Case Report

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Orbital Pseudotumor: A Mimic of Orbital Cellulitis

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ABSTRACT

Orbital pseudotumor (OP) also referred to as Non-specific orbital inflammatory syndrome (NOIS) has been associated with a wide range of inflammatory and autoimmune disorders and the exact etiology of this syndrome remains unknown. The differentiation of orbital cellulitis (OC) from OP is often complex leading to delays in appropriate treatment. Timely decision is crucial as both conditions are associated with intracranial complications and result in loss of vision. As compared to the few cases reported in literature, our case is unusual due to a history of mild chronic, relapsing-remitting course for over a year, without a clear diagnosis. Diagnosis is by exclusion, based on a thorough history, clinical presentation, and rapid response to corticosteroid treatment. It mimics orbital cellulitis or malignant lymphoma of the orbit because of the overlapping clinical manifestations. Our case emphasizes the importance of including this entity in the differential diagnosis of orbital cellulitis and the need for timely diagnosis and treatment to halt the progression of disease. This article provides a brief overview of OP, critical nature of the condition, clinical clues to diagnosis, and novel treatment options (steroid sparing agents) currently available for this condition. OP and NOIS are used interchangeably in this document.

Keywords

Pseudotumor, Orbital inflammation, Cellulitis, Autoimmune, Mimic, Immunosuppression.

Introduction

Orbital pseudotumor (OP) often referred to as non-specific orbital inflammatory syndrome was first described in 1905. As the name suggests, it is a non-specific, non-neoplastic, benign condition secondary to accumulation of inflammatory lymphoid tissue in the orbital and peri-orbital tissue [1-3]. Although it is presumed to be associated with infectious, inflammatory and/or autoimmune disorders, the exact etiology of this syndrome remains unknown [4-6]. The incidence rate reported in literature is ~5-7%. This could be an underestimate of the true incidence due to lack of a standard definition criteria and awareness of this condition.

Demographics

The incidence of OP is similar in men and women and is diagnosed in patients 25-65 years of age, with a wide range of age distribution with no racial, age or sexual predilection. Most patients described in literature had a coexistent autoimmune disease or were diagnosed with an autoimmune disease later in their life.

Case report and Infectious Disease Perspective

A 68-year-old man with a history of Crohn's disease (on mesalamine), hypertension, and benign prostatic hyperplasia, presented to the hospital with gradually worsening right-sided headache, swelling and pain involving his right eye with blurring of vision for ~3-4 days. He stated that the headache started in the neck and occipital region and progressed to involve the entire right side of his face. The patient's right upper and lower eyelids were significantly edematous, limiting his vision (as similarly represented in Figures 1 and 2). His vision had gradually diminished over the last several weeks. He described pain on eye movement but retained full range of eye motion. Most importantly, there was absence of erythema of his eyelids and peri-orbital area, lack of tenderness on palpation of his eyelids (clearly disproportionate to his pain), and pupillary reflexes were intact. The symptoms were not associated with systemic manifestations (fevers or chills), and he denied recent trauma. The pain and swelling was ongoing with

no improvement for 3 days prior to admission.

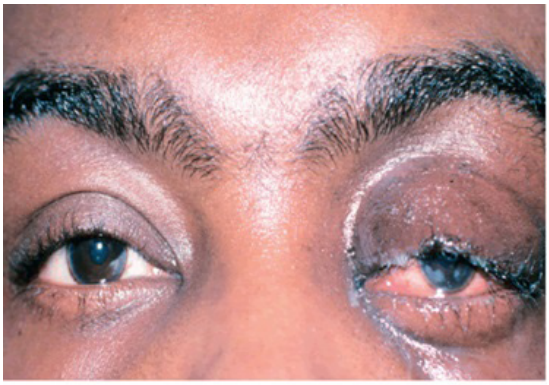

Figure 1: Orbital Pseudo tumor aka nonspecific orbital inflammation. Notice the proptosis, injection, and soft tissue swelling. Image courtesy of Kanski, JJ. Clinical ophthalmology: a systematic approach. Elsevier/Saunders; 2011.

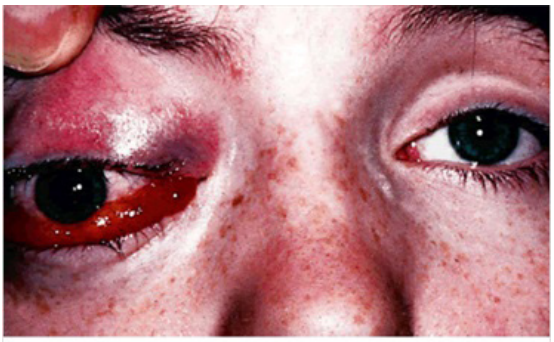

Figure 2: Orbital Cellulitis, which shows many signs of orbital inflammation. This patient's right eye also demonstrates hypoglobus. Often orbital cellulitis and orbital pseudotumor can have identical signs and symptoms. Image courtesy of Kanski, JJ. Clinical ophthalmology: a systematic approach. Elsevier/Saunders; 2011.

During further questioning he also described a history of recurrent headaches in the past, with minimal edema of right eyelid that spontaneous resolved when he did not seek medical attention. On occasion, he had received either short courses of antibiotics and/or prednisone and stated that his symptoms recurred post prednisone taper a few weeks prior to this admission. He was also diagnosed with a spontaneous right internal jugular vein thrombosis, of unclear etiology. Previous work up, including a complete autoimmune work up, complete blood count, and imaging were all normal. He had a slightly high/normal erythrocyte sedimentation rate. There was suspicion\ of temporal arteritis but a biopsy of a long stretch of temporal artery was unrevealing.

On admission his vitals were stable, was afebrile, had no leukocytosis, blood cultures were negative, and a CT scan of the head without contrast was unremarkable. The primary team was concerned for orbital cellulitis and started the patient on intravenous Vancomycin and Ceftriaxone and infectious disease consultation was requested. The patient failed to show any response to 48-72 hours of antibiotic therapy. A CT scan of the orbit with contrast revealed significant diffuse soft tissue thickening and fat stranding around the superior medial aspect of the right eye globe, no definite mass, abscess, bony erosion, or intracranial involvement (Figure 3). Given the absence of erythema, tenderness, fever, peripheral leukocytosis, and a normal retinal examination by ophthalmology team, a non-infectious entity (OP versus tumor) was entertained and all antibiotics were discontinued. Given the fact that patient had no definite mass on CT scan and the diffuse nature of the tissue infiltration seen close to neurovascular bundle, the ophthalmology team deferred a biopsy. Interestingly our patient had remitting-relapsing presentation in the past with a known history of Crohn's disease and hence was suspected to have OP. The patient was started on a trial of high dose intravenous corticosteroid with rapid and remarkable improvement in symptoms and signs, and was discharged home on tapering course of prednisone.

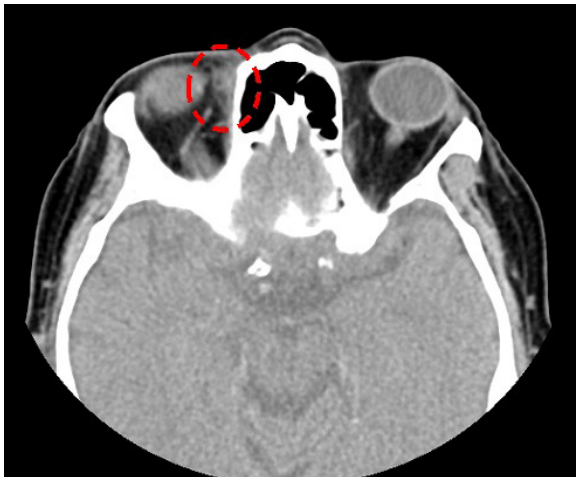

Figure 3: An image obtained from the CT orbit of our patient with OP. The image highlights diffuse soft tissue swelling and fat stranding located over the superior medial aspect of the right eye globe (Red dashed circle). No definite mass, abscess or bone involvement visualized.

Pathophysiology

Despite being described a century ago, the etiology and pathogenesis of OP remains an enigma. It often masquerades as orbital cellulitis or lymphoma which is the two overlapping conditions that need to be ruled out [7-9]. Mild episodes of orbital inflammation may resolve spontaneously. Based on current knowledge, a strong causal association with autoimmunity has been established. Autoimmune conditions frequently reported with OP include Crohn's disease [10], rheumatoid arthritis, systemic lupus erythematosus [11], Myasthenia gravis [12], Wegener's granulomatosis [13], sarcoidosis [14], Grave's disease [15], ulcerative colitis, Tolosa-Hunt syndrome [16], and ankylosing spondylitis. Infectious agents have not been implicated although there are cases of OP reported a few weeks post Group A strep pharyngitis or upper respiratory infections suggesting their possible role [17]. Most patients eventually diagnosed with OP were thought to have orbital cellulitis at the time of initial presentation, initiating an infectious disease consultation as in the case presented above. Unilateral presentation although frequently seen, might question autoimmunity as the primary mechanism for OP. Bilateral OP has been reported but is rare. It is logical to speculate that an antigenic trigger (eye muscle antigen) in and around the orbital muscles initiates a cascade of pro-inflammatory and inflammatory cytokines, consisting of specific T lymphocytes, NK cells, eosinophils, interleukins and dendritic cells, infiltrating the orbital and extraocular muscle, orbital apex, orbital fat, optic nerves, and lacrimal glands with intense vasculitis, followed by

fibrosis and granuloma formation. Histopathological features have not been well studied, as biopsy is not indicated unless there is failure of corticosteroid therapy or suspicion for lymphoma.

Atabay et al. studied eight patients with diffuse or localized nonspecific orbital inflammation. The study patients were evaluated for the presence of autoantibodies reactive with pig eye muscle membrane antigens and 1D, a recombinant 64 kilodaltons (kd) thyroid and eye muscle protein. They demonstrated that the most frequently detected antibodies were those reactive with eye muscle membrane proteins of 55 and 64 kd, which were both demonstrated in 62.5% of patients with NOIS. The authors concluded that autoimmunity against eye muscle antigens is a plausible mechanism [18].

Wladis et al. performed quantitative cytokine assays to assess the levels of 9 different molecules for IOI and control patients. Six cytokines, namely interleukin-2 (IL), IL-8, IL-10, IL-12, gamma interferon, and tumor necrosis factor-alpha, were elevated in patients with NOIS. The expression of Gamma interferon and IL-12 was 10 times higher in NOIS patients compared to controls suggesting an intense innate immune-specific cytokine response in these patients. Based on their findings, authors concluded that discrete elevations of specific cytokines could be implicated in the pathogenesis of this disease [19]. Based on data from similar studies, cytokines were identified as novel therapeutic targets in the management of OP.

A subsequent study sought to determine the potential role of toll-like receptors (TLRs) in NOIS. Immunohistochemical staining for TLR2, TLR3, and TLR4 was performed on tissue specimens biopsied from patients with IOI, and results were compared with an isotype control of orbital adipose tissue taken from patients without evidence of inflammation. All IOI specimens demonstrated positivity for all 3 TLRs, and sections stained for isotype controls did not demonstrate any positivity. This was one of the first studies that documented the role of TLRs in NOIS [20]. Authors concluded that NOIS likely represents an aberrant innate immune response triggered in the orbital tissues. Given this interesting finding, TLR blockers were postulated to represent an additional potential therapeutic mechanism in the management of NOIS. Most recently, Zhao et al. discovered an IgG4-IgE co-positive group as well as Th17 cell immune involvement in IgG4-IgE co-negative subgroup in OP for the first time. The authors report that the pathogenesis of OP could differ from different subgroups according to the IgG4 and IgE detection and recommend that treatment decisions should be made according to the clinical assessment of IgG4-IgE and Th17 profile detection [21].

Clinical Features

Patients present with acute to sub-acute onset of orbital pain (70%), diplopia (35%), periorbital edema (75%), proptosis (55%), restriction of extra-ocular movements (50%), headache (20%), scalp pain (10%), blurring of vision (20%), conjunctivitis (45%), lacrimal enlargement (20%) and erythema (20%) and ptosis (15%) [3-5]. It is important to note that erythema is absent in ~80% of patients and most patients do not present with systemic manifestations such as fever. Although patients complain of pain behind the eye, pain with eye movements, headache, and tenderness is not solicited on palpation of the orbital or periorbital area. These are significant features that would aid the clinician in distinguishing OP from orbital cellulitis (Table 1). Orbital inflammation could present as a localized process such as orbital myositis, dacryoadenitis, scleritis, uveitis, cavernous sinus inflammation/thrombosis (Tolosa-Hunt syndrome) or a diffuse process with infiltrations involving orbital and periorbital fatty tissue [22,23]. Occasional intracranial complications include involvement of cerebral sinus, cavernous sinus with thrombosis (our patient presented with right internal jugular vein thrombosis) or meningeal inflammation presenting as meningitis. Mild cases may resolve spontaneously with multiple recurrences, as in our patient. The diagnosis is made clinically, by a process of exclusion, and is often delayed before requiring hospitalization and complete evaluation. Patients may also have symptoms and signs consistent with rheumatological and/or autoimmune conditions. Not infrequently, evaluation for OP could lead to diagnosis of other autoimmune conditions. Hence a detailed history and a meticulous physical examination play a key role in identifying OP.

	Orbital Cellulitis (Figure 2)	OP (Figure 1)
Physical Exam	Significant Erythema and tenderness, ophthalmoplegia, diplopia, chemosis, proptosis, ptosis, periorbital edema	Minimal or no erythema or tenderness, chemosis, ophthalmoplegia, diplopia, ptosis, periorbital edema, lacrimal edema
Symptoms	Fever, Pain with eye movement, headache, rhinorrhea (+/- purulence), malaise	Pain with eye movement, headache, usually no fever
Recurrence	Rare	Recurrences reported
Labs	Neutrophil predominant leukocytosis May have positive blood culture	No peripheral leukocytosis Elevated CRP and/or ESR
Imaging	Decreased fat signal, sub-periosteal abscess, venous thrombosis, sinus infection	Enlargement of intra-/extra-ocular muscles with fat stranding
Response to treatment	Good response to IV antibiotic therapy within 24-48hrs (if no other intracranial complications)	No response to antibiotics Rapid response to corticosteroids/ immune-suppressants

Table 1: Prominent Differentiating Features.

Investigation

Given the strong causal association with autoimmune diseases, initial work up for possible OP includes CBC, differential (evaluate for lymphocytosis and eosinophilia), thyroid function tests (Grave's disease), metabolic panel, erythrocyte sedimentation rate, C-reactive protein (elevated, but nonspecific), antinuclear antibody (ANA), rheumatoid factor (RF), anti-ds DNA antibody, anti-neutrophilic cytoplasmic antibody (C-ANCA), syphilis profile, angiotensin converting enzyme levels and if evidence of a recent respiratory infection (anti-DNAse antibodies, anti-streptolysin antibodies). Biopsy is usually not indicated. The orbital inflammation is typically non-granulomatous and extra orbital extension is reported in 8.9% of cases. In cases of

extraorbital extension, a biopsy is mandatory to rule out infectious and systemic diseases with clinical similarities [23]. However, chronic and recurrent cases present a diagnostic and therapeutic challenge, as they may masquerade as another diagnosis.

Radiological features

Historically, standard CT scan of the orbit was widely used in the diagnosis of OP. However it was not a sensitive or specific test, as it was unable to differentiate cellulitis from myositis, mass or OP. With advances in the field of radiology, high resolution CT scan (HRCT) of the orbit and MRI are currently being used in patients with suspected orbital cellulitis or OP [24-27]. Kapur et al., compared MRI-gadolinium contrast findings in patients with OP, lymphoma, and orbital cellulitis and were able to differentiate the three conditions based on diffusion weighted images (DWI). Based on our review of literature, we recommend HRCT scan or MRI with gadolinium contrast with DWI as the preferred imaging modality for suspected OP [26]. Imaging would indicate the site of pathology (lacrimal gland, optic nerve, orbital fat or muscle, sinuses, bone, fascia), intra-ocular pathology, and any intracranial complications (cerebral or cavernous sinus and meningeal involvement). Various findings on MRI include enlargement of lacrimal gland with edema, enlargement of ocular and extra-ocular muscles with fat stranding in orbital fat, blurring of muscle margins, due to accumulation of inflammatory cells, enhancement around optic nerve (tram line sign), cerebral and cavernous sinus enlargement with or without thrombosis and meningeal thickening with enhancement [27].

Diagnosis

Diagnosis is complicated as multiple conditions have overlapping features and have a similar clinical presentation (Table 2). A high index of clinical suspicion, based on a detailed history, clinical presentation, and imaging findings helps clinch the diagnosis. Rapid response to corticosteroids within 48-72 hours is considered a clinical confirmation of diagnosis. Biopsy of orbital and periorbital tissue is frequently deferred and indicated only for progressive/refractory disease and/or failure of corticosteroid therapy. The main indication for biopsy in such cases would be to rule out possible malignancy/lymphoma. As orbital cellulitis is a serious condition, it needs to be ruled out prior to initiating high dose corticosteroid therapy. Based on current literature and review of clinical presentations, we propose the clues listed in Table 1 to aid in diagnosis of OP and to specifically differentiate it from orbital cellulitis.

Infections	Inflammatory/ Autoimmune	Rheumatologic	Trauma/ Injury	Drug-Induced (local)	Benign or Cancerous mass
Orbital Cellulitis	Allergic	Sarcoidosis	Hematoma	NSAIDs	Orbital Malignancy/ Lymphoma
Pre-septal Cellulitis	Thyroid orbitopathy	Temporal arteritis		Tretinoin	Schwannoma

Syphilis (uveitis)	Xanthogranulomatous disease	Wegener's Granulomatosis with polyangiitis	Insect Bite	Uveitis	Hemangioma
	Systemic lupus erythematosus				Lymphangioma
	Dermatomyositis				

Table 2: Differential Diagnosis for OP.

Management

Diagnosis of OP is a clearly a process of exclusion. Once the diagnosis is established, it is prudent to withdraw any antibiotic therapy if they were initiated earlier based on suspicion for orbital or pre-septal cellulitis related to bacterial infection. The second step is to assess the clinical progression of the disease. If patients have mild disease with improvement in their symptoms and signs, they can be observed without corticosteroid therapy. Swamy et al. reported that in his experience, 20% of patients diagnosed with OP who were followed over a 6 month period without treatment, had spontaneous resolution [1]. NSAIDS have been tried in mild cases but there is not enough data to recommend the same. If there is a clear progression or lack of spontaneous improvement, corticosteroid therapy at doses of 0.5mg/kg-1mg/kg/day must be initiated for 2 weeks followed by gradual tapering over an 8 week period.

Failure of corticosteroid therapy with recurrence of OP has been reported in ~20% of patients. Refractory cases and patients intolerant to steroid therapy have been successfully treated with adjunctive radiation therapy [28]. Patients who required long term corticosteroid suppression experienced adverse effects. Although steroids have been the main stay of therapy, patients have been successfully treated with steroid-sparing agents including methotrexate and azathioprine. Two patients with steroid-dependent idiopathic orbital inflammation, one with myositis and the other with dacryoadenitis, and were also intolerant to methotrexate and azathioprine, were treated with infliximab, a monoclonal antitumor necrosis factor alpha antibody. In both patients, orbital manifestations disappeared following treatment. After follow-up for at least 20 months, the 2 patients continued to be in remission. Infliximab enabled steroid tapering to less than 5 mg per day, suggesting that infliximab could constitute an alternative to conventional steroid sparing agents [29-32].

Over the last few years, several biologic response modifiers have been added to the armamentarium for treatment of OP [33,34]. IVIG and plasmapheresis have been tried in refractory cases with good success [35] (Table 3).

Surgery

Diagnostic biopsy or surgery is not usually indicated as most cases of OP present with diffuse inflammatory infiltrate. Also, the lymphocytic infiltrate may be extensive around neurovascular

bundles and vital areas that may pose a high risk for any surgical intervention. However surgical resection may be considered if the lesion is well defined and localized. Surgical enucleation with exenteration has rarely been performed in cases with complete loss of vision with ongoing pain and fibrotic mass [5].

Mild Disease	Observation and/or NSAIDs
Severe Disease	Symptoms usually respond rapidly to systemic steroids (methylprednisolone or prednisone)
Secondary options (with varying degrees of efficacy)	Methotrexate, azathioprine, cyclosporine, cyclophosphamide, tacrolimus, biologic agents (such as rituximab), IVIG, or plasmapheresis
Severe refractory disease	Surgery can be considered for localized lesions Rarely require exenteration (if complete loss of vision and severe painful eye)

Table 3: Management Options.

Outcomes

Outcomes of OP differ based on duration of disease, severity, and a treatment protocols. Retrospective data from various studies has indicated that academic centers treating these cases reported a higher rate of corticosteroid failures than observed in the community as these centers were involved in the management of severe or recalcitrant disease. Therapeutic modalities have frequently included observation alone, antibiotics, oral corticosteroids, intravenous corticosteroids, adjunctive radiation therapy and systemic immunosuppressive drugs (methotrexate, azathioprine, mycophenolate, and cyclosporine). A retrospective review of 17 articles with 56 biopsy proven cases, treated with 15 different modalities, reported that the overall response was good in 19 (34%) patients, partial in 24 (43%), and poor in 13 (23%) [36].

Conclusion

OP may be considered a well described entity in the field of ophthalmology, but a less familiar condition for many clinicians. This review is an attempt to create awareness and provide a review of this entity to physicians in all fields of medicine. It still falls under the definition of "idiopathic" as the cause remains unclear. Research on OP is sparse and not much progress has been made over decades regarding the exact nature, pathophysiology and evolution of this syndrome. It continues to intrigue physicians because of its crucial anatomical site, severity of presentation, and the emergent measures needed to diagnose and protect vision in a timely fashion. Its unilateral presentation with significant orbital/periorbital edema, and a broad differential diagnosis, tends to confound the diagnosis even for a seasoned physician. Consultations with ophthalmology and infectious disease specialists on initial presentation is recommended in suspected cases. The availability of cell receptor, immunoglobulin, protein and cytokine specific monoclonal antibodies has opened novel treatment options for this syndrome. More research is needed in future to clearly understand the pathophysiology of this entity.

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