyes showed grade 1 media clarity with normal vessels, clear and well defined disc margins, with CDR 0.3:1, healthy macula and normal peripheral fundus as far as could be seen.

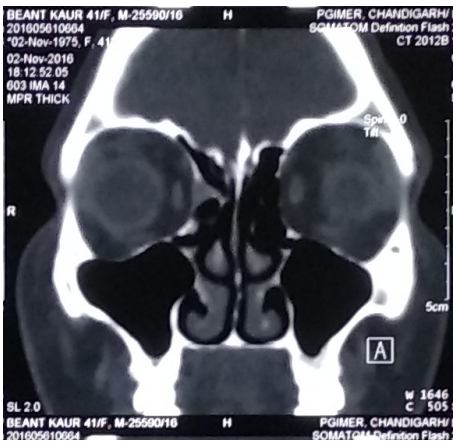

Fig. 2: MRI Orbit (plain) showed mild proptosis of left globe with diffuse edema of the inferior rectus muscle and adjacent fat with a probable diagnosis of thyroid ophthalmopathy, with orbital pseudotumor as a differential diagnosis.

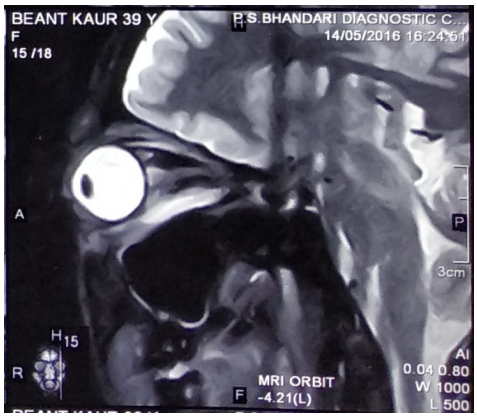

Fig. 3: So after ruling out other causes of proptosis, a diagnosis of Orbital Pseudotumor was made and she was started on Tab.Wysolone 50 mg for 1 week to be tapered by 10 mg every week and Cap.Pantop DSR OD (empty stomach)

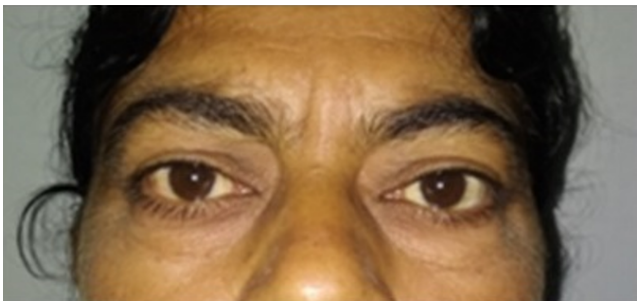

Fig. 4: After one month, herproptosis had improved with exophthalmometry readings as 1.8 cm (OD) and 2.0 cm (OS). On subsequent visits the proptosis kept on improving with oral steroids.

Her blood investigations showed normal Complete Blood Counts, Liver Function Tests, Renal Function Tests and Thyroid Function Tests.

As a further step to rule out other causes of proptosis, we got her radiological investigations done which showed Left medial and inferior recti hypertrophy with minimal retroorbital fat stranding in CECT Orbit.

6. Conflict of Interest

The authors declare that they have no conflict of interest.

7. Source of Funding

None.

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