True Pseudotumors and “Pseudo” – Pseudotumors: A Case Series

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ABSTRACT

Objective: To characterize the clinical and pathological features of 4 patients with histopathology-confirmed idiopathic orbital inflammatory disease (OID) initially diagnosed as an orbital neoplasm and 9 patients with histopathology-confirmed orbital neoplasm that presented as idiopathic OID.

Methods: The medical records of 13 patients with orbital mass were reviewed. All biopsies were performed by one orbit surgeon.

Results: There were 4 patients in the histopathology-confirmed idiopathic OID group with preoperative diagnosis of orbital neoplasm. Mean age at presentation was 27 years. Follow-up period ranged from 6 to 41 months. The left orbit was predominantly involved (3/4). The presenting symptoms and signs included proptosis (2/4), diplopia (1/4), and inflammation (1/4). The preoperative best-corrected decimal acuity mean was 0.92. Three of 4 patients retained their preoperative visual acuity postoperatively. There was recurrence of inflammatory signs in only 1 patient, which responded well to oral corticosteroids. In the histopathology-confirmed orbital neoplasm with preoperative diagnosis of idiopathic OID group, there were 9 patients with mean age at presentation of 52 years. Follow-up period averaged 7.5 months (range: 0.5 - 83 months). The presenting symptoms and signs included proptosis (4/9), inflammation (3/9), orbital pain (1/9), and epiphora (1/9). The preoperative best-corrected decimal acuity mean was 0.78. Histopathology and immunohistochemistry of the orbital masses revealed malignancy in 80% (7/9) of these cases.

Conclusions: Idiopathic OID remains a diagnostic dilemma for many physicians. A detailed history, comprehensive physical examination, and appropriate radiological evaluation are essential to differentiate OID and non-inflammatory orbital conditions such as neoplasms. Biopsy is recommended when there is poor or equivocal response to steroids or suspicion of orbital malignancy.

Keywords: Pseudotumor, orbital inflammatory disease, neoplasm, biopsy, histopathology

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First described in 1905 by Birch-Hirschfield, idiopathic orbital inflammatory syndrome (OID), also known as orbital “pseudotumor”, is a heterogeneous group of disorders characterized by orbital inflammation without identifiable local or systemic causes. Any structure in the orbit can be affected and the presentation can range from abrupt to insidious onset. It is clinically categorized as myositis, dacryoadenitis, anterior, apical, and diffuse process. Patients may present with pain, periorbital swelling, diplopia, chemosis, and proptosis with associated optic neuropathy. Diagnosis is based on careful history and diagnostic imaging which may include ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) of the orbit. Systemic corticosteroids administered orally or intravenously is the cornerstone of managing orbital pseudotumors. The response towards steroid is so rapid, that steroid administration is often considered as a diagnostic test. However, Mombeart et al. cautioned that such a method of diagnostic evaluation has only 78% sensitivity. Also, some experts object to using clinical response to steroids as a diagnostic tool since there are several reports of steroid-unresponsive orbital pseudotumors. Biopsy is recommended in cases suspicious for an orbital malignancy or when there is poor or equivocal response to corticosteroids.

METHODS

We performed a retrospective review of medical records of all patients with histopathology-confirmed idiopathic OID that presented as orbital neoplasms based on clinical evaluation and diagnostic imaging or histopathology-confirmed orbital neoplasms that were referred with a diagnosis of idiopathic OID from May 2004 to April 2015.

Data extracted from the medical charts included age, gender, presenting signs and symptoms, diagnostic imaging features, histopathological features, clinical course, treatment regimen, and outcome.

RESULTS

The study included 10 male and 3 female patients. There were 4 patients with histopathology-confirmed idiopathic OID that presented as orbital neoplasms and 9 patients with histopathology-confirmed orbital neoplasms that were referred with an initial diagnosis of idiopathic OID.

Histopathology-confirmed Idiopathic OID

There were 4 patients in the histopathology-confirmed idiopathic OID with preoperative diagnosis of orbital neoplasm group. Three (3) were males. The mean age of patients was 27 years. The mean follow-up period was 22 months (range: 6 to 41 months). The left orbit was predominantly involved (3/4). The presenting symptoms and signs included proptosis (2/4), diplopia (1/4), and inflammation (1/4). The mean preoperative best-corrected decimal visual acuity was 0.92. Three of 4 patients (75%) retained their preoperative visual acuity postoperatively. Case 4 had a 2-line decrease in visual acuity due to dry eye disease. Case 2 had recurrence of inflammatory signs which responded well when oral steroid therapy was reinitiated.

All 4 cases had previous orbital imaging that were signed out as OID by the interpreting radiologist.

Review of the orbital imaging of 3 patients (Cases 1, 2, and 4) showed a superolateral orbital mass with nonaxial globe displacement. CT imaging of Case 3 showed a unilateral, well-circumscribed, ovoid intraconal mass. Two out of 4 patients (Case 2 and 3) reported previous treatment with oral prednisone which afforded incomplete relief. Absent or incomplete response to steroids, persistence of proptosis secondary to the orbital mass, and imaging characteristics led to a preoperative clinical diagnosis of lacrimal gland tumor for Cases 1, 2, and 4 and cavernous hemangioma for Case 3.

Case 1 was a 33/M referred due to a 12-month history of diplopia on left upward gaze. He underwent repair of wound laceration at the right frontotemporal area 25 years prior to consultation due to a fall. Examination revealed nonaxial proptosis with inferior globe displacement and limitation on left upward gaze. Orbital CT scan revealed an ovoid, extraconal, expansile, soft tissue mass in the left orbit slightly compressing the globe inferiorly and thinning of the superior orbital wall. Excision biopsy of the orbital mass was done through a lateral orbitotomy with bone flap. Histopathology revealed foreign-body giant cells, hemosiderin-laden macrophages, and lipid-laden histiocytes with interspersed lymphocytes and plasma cells (Figure 1).
Case 2 was an 8/F initially managed as cellulitis by the Pediatric Service and treated with antibiotics and oral corticosteroids which did not afford relief. Orbital CT scan showed a soft tissue density in the superolateral left orbit. A lacrimal gland neoplasm cannot be ruled out. An orbital mass measuring 2 cm in its widest diameter was excised via lateral orbitotomy with bone flap. Histopathology showed lacrimal tissue composed of lacrimal glands diffusely infiltrated by mononuclear cells, predominantly lymphocytes, and areas forming lymphoid follicles with prominent germinal center. There were areas of fibrosis and scattered eosinophils in the stroma. Three (3) months later, there was recurrence of left upper eyelid edema with resistance to globe retropropulsion. Repeat axial and coronal orbital CT scan revealed an enhancing soft tissue mass that could be fibrosing tissue or recurrence. A review of histopathology slides reaffirmed the diagnosis of pseudotumor. The patient responded well to restarted steroid therapy. Other signs of immune disorder were identified 3 years later with the patient requiring dialysis for focal segmental glomerular nephritis (Figure 2).

Case 3 was a 46/F with 3-year history of proptosis, hypertropia, and limitation on lateral and downward gaze of the left eye. Orbital CT scan showed an intraconal mass, measuring 2 cm in its widest diameter, with pseudotumor as a consideration. She was prescribed with oral steroids by private physicians which afforded no relief. Progression of proptosis with worsening of diplopia prompted consult to our institution. The orbital mass was excised through an anterior orbitotomy. Histopathology showed eosinophilic deposits with plasma cells, lymphocytes, and multinucleated giant cells. Negative Congo red stain ruled out amyloidosis (Figure 3).

Case 4 was a 23/F with a 7-mm right-sided proptosis of 2-years duration. Orbital CT scan revealed an extracanal mass in the lateral and superior aspects of the right orbit. Since a lacrimal gland neoplasm cannot be ruled out, an en bloc excision biopsy was done through a lateral orbitotomy with bone flap. Histopathology showed normal orbital tissue composed of the lacrimal gland, adipose...
3 (33%) underwent previous biopsy that showed OID.

Case 5 was a 54/M referred due to right-sided proptosis for 11 months. An orbital CT scan was ordered by his previous physician due to persistence of periorbital inflammation and progression of proptosis. Radiologic diagnosis was pseudotumor involving the inferior rectus muscle. He was started on prednisone, slowly tapered over a period of 2 months, which resulted in partial resolution of proptosis. Prior to consultation at our institution, inflammation recurred twice, for which he was restarted on prednisone at 1 mg/kg/day each time, which only afforded temporary relief of inflammation and no complete resolution of proptosis. Our review of the CT scan images showed sections suspicious of an ovoid, retrobulbar mass with proportional recti muscles. The possibility of an orbital mass mistaken as the inferior rectus cannot be ruled out. Excision biopsy through an orbitotomy without a bone flap showed an orbital mass confirmed on immunomorphology as a solitary fibrous tumor (Figure 4).

There were 9 patients (7 males, 2 females) in the group with histopathology-confirmed orbital neoplasm. These patients were referred with a diagnosis of idiopathic OID. The mean age of patients was 52 years. Follow-up period averaged 7.5 months (range: 0.5 - 83 months). The presenting symptoms and signs included proptosis (4/9), inflammation (3/9), orbital pain (1/9), and epiphora (1/9). The mean best-corrected decimal visual acuity before and after orbitotomy were 0.78 and 0.86, respectively. Of the 9 patients, 7 (78%) were unresponsive to treatment with appropriately-dosed corticosteroids and 3 (33%) underwent previous biopsy that showed OID.

Case 6 was a 77/M referred on admission with a profusely bleeding left orbital mass. One month prior to admission, the patient had no light perception in the involved eye and was treated with intralesional triamcinolone, which afforded no relief. Excision of the mass was done with intraoperative blood transfusion. Clearance of the visual axis afforded by the excision resulted in 20/100 vision on the involved eye. Histopathology showed a malignant neoplastic process arranged as interlacing bundles of spindle cells with brisk mitotic activity. Histopathologic diagnosis

**Histopathology-confirmed Orbital Neoplasm**

Histopathology shows eosinophilic deposits with plasma cell infiltrates, lymphocytes, and multinucleated giant cells suggestive of amyloidosis with negative Congo red stain (E & F).

**Figure 3.** Case 3 with histopathology-confirmed non-idiopathic orbital inflammatory disease. Axial and coronal CT images taken 3 years prior to consult show a 2 x 1 cm intraconal mass displacing the globe superiorly (A1 & A2). Axial and coronal CT images taken 2 years prior to consult show no significant change in size and consistency (B1 & B2). Axial and coronal MRI 1 year prior to consult (C1 & C2). Preoperative photograph demonstrating proptosis of the left side with superior displacement of the globe (D1). One week postoperative photograph shows monocular fixation (D2). Two months postoperative photograph shows central fixation of the left eye and binocularity (D3). Histopathology shows eosinophilic deposits with plasma cell infiltration, compatible with sequalae of inflammatory pseudotumor.

**Figure 4.** Preoperative photograph of Case 5 with histopathology-confirmed orbital neoplasm (A). Excised orbital mass measuring 2.2 x 1.9 x 1.5 cm (B). Patient at 2 weeks postoperative with resolution of proptosis (C). Preoperative axial and coronal CT images show a well-circumscribed lesion (dashed lines) suspicious of an orbital mass (D1 & D2). Coronal CT shows inferior rectus muscle (arrow) proportional to the other recti muscles of the right eye (D3).

**Histopathology-confirmed Orbital Neoplasm**

There were 9 patients (7 males, 2 females) in the group with histopathology-confirmed orbital neoplasm. These patients were referred with a diagnosis of idiopathic OID. The mean age of patients was 52 years. Follow-up period averaged 7.5 months (range: 0.5 - 83 months). The presenting symptoms and signs included proptosis (4/9), inflammation (3/9), orbital pain (1/9), and epiphora (1/9). The mean best-corrected decimal visual acuity before and after orbitotomy were 0.78 and 0.86, respectively. Of the 9 patients, 7 (78%) were unresponsive to treatment with appropriately-dosed corticosteroids and 3 (33%) underwent previous biopsy that showed OID.
was malignant spindle cell tumor, with negative surgical margins. There was recurrence of the orbital mass at 7 weeks postoperative with no light perception in the involved eye. Exenteration was done. Histopathology with immunohistochemistry (Vimentin, S-100, Cytokeratin, EMA, CD99, Desmin, BCL-2, HMB 45, CK 7, CK 19) showed a high-grade sarcoma most compatible with malignant peripheral nerve sheath tumor. Patient died 2 years later from pulmonary metastasis (Figure 5).

Case 7 was a 46/F patient, post-mastectomy for breast adenocarcinoma. She was referred by her primary ophthalmologist due to persistent redness of the left eye. She relayed that her positron emission tomography (PET) scan done 1 month prior to consult was negative for disease. Examination showed gross enophthalmos with limitation of extraocular movement of the left eye and a palpable mass on the left inferior orbit. Preoperative CT scan impression was inferior rectus myositis. Incision biopsy revealed metastatic breast carcinoma (Figure 6).

Case 8 was a 36/M referred due to loss of vision of the right eye. He had a 2-year history of anosmia, recurrent nasal congestion, and right orbital pain. Preoperative CT scan showed a maxillary mass on the right side, with extension to the ethmoid sinuses and nasal cavity. Prior to the ophthalmology referral, he had undergone 2 biopsies that showed inflammatory disease with no signs of malignancy. On examination, there was no light perception on the right eye, with a 15 mm proptosis, superomedial globe displacement, lack of eye movement, and a dilated, unreactive pupil. Incision biopsy of the orbital mass was done. Immunohistopathology (CD3, CD20, B cell marker, & CD45Ro) showed B-cell lymphoma (Figure 7).
Case 9 was a 33/M who consulted for painless proptosis of the right eye which started 1 year prior to consult. CT imaging done showed a well-circumscribed, fairly homogenous, intensely-enhancing mass in the intraconal superolateral aspect of the right globe. His previous physician performed fine needle aspiration biopsy (FNAB) with histopathologic diagnosis of inflammatory pseudotumor. Oral prednisone at 1 mg/kg/day afforded no relief. On examination, vision was 20/20 in both eyes with no signs of inflammation. There was a 6-mm proptosis of the right eye. Excision biopsy through a lateral orbitotomy with bone flap was done. Histopathology showed multiple cavernous spaces mostly filled with blood, separated by fibrous septae, characteristic of cavernous hemangioma (Figure 8).

Case 10 was a 47/M with 3-year history of right upper eyelid mass with persistent conjunctival inflammation. He was previously diagnosed with OID and prescribed oral prednisone, which afforded no relief. A review of his CT scan plates showed a right superomedial orbital mass molding to the orbital bones and globe, without bony erosion. Examination showed best-corrected visual acuity of 20/25 and a 4-mm non-axial proptosis of the right eye. There was also diplopia on left lateral gaze. An irregularly-shaped dark-brown tissue in the superomedial orbit was excised through an anterior orbitotomy. Immunohistopathology (CD3, CD 20) showed B-cell lymphoma.

Case 11 was a 65/M referred due to swelling of right upper lid. He had a history of basal cell carcinoma (BCCA) excised from the right lower eyelid. Best-corrected visual acuity was 20/20 on both eyes. The right eye showed a 2 mm non-axial proptosis, a 2 mm ptosis, and a superolateral orbital mass. Due to an enlarging mass, the previous physician performed a fine needle aspiration biopsy which showed pseudotumor. A review of his CT scan plates showed a soft tissue mass anterior to the right globe. A reddish-brown, irregularly-shaped orbital mass measuring 4 x 3 x 1 cm was excised. Histopathology showed small- to medium-sized lymphocytes scattered in the stroma with hyperchromatism of the nuclei and abortive germinal cell formation in focal areas, characteristic of B-cell lymphoma. He was referred to Oncology Service for chemotherapy (Figure 9).

Case 12 was a 44/F with tearing and left upper eyelid mass which was noted 8 months prior to referral to our institution. She was diagnosed with OID and treated with prednisone, which afforded no relief. A previous MRI showed an enhancing mass-like lesion in the superolateral quadrant of the left orbit. She was then referred to the orbit service. On examination, the patient had best-corrected visual acuity of 20/20 on both eyes, a 3 mm proptosis on the left eye with a firm, palpable mass on the superolateral orbit that displaced the globe inferomedially. Excision biopsy through a lateral orbitotomy with bone flap revealed a 2.5 x 2.5 x 1.5 cm orbital mass. Histopathology showed fibrocollagenous tissue harboring tumor cells arranged in acinar and cribriform pattern surrounded by bands of hyalinized tissue. There were also nerve bundles surrounded by tumor cells. Histopathologic
Figure 11. Preoperative diagnostic imaging of Case 13: axial CT scan at 2 years prior to consult (A1); T1-weighted axial MRI at 1 year prior to consult (A2); and T1-weighted axial MRI at 3 months prior to consult (A3). The images show an ill-defined soft tissue mass in the right retrobulbar region, adherent to the globe and optic nerve. Despite steroid therapy, there was no significant change in the size nor configuration of the mass over time. Immunohistopathology revealed a B-cell lymphoma.

DISCUSSION

Orbital diseases are classically divided into one of the following processes: inflammation, neoplasia, structural abnormality, vascular origin, and degeneration. Idiopathic OID accounts for approximately 16% of all cases of unilateral proptosis and up to 42% of space-occupying lesions of the orbit. It is subclassified on the basis of the involved anatomic areas within the orbit.

In our case series, the histopathology-confirmed idiopathic OID group presented more of proptosis with diplopia and only mild to no orbital pain. This is in contrast to other studies that suggested pain to be the predominant symptom in idiopathic OID. Since OID mimics several types of orbital disease, it is also important to consider presence of a neoplasm until proven otherwise.

Systemic corticosteroid therapy is the cornerstone of management for OID. Over 75% of patients show dramatic improvement within 24 to 48 hours of treatment. Intraorbital injection of corticosteroid has been found to be an effective treatment in select patients. In our study, poor steroid responders were observed in both groups. However, non-resolution of signs and symptoms do not necessarily point out to another disease entity or rule out idiopathic OID in general.

Biopsy is recommended when there is poor or equivocal response to steroids and suspicion of orbital malignancy. FNAB came with the evolution of more conservative surgical approaches. Moreover, a study involving 38 patients demonstrated FNAB under CT guidance resulted to zero false positive result in the diagnosis of orbital OID. The wrong diagnosis of inflammatory pseudotumor in Cases 9...
and 11 could have been avoided if the FNABs were image-guided. Orbital pseudotumor comprises of nonspecific polymorphic, lymphocytic infiltrates with macrophages, polymorphonuclear leukocytes and eosinophils.\textsuperscript{10} In general, the histopathological findings can be categorized into three subtypes: predominantly lymphoid infiltrative, predominantly fibrotic, and mixed.\textsuperscript{11}

Orbital examination and review of orbital imaging studies will usually suggest whether a lesion is benign or malignant. Smooth, well-outlined masses with no invasion of surrounding tissues are usually benign. Tumors with diffuse borders and evidence of invasion into the surrounding tissues, including orbital fat or bone, are usually indicative of malignancy. Exceptions to these clinicoradiologic characteristics include malignant lymphoma and OID or pseudotumors.\textsuperscript{12}

A Jules Stein Eye Institute study on biopsy-proven orbital tumors noted that benign lesions were more circumscribed and oval.\textsuperscript{12} Furthermore, the study showed none of the malignant or inflammatory lesions was oval. Thus, excision biopsy was done on Case 9 despite a previous FNAB result indicating inflammatory pseudotumor, since preoperative CT showed an ovoid, intraconal mass. This resulted in the correct diagnosis of cavernous hemangioma.

Tumor characteristics that indicate its benign or malignant nature affect the decision of whether an incisional or excisional biopsy should be done. An excision biopsy removes an orbital mass in its entirety. This is ideal for well-localized, well-circumscribed, encapsulated lesions particularly benign mixed tumors of the lacrimal gland or orbital dermoid cysts. Font and Gamel's series from 1978 documented an increased 5-year recurrence rate of 32\% for incompletely excised pleomorphic adenomas, compared to 3\% for completely excised lesions.\textsuperscript{13} Thus, an en bloc excision biopsy through a lateral orbitotomy with beveled osteotomies was done for the 3 patients (Cases 1, 2, and 4) with a preoperative diagnosis of lacrimal gland neoplasm.\textsuperscript{14}

An incision biopsy removes a representative piece of tissue. This is preferred for confirmation of a clinical diagnosis before proceeding with medical or radiation therapy and definitive surgical treatment i.e. exenteration or more extensive surgery. Incision biopsy was done on Cases 8 and 13 with preoperative diagnosis of lymphoma based on orbital imaging which showed molding of the mass to the globe without bone erosion. Case 7 who had a preoperative diagnosis of metastatic breast carcinoma also underwent incision biopsy. In general, malignant lesions of the orbit are not amenable to excisional biopsies because tumor-free microscopic margins cannot be obtained in orbital fat.

The biopsy slides of over 6,000 patients referred to Johns Hopkins for cancer treatments were reviewed. The rate of error was 1.4\%, low but not insignificant. This is equal to 1 cancer patient a week with a wrong diagnosis or 30,000 mistakes a year across the United States.\textsuperscript{15} Also, a wellness and cancer coach reported that gynecology pathology errors range from 2 – 20\% and non-gynecology cases 5 – 12\%. A review of biopsy slides is advised when symptoms do not correlate with the diagnosis and the cancer type is rare.\textsuperscript{16}

A reduction in life expectancy attributed to a deviation in the standard of care always has been grounds for a lawsuit.\textsuperscript{17} In October 2011, the Washington State Supreme Court recognized “loss of chance” and “what might have been” as new causes of action if medical treatment or a diagnosis had taken place earlier. There are at least 4 Courts in the United States that allow damages for lost survival chance or medical improvement due to misdiagnosis.\textsuperscript{18} State laws on loss of chance of survival continue to evolve.

In an era of unprecedented liability and expectation, improved diagnostic accuracy should be a priority. Advances in orbital imaging correlated with clinical findings, surgical judgement and skill allow physicians to define the most efficient management of orbital diseases.

CONCLUSION

The clinical presentation of orbital pseudotumor may vary depending on the tumor location and effect of inflammatory tissues. The clinical picture can range from pain, redness, edema to proptosis, diplopia, compressive optic neuropathy, and visual loss from a space-occupying lesion. Differentiating between orbital inflammatory causes such as idiopathic OID and non-inflammatory conditions such as neoplasms is crucial to be able to provide appropriate treatment.

The optimal approach to an orbital disease is best determined by a detailed history, meticulous, cautious and comprehensive clinical examination,
appropriate and thorough radiological evaluation and histopathologic investigations. Patients must be evaluated on an individual basis. The justification for surgical intervention must consider the presence or possible development of a functional deficit, the risk of further progression of a biologically active or aggressive lesion, suspected risk of malignancy, lesion location, and aesthetic considerations.

REFERENCES

Table 1: Imaging procedure and findings, lesion size, history of steroid administration, preoperative diagnosis, surgical intervention, preoperative and postoperative visual acuity, and histopathologic diagnosis of idiopathic OID in 4 cases with initial diagnosis of orbital neoplasm

<table>
<thead>
<tr>
<th>Case</th>
<th>Imaging procedure</th>
<th>Imaging Findings</th>
<th>Lesion Size (mm)</th>
<th>History of Steroid Treatment</th>
<th>Preoperative Diagnosis</th>
<th>Surgical Intervention</th>
<th>Preoperative Visual Acuity</th>
<th>Postoperative Visual Acuity</th>
<th>Histopathologic Diagnosis</th>
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Table 2. Imaging procedure and findings, lesion size, history of steroid administration, prior biopsy result, surgical intervention, preoperative and postoperative visual acuity, and histopathologic diagnosis & immunohistochemistry of 9 cases with histopathology-confirmed orbital neoplasm

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<tr>
<th>Case</th>
<th>Imaging Procedure</th>
<th>Imaging Findings</th>
<th>Lesion Size (mm)</th>
<th>History of Steroid Treatment</th>
<th>Prior Biopsy Result</th>
<th>Preoperative Visual Acuity</th>
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<th>Postoperative Visual Acuity (Snellen)</th>
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<th>Immunohistochemistry</th>
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