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**Idiopathic Orbital Inflammation/Inflammatory Orbital Pseudotumor**

**with Bone Erosion and Extension into the Paranasal Sinuses**

**ABSTRACT**

Idiopathic orbital inflammation developed in the right orbit of a woman in her middle 30s causing tearing, a crusty discharge, itching, photophobia, diplopia, altered depth perception, proptosis, and pain on eye movement. Computed tomography disclosed a mass involving the intraconal and extraconal nasal right orbit and extending to the orbital apex with anterior displacement of the globe, effacement of the medial rectus muscle, portions of the fat plane, and the superior oblique muscle, and erosion of the mass through the orbital floor into the superior maxillary sinus and into the ethmoid sinus through the lamina papyracea. Two biopsies, one including tissue from the areas of eroded bone and the sinuses, disclosed dense fibrous connective tissue with numerous lymphocytes and macrophages. Immunohistochemical stains supported a diagnosis of idiopathic inflammatory pseudotumor involving the orbit and sinus mucosa. Treatment with a prednisone taper and a retrobulbar injection of triamcinolone acetonide have stabilized her symptoms and diminished her proptosis. This patient highlights the rare potential of idiopathic orbital inflammation to erode though bone into adjacent cranial structures.

**Key words:** Idiopathic orbital inflammation, orbital pseudotumor, bone erosion, extraorbital extension, intracranial extension

1. **Introduction**

 Idiopathic orbital inflammation (IOI) refers to an enlarged structure or mass in the orbit that is of unknown cause and is manifest histologically by nonspecific inflammation with varying degrees of fibrosis.1; 2 IOI has been referred to by a wide variety of names including orbital pseudotumor,1; 3; 4; 5 idiopathic orbital pseudotumor,6 inflammatory orbital pseudotumor,7 idiopathic orbital inflammatory syndrome,8 and non-specific orbital inflammation.9 In three recent series of orbital tumors, IOI accounted for 11% of lesions at Wills Eye Hospital Philadelphia, PA,10 8.5% at Erasmus University Medical Center, Rotterdam, Netherlands,11 and 5.2% at The University of Texas M.D. Anderson Cancer Center, Houston, TX.12

Extraorbital extension of IOI is reported only rarely and may occur by eroding through the bone or extension of the IOI through fissures and foramina, with the latter being about twice as common as the former. This report highlights the rare potential of IOI to extend outside the orbit and provides a review of the literature on this subject.

1. **Clinical presentation**

A woman in her middle 30s was evaluated due to four months of constant tearing, a crusty discharge, itching, and photophobia in her right eye. She had difficulty focusing and eye strain after closing and then reopening her eyes.  She felt as if her depth perception was abnormal, and she noted loss of peripheral vision when looking straight ahead, vertical diplopia when looking to the right and keeping her head straight, and horizontal diplopia when looking to the left.  For the past month, looking at objects too close to her face made her feel nauseated. She had pain in her right eye during up, down, left, and right gaze; dull migraine headaches in the back of her head; and she felt her right eye was "puffy", causing her to occasionally walk with her right eye closed.  She had eye strain and pain when concentrating on distant objects.  She also thought that her right eye was protruding more than her left eye. All of the symptoms had been gradually getting worse over the prior four months.   She had no history of ocular surgery or trauma and no other health problems.

Ophthalmological examination noted mild swelling of the right and left upper eyelids; proptosis of the right eye with exophthalmometer measurements of 23 mm O.D. and 20 mm O.S. with a base of 106; visual acuity of 20/20 O.U.; intraocular pressure of 23 mmHg O.D. and 19 mmHg O.S.; unremarkable pupils with normal reaction to light and accommodation; full extraocular movements but with pain in her right eye during left, right, up, and down movement; normal color plate testing; and unremarkable slit lamp and fundus examinations. Laboratory testing noted mild anemia; a normal comprehensive metabolic panel; and normal thyroid stimulating hormone and free thyroxine levels. Computed tomography disclosed an approximately 2.8 x 1.9 x 3.2 cm mass involving the intraconal and extraconal nasal right orbit and extending to the orbital apex; anterior displacement of the globe; mass abutting the globe with loss of fat margin; effacement of the medial rectus muscle, portions of the fat plane, and the superior oblique muscle; and erosion of the mass through the orbital floor into the superior maxillary sinus and into the ethmoid sinus through the lamina papyracea. The left orbit was within normal limits. There was minimal generalized right maxillary sinus mucosal thickening without an air-fluid level.

Following the patient’s second surgery, she was prescribed 30 mg oral prednisone twice per day with a 10 mg per day taper each following week. One month following the second surgery, she had a retrobulbar injection of 40 mg of triamcinolone acetonide in the right orbit. At her most recent visit, two months following the second surgery, the patient felt that her symptoms were stable with improved, though still mild, proptosis.

1. **Pathology**

A biopsy through an anterior orbitotomy consisted of multiple irregularly-shaped pieces of tissue with an aggregate dimension of 1.0 x 0.9 x 0.3 cm. Histological examination disclosed dense fibrous connective tissue with numerous lymphocytes and macrophages, and rare cells mostly along the edges of the biopsy expressing cytokeratins immunohistochemically. Due to clinical history and radiographic findings, a second biopsy was recommended to exclude the possibility that the first biopsy findings represented a reaction surrounding a neoplasm located deeper in the orbit.

A second anterior orbitotomy was done one month later with biopsy of the right ethmoid and maxillary sinuses. A 2.0 x 1.2 x 0.3 cm piece of tumor was used for frozen section analysis, while a 3.5 x 2.5 x 0.4 cm aggregate of soft, lobulated and tan-red tissue was submitted for paraffin sections. There was a dense lymphoplasmacytic infiltrate in a background of fibroadipose tissue, within bone, and in sinus mucosa. There was no atypia of the plasma cells. There were areas of marked fibrosis accompanying the lymphoplasmacytic infiltrate. Immunohistochemical stains using antibodies to CD3 and CD20 disclosed a mild predominance of CD3+ T-lymphocytes, though there were numerous plasma cells that were negative for CD3 and CD20 but were highlighted with antibodies against CD138. The plasma cells were a mixture of kappa and lambda light chain expressing cells. Immunostains using antibodies to IgG and IgG4 showed an IgG4/IgG ratio of <40% with many fewer than 100 IgG4+ cells/high power field; these results indicated that this was not IgG4-related disease.13 The pathological diagnosis was idiopathic orbital inflammation/idiopathic inflammatory pseudotumor involving orbital fibroadipose tissue, bone fragments, and sinus mucosa.

1. **Discussion**

IOI is subclassified by anatomic distribution, though sites and incidence vary depending on author. Mombaerts proposes classifying IOI into four groups: idiopathic dacryoadenitis when inflammation is limited to the lacrimal gland, idiopathic orbital myositis when the process is limited to one or more extraocular muscles, diffuse IOI if several structures in the orbit are involved, and idiopathic optic perineuritis if only the optic nerve sheath is the site of inflammation.2 Rootman presented data on 113 patients with IOI: 51 (45%) had myositic IOI, 25 (22%) dacryoadenitis, 23 (20%) anterior IOI, 3 (3%) diffuse IOI, and 11 (10%) had apical IOI.14 Yuen and Rubin reported 65 patients with IOI: 21 (32%) had dacryoadenitis, 19 (29%) had myositis, 5 (8%) had both dacryoadenitis and myositis, 6 (9%) had orbital apex syndrome, and 14 (22%) involved the supraorbital region, orbital fat, sclera, Tenon capsule, or optic nerve.15 Yan, Wu, and Li studied 209 patients: 90 (43%) had a localized orbital mass (sites not specified), 66 (32%) had dacryoadenitis, 21 (10%) diffuse IOI, 16 (8%) myositis, 5 (2%) perineuritis, and 4 (2%) periscleritis.16 In most studies, the right orbit is more often affected with IOI than the left orbit. Blodi and Gass found 63 cases of IOI in the right orbit, 48 in the left orbit, and 8 bilateral cases without subsequent systemic disease.17 The right orbit was involved with IOI in 90 patients, the left orbit in 81subjects, and both orbits in 38 patients in study of Yan, et al.16 In contrast to these studies, Swamy and coworkers reported the left orbit affected by IOI in 13 patients, the right orbit in10, and both orbits in 1 patient.8 Bilateral IOI has an incidence of 8% to 20% in nonmyositic IOI and 14% in myositic IOI.18

Gender predilection for IOI differs among studies. Blodi and Gass had 69 males and 61 females in their report,17 Chavis, Garner, and Wright’s study incorporated 33 male and 22 female patients,7 Rootman and Nugent reported 11 females and 6 males,19 the study by Yan, Wu, and Li had 118 males and 91 females,16 Yuen and Rubin had 43 women and 22 men,15 and most recently the study by Swamy et al. included 14 males and 10 females.8 Tallying these studies yields 262 males and 238 females, indicating a slight predominance (ratio of 1.1) of males affected by IOI.

IOI affects all age groups.17; 18; 20; 21 The study by Blodi and Gass included patients with this age distribution: age 1-10 years, n=6; age 11-20, n= 17; age 21-30, n=15; age 31-40, n=24; age 41-50, n=20; age 51-60, n=23; age 61-70, n=13; and age 71-80, n=12.17 The average age of the IOI patients reported by Yan and coinvestigators was 44.4 years (range = 4 to 80 years),16 and the mean age in the Swamy et al. study was 45.2 years (range 14 to 75 years).8 In the recently proposed consensus criteria for diagnosing IOI, the authors caution “Although patient age has no absolute limit with regards to IOI, younger (<10 years) and older (>75 years for nonmyositic and >60 years for myositic IOL) patients are more likely to be classified as having another disease.”18

The most common symptom of IOI is pain, but the percentage of patients with pain varies widely between studies. Pain was present in 69% of patients reported by Yuen and Rubin,15 58% in the paper by Swamy et al.,8 but only 24% of those in the Blodi and Gass publication.17 This difference may reflect the proportion of patients with myositic IOI since myositic IOI is the form of IOI most frequently manifesting pain.18 Diplopia and decreased vision are the next most frequent symptoms of IOI with diplopia present in 19%,16 31%,15 38%,8 and 42%17 of patients, and decreased vision in 17%,17 21%,8 and 24%16 of patients depending on the study. Periorbital swelling (edema), proptosis/exophthalmos, and restricted eye motility are the most frequent signs of IOI. The percentage of patients with periorbital swelling ranges from 43%17 to 75%15; proptosis/exophthalmos varies from 32%15 to 77%17; and restricted eye motility is reported in about one-half of people with IOI.8; 16; 17 Ptosis is a less common sign of IOI and has an incidence of 12%16 to 19%17 of patients. The duration of symptoms prior to biopsy was under 1 month in 15 patients, 1-3 months in 31 people, 4-6 months in 22 patients, 7-12 months in 16 patients, 1-5 years in 17 patients, and more than 5 years in 3 patients in the study by Blodi and Gass.17 Duration of symptoms prior to presentation ranged from 0.3 to 12 weeks with a median of 4 weeks in the study by Swamy and coworkers.8

IOI is characterized histologically by a nonspecific chronic inflammatory infiltrate of lymphocytes, plasma cells, histiocytes, eosinophils with degranulation, and sometimes neutrophils.22; 23; 24; 25 The number of eosinophils may be prominent in children, and there may be accompanying peripheral blood eosinophilia.21 Lymphoid follicles with germinal centers may be present22; 23 and are most common in the chronic stage of the disease.22 The degree of fibrosis is variable, progresses over time, and when present helps to distinguish IOI from lymphoid tumors.22 T-lymphocytes predominate over B-lymphocytes in IOI, and the B-cells are a mixture of cells expressing kappa or lambda light chain (i.e., they are polyclonal).24; 25; 26 Variants of IOI include those in which granulomatous inflammation predominates and mimics sarcoidosis27 and idiopathic sclerosing orbital inflammation that features dense fibrosis with a sparse inflammatory infiltrate.28; 29 Biopsy is important for confirming IOI in cases that are clinically and radiologically inconclusive and is essential to distinguish idiopathic sclerosing orbital inflammation from IgG4-related disease.30

Treatment of IOI usually begins with corticosteroids.1; 2 Almost all patients with idiopathic myositis respond to corticosteroid therapy, while about 80% of nonmyositic patients respond.2 Approximately one-half of those responding initially will relapse on tapering or ceasing steroid therapy.2 In patients with steroid non-responsive IOI, extensive disease, or recurrent IOI, alternatives include radiotherapy, immunosuppressive drugs, and/or surgical debulking.1; 2 The response of idiopathic sclerosing orbital inflammation to corticosteroids is much poorer than that of conventional IOI, and the sclerosing variant also does not respond well to radiotherapy.28

IOI with extraorbital extension is reported uncommonly, with extension due to bone erosion being about half as frequent as extension through orbital fissures and foramina (Tables 1 and 2). In 16 published reports of IOI accompanied by bone erosion, extraorbital extension of the inflammatory process was noted in all but the reports by Yan31 and Pimpha, Vahdani, and Kim.32 If my patient is included with the prior 16 reported cases of IOI with bone erosion, then the clinical and pathological features are as follows: 1) The male/female ratio = 9/8; 2) The age of the patients ranged from 4 years to 72 years with a mean ± 1 standard deviation of 43.1 ± 21.2 years; 3) The right orbit was involved in 10 patients, the left orbit in 6, and 1 patient had bilateral disease; 4) Using the anatomical classification scheme of Mombaerts, there were 15 cases of diffuse IOI involving more than one orbital structure, one case of idiopathic optic perineuritis,33 and one case of bilateral idiopathic dacryoadenitis;32 5) The most common symptoms and signs were proptosis (76%), pain (59%), periorbital swelling (41%), decreased vision (35%), diplopia (35%), ptosis (29%), and extraocular motility abnormalities (24%); 6) The duration between onset of symptoms/signs and diagnosis of bone erosion ranged from 0 to 29 years with a mean ± 1 standard deviation of 2.3 ± 7.0 years; 7) The histopathological description in four cases was of idiopathic sclerosing orbital pseudotumor, while 13 best fit conventional IOI; and 8) 76% of those treated with steroids responded, at least initially. Several features stand out if one compares these findings for patients with IOI having bone erosion with those cited previously for IOI without bone erosion. First, bone erosion occurs predominantly in diffuse IOI, whereas idiopathic dacryoadenitis and idiopathic myositis predominate in patients without bone erosion. Second, the duration between onset of symptoms and signs to diagnosis tended to be longer in patients with bone erosion than in those without erosion, though this is a “soft” finding since there is such great variability between patients in each group. However, it is not possible from these results to predict *a priori* which patient with diffuse IOI will exhibit bone erosion.

IOI with extraorbital extension in the absence of bone erosion has been reported more often than cases with bone erosion, but the number of published cases is still small. I identified 32 such cases, though I excluded several cases cited in other publications. I excluded from Table 2 a patient reported by Olmos et al. since their diagnosis was multifocal fibrosclerosis, and the cranial tumor occurred 7.5 years after apparently complete excision of the left orbital tumor.34 I also excluded from Table 2 the patients reported by Fortson and colleagues since one patient had orbital granulomatosis with polyangiitis (Wegener’s disease) while the other four had sinusitis clinically and there were no biopsies indicating extraorbital IOI.35 Finally, the recent paper by Raj et al. was excluded from Table 2 due to the diagnosis of orbital tuberculosis two months prior to the diagnosis of IOI.36 Based on case reports, extraorbital extension is rare, though Clifton and coworkers found extraorbital extension in CT scans of 8/90 (9%) of patients with biopsy confirmed IOI.37 The clinical and pathological features of the 32 patients in Table 2 can be summarized as follows, though complete data were not provided for all patients in all of the publications: 1) The male/female ratio = 17/15; 2) The age of the patients ranged from 5.5 years to 86 years with a mean ± 1 standard deviation of 46.8 ± 18.4 years; 3) The right orbit was involved in 11 patients, the left orbit in 13, and 3 patients had bilateral disease; 4) Using the anatomical classification scheme of Mombaerts, there were 23 cases of diffuse IOI involving more than one orbital structure and one case of idiopathic dacryoadenitis; 5) The most common symptoms and signs were proptosis (75%), pain or headache (69%), decreased vision (56%), extraocular motility abnormalities (40%), diplopia (22%), periorbital swelling (13%), and ptosis (13%); 6) The duration between onset of symptoms/signs and diagnosis of extraorbital extension ranged from 2 weeks to 6 years with a mean ± 1 standard deviation of 1.1 ± 1.5 years (n=25); 7) The histopathological description in three cases was of idiopathic sclerosing orbital pseudotumor, while 22 best fit conventional IOI and one was idiopathic dacryoadenitis; and 8) 71% of those treated with steroids responded, at least initially. As was the situation for IOI patients having bone erosion, most of the IOI patients having extraorbital extension have diffuse IOI instead of the more common idiopathic dacryoadenitis and idiopathic myositis. Similar to patients with IOI and bone erosion, these data do not provide a way to predict which patients with diffuse IOI will develop extraorbital extension.

The mechanism by which IOI results in bone erosion is not known, but I postulate that it is an example of “inflammatory osteolysis” during which cytokines produced by inflammatory cells stimulate osteoclastic activity and thus bone resorption. Macrophages and lymphocytes produce cytokines that can stimulate (macrophage colony stimulating factor, tumor necrosis factor-α, RANKL, interleukin [IL]-6, IL-17, and IL-1β) or inhibit (osteoprotegerin, IL-4, and IL-10) osteoclast formation and differentiation into resorbing osteoclasts, with the balance between stimulatory and inhibitory cytokines being critical for inflammatory osteolysis.38 Why this balance in cytokines should be disturbed to favor osteolysis in only a minority of patients with IOI is unclear. Similarly, a shifted balance in the cytokines may explain why other patients with IOI exhibit bone sclerosis.39

1. **Conclusion**

Bone erosion is a rare manifestation of IOI, and it occurs mostly in patients with the diffuse form of the disease. I could not identify and clinical or histopathological features predictive of bone erosion based on a review of the literature. The response to corticosteroid therapy is similar to that for diffuse IOI without bone erosion. I postulate that bone erosion is a manifestation of inflammatory osteolysis.

1. **Method of literature search**

Literature search was completed using Google Scholar with the following search terms and combinations: “orbital pseudotumor + extraorbital extension,” “orbital pseudotumor + bone erosion,” “orbital pseudotumor + intracranial extension,” “orbital pseudotumor + review,” “idiopathic orbital inflammation + extraorbital extension,” “idiopathic orbital inflammation + extension,” “idiopathic orbital inflammation + bone erosion,” “idiopathic orbital inflammation + intracranial extension,” and “idiopathic orbital inflammation + review.” In addition, the “cited by” and “related articles” features of Google Scholar were used for selected articles to locate more recent or overlooked papers. The Google Scholar searches did not include any language or date restrictions. The publication list for each of the references was searched for prior publications related to extraorbital extension and/or bone erosion in patients with idiopathic orbital inflammation.

1. **Disclosures**

There are no disclosures to report.

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**Material Distributed**

1 Protocol

1 Slide of the right orbital inflammatory pseudotumor stained with hematoxylin & eosin

**Table 1: Cases of idiopathic orbital inflammatory pseudotumor with bone erosion and extraorbital extension**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **Year** | **Reference** | **Age** | **Sex** | **Side** | **Major symptoms and signs** | **Orbital location** | **Bone erosion/time****interval\*** | **Extraorbital extension** | **Histopathology** | **Treatment** **And Response** |
| 1 | 1982 | Edwards et al.40 | 32 | F | O.S. | Proptosis | Medial | Lamina papyracea/4 years | Ethmoid sinus | “Non-specific inflammatory granulomatous process” | Complete response to steroids with resolution of mass |
| 2 | 1984 | Kaye et al.41 | 71 | M | O.D. | Swelling, increased lacrimation, orbital mass, slight proptosis | Superior-medial  | Right and left lamina papyracea, cribriform plate/1 year | Right and left ethmoid sinuses, anterior cranial fossa  | Lymphocytes, plasma cells, and macrophages, embedded in fibrous stroma | Slight temporary decrease in mass size following steroids, radiotherapy, and immunosuppressive therapy. Developed hydrocephalus, dementia, difficulty walking. |
| 3 | 1986 | Frohman et al.42 | 72 | M | O.D. | Loss of vision, pain, decreased sensation, ptosis | Apex | Medial cortex of anterior clinoid/4 weeks | Superior orbital fissure, sphenoid sinus | Fibroblasts, histiocytes, acute and chronic inflammatory cells, plasma cells | Progression by CT scan following steroids. No further progression and relief of pain after radiotherapy. |
| 4 | 1986 | Frohman et al.42 | 48 | M | O.S. | Proptosis | Posterior- lateral | Lateral wall of sphenoid sinus/1.75 years | Superior orbital fissure, optic canal, sphenoid sinus | Dense collagenous tissue with focal lymphocytes and plasma cells | Return of vison within 48 hours of steroid therapy. |
| 5 | 1986 | Frohman et al.42 | 48 | F | O.D. | Proptosis | Complete orbit | Right sphenoid bone, right lamina papyracea/29 years | Cavernous sinus, ethmoid sinus, middle cranial fossa | Dense collagenous tissue with focal lymphocytes and plasma cells | “Symptomatic relief” with steroid therapy. |
| 6 | 1986 | Noble et al.33 | 46 | F | O.S. | Decreased vision, ptosis, afferent pupillary defect, no light perception | Optic foramen | Sphenoid bone/4 weeks | Sphenoid sinus (later into middle cranial fossa and meninges) | Acute and chronic inflammation with numerous plasma cells and lymphocytes | No response to steroid therapy for treatment of third recurrence. Forth recurrence treated with radiotherapy but no follow-up provided. |
| 7 | 1991 | McNicholaset al.43 | 67 | M | O.S. | Malaise, pain, diplopia, decreased vision, proptosis | Posterior | Lamina papyracea, superior orbital fissure, sphenoid bone/4 months | Ethmoid sinus, cavernous sinus, middle cranial fossa | “Inflammatory pseudotumor” | “Good symptomatic improvement” with steroids, but lesion recurred. Complete regression of mass with radiotherapy, but no recovery of vision. |
| 8 | 1992 | Whyte et al.44 | 71 | F | O.D. | Pain, diplopia, decreased vision, proptosis, palpable mass in orbit, chemosis, abnormal eye movement | Inferior-lateral  | Zygomatic bone/3 months | Maxillary sinus, deep temporal fossa | Granulomatous inflammation with foci of central necrosis, non-necrotizing vasculitis, acid fast and fungal stains  | Rapid symptomatic relief followed by recurrent proptosis. Recurrent proptosis resolved with radiotherapy, and no proptosis, diplopia, or pain with maintenance on 10 mg prednisone daily. |
| 9 | 2003 | Cruz et al.45 | 35 | M | O.D. | Pain, diplopia, proptosis, hyperglobus, marked restriction on downgaze | Inferior | Sphenoid bone/1 month | Inferior orbital fissure, infratemporal fossa, pterygopalatine fossa | Dense collagenous tissue with sparse lymphocytes | Improved ocular motility and relief of symptoms with combined steroids and radiotherapy. |
| 10 | 2006 | Zborowska et al.46 | 32 | M | O.S. | Retroorbital pain, rapid decrease in vision, proptosis, hyperglobus | Inferior | Orbital floor/at presentation | Pterygopalatine fossa, parasellar region of middle cranial fossa, sphenoid sinus and adjacent medial aspect of left temporal lobe, infratemporal fossa, left cavernous sinus, pituitary fossa, edge of tentorium | Chronic inflammation with prominent fibrosis | Initial improvement in vision on steroids, then relapse. Regression in size of mass using cyclophosphamide and dexamethasone. Symptom free with unchanged clinical signs at 2 years. |
| 11 | 2006 | Zborowska et al.46 | 48 | F | O.D. | Retrobulbar pain, diplopia, ptosis, mild periorbital swelling, proptosis, medial globe displacement, afferent pupillary defect, limitations in eye movement | Lateral and superior rectus muscles, lacrimal gland, lateral and superior intraconal fat | Posterior portion of greater wing of sphenoid, early erosion of orbital roof/4 months | Superior orbital fissure, middle cranial fossa, anterior cavernous sinus | Sclerosis with paucicellular infiltrate of lymphocytes and histiocytes | Complete resolution with steroids, cyclosporine, and cyclophosphamide. No clinical evidence of recurrence at 2 years. |
| 12 | 2012 | Shinder at al.47 | 18 | M | O.D. | Pain, diplopia, ptosis, decreased vision, proptosis, hyperglobus, facial anesthesia involving V1, V2, V3, limited eye movements, tenderness in lacrimal fossa, choroidal folds | Lacrimal fossa, orbital apex | Medial wall of maxillary sinus/6 weeks | Maxillary sinus | Mixed chronic inflammatory cells with large fibrotic component | Subjective improvement on steroids but flare on taper. Improvement in vision, ocular movement, diplopia, and hyperglobus with methotrexate and prednisone. Proptosis stable at 15 months. |
| 13 | 2012 | Shinder at al.47 | 5 | F | O.D. | Pain, periorbital swelling, proptosis, ptosis, diplopia in up- and down gaze, diminished supra- and infraduction, firm mass in temporal and lacrimal fossae | Superior lateral orbit | Lateral orbital wall (zygomatic bone)/3 months | Temporalis muscle | Chronic inflammatory cells with fibrotic bands | Improvement in vision, pain, ocular movements, diplopia, proptosis, and ptosis on steroids. Almost complete resolution of lesion on CT scan after 5 months. |
| 14 | 2013 | Balci et al.48 | 4 | M | O.D. | Periorbital swelling, ptosis | Lateral | Zygomatic bone/2 months | Temporal fossa | Fine needle biopsy: chronic inflammation with predominance of eosinophils | Rapid relief of pain and decrease in swelling on prednisolone. Resolution of mass and repair of bone destruction by CT at 6 months. |
| 15 | 2016 | Yan31 | 56 | M | O.S. | Proptosis, limited left adduction | Lateral and inferior orbit | Lateral and inferior walls of orbit/6 months | None reported | Infiltrate of lymphocytes and plasma cells | Dramatic improvement in proptosis and ocular movement with dexamethasone followed by prednisone. No recurrence at 6 years. |
| 16 | 2018 | Pimpha, et al.32 | 44 | F | O.D., O.S. | Bilateral periorbital pain and tenderness, swelling, and erythema, diplopia on extremes of gaze | Lateral orbit and lacrimal glands, bilaterally | Lateral orbital wall adjacent to lacrimal glands, bilaterally/7 months | None | Lacrimal gland with chronic inflammation with multifocal lymphoid follicles, no fibrosis | Improvement in symptoms and signs with prednisolone. Resolution of lateral wall bony erosions and decreased size of lacrimal glands on CT scan 2 years later. Asymptomatic at 3 years with no recurrence. |
| 17 | 2018 | Present case | 36 | F | O.D. | Tearing, itching, photophobia, diplopia, pain during eye movement, swelling of right and left upper eyelids, proptosis O.D. | Medial and inferior with extension to orbital apex | Orbital floor, lamina papyracea/4 months | Maxillary and ethmoid sinuses | Polyclonal lymphoplasmacytic infiltrate with areas of marked fibrosis | Treated with surgical debulking, oral prednisone, and retrobulbar triamcinolone injection; symptoms stable with improved proptosis at 2 months |

Note: \* indicates the interval between onset of symptoms or signs and the diagnosis of bone erosion

**Table 2: Cases of idiopathic orbital inflammatory pseudotumor with extraorbital extension without erosion though the bone**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **Year** | **Reference** | **Age** | **Sex** | **Side** | **Major symptoms and signs** | **Orbital location** | **Extraorbital extension/time interval\*** | **Histopathology** | **Treatment****And Response**  |
| 1 | 1958 | Jackson49 | 25 | F | O.D. | Pain, proptosis, ptosis  | Posterior | Sphenoidal fissure, meninges, middle fossa/5 months | “Round cells”, plasma cells, neutrophils | No treatment reported |
| 2 | 1981 | Eshaghian and Anderson50 | 41 | M | O.D. | Vertical diplopia, proptosis, palpable mass in orbit | Inferior | Right maxillary sinus via communicating vessels/2 weeks | “Mainly histiocytes” | Prednisone stopped due to nervousness and stomach upset). “Done well” at 18 months. |
| 3 | 1981 | Eshaghian and Anderson50 | 40 | F | O.S. | Intermittent sharp pain, proptosis, abnormal eye movement | Medial superior  | Ethmoid sinus/2 months | “Mainly lymphocytes and plasma cells” | Resolution of proptosis and extraocular motility problems on steroids with complete response at 14 months. |
| 4 | 1982 | Edwards et al.40 | 73 | F | O.S. | Diplopia, discomfort in maxillary nerve distribution, proptosis | Inferior | Infraorbital fissure and foramen/1 year | Granulomatous inflammation (maxillary nerve biopsy) | No improvement on steroids, and no outcome reported. |
| 5 | 1988 | Pillai and Saini51 | 5.5 | F | O.D., O.S. | Bilateral proptosis | Inferior and medial | Right and left ethmoid and maxillary sinuses/5 months | Fibrous tissue, lymphocytes, macrophages, plasma cells, “few” eosinophils | No response to steroids, and no outcome reported. |
| 6 | 1991 | McNicholas et al.43 | 43 | F | Not reported |  Headache, orbital pain, extraocular muscle palsies | Posterior | Superior orbital fissure/not reported | No biopsy | “Responded” to steroids with no recurrence. |
| 7 | 1991 | McNicholas et al.43 | 67 | F | Not reported | Headache, orbital pain, reduced vision, extraocular muscle palsies | Posterior | Cavernous sinus/not reported | No biopsy | Responded to steroids with significantly improved vision and no recurrence of mass. |
| 8 | 1992 | Clifton et al.37 | 49 | M | O.D. | Decreased vision, pain, proptosis, papilledema, cranial nerve 3,4, 6 palsies | Not reported | Superior orbital fissure, middle cranial fossa, cavernous sinus/1 year | “Non-specific inflammatory tissue and/or fibrosis” | Good response to steroids. |
| 9 | 1992 | Clifton et al.37 | 69 | M | O.D. | Decreased vision, proptosis, cranial nerve 3,4, 6 palsies | Not reported | Superior orbital fissure, middle cranial fossa/7 months | “Non-specific inflammatory tissue and/or fibrosis” | No treatment reported.  |
| 10 | 1992 | Clifton et al.37 | 54 | F | O.S. | Decreased vision, pain, proptosis, cranial nerve 6 palsy | Not reported | Superior orbital fissure, middle cranial fossa, cavernous sinus/3 years | “Non-specific inflammatory tissue and/or fibrosis” | No treatment reported.  |
| 11 | 1992 | Clifton et al.37 | 36 | M | Not reported | Decreased vision, pain, proptosis | Not reported | Superior orbital fissure, middle cranial fossa/1 month | “Non-specific inflammatory tissue and/or fibrosis” | No treatment reported.  |
| 12 | 1992 | Clifton et al.37 | 86 | M | O.D., O.S. | Decreased vision, pain, proptosis, bilateral papilledema, right cranial nerve 3, 4, and 6 palsies | Not reported | Superior orbital fissure, middle cranial fossa, cavernous sinus, meninges/18 months | “Non-specific inflammatory tissue and/or fibrosis” | Poor response to steroids. |
| 13 | 1992 | Clifton et al.37 | 71 | F | Not reported | Decreased vision, pain, proptosis | Not reported | Superior orbital fissure, middle cranial fossa, cavernous sinus/6 years | “Non-specific inflammatory tissue and/or fibrosis” | No treatment reported.  |
| 14 | 1992 | Clifton et al.37 | 30 | M | O.S. | Decreased vision, pain, proptosis, papilledema, left cranial nerve 3, 4, 5, and 6 palsies | Not reported | Superior orbital fissure, middle cranial fossa, cavernous sinus, meninges/1 month | “Non-specific inflammatory tissue and/or fibrosis” | Good response to steroids initially but then deteriorated. |
| 15 | 1992 | Clifton et al.37 | 61 | M | Not reported | Decreased vision, pain, proptosis, pale optic discs | Not reported | Superior orbital fissure, middle cranial fossa, cavernous sinus/1 year | “Non-specific inflammatory tissue and/or fibrosis” | Poor response to steroids. |
| 16 | 1993 | Bencherif, et al.52 | 23 | M | O.S. | Asthenia, diplopia, proptosis, complete ophthalmoplegia | Superior-temporal | Superior orbital fissure, left frontotemporal dura, lateral wall of cavernous sinus, inferior orbital fissure (probable), pterygopalatine fossa, infratemporal fossa/8 months | Fibrocollagenous stroma with mononuclear cells surrounding lacrimal gland acini | Dramatic reduction of proptosis and ophthalmoplegia on steroids. Disease free at one month follow-up. |
| 17 | 1996 | De Jesus et al.53 | 16 | F | O.S. | Decreased vision, diplopia, proptosis, ptosis | Superolateral-posterior | Optic canal, superior orbital fissure, middle cranial fossa/1 year and a few months | Lymphocytes, plasma cells, histiocytes, neutrophils, eosinophils, “some areas of necrosis” | Poor response to steroids. Complete resolution of headache and reduced proptosis with radiotherapy. |
| 18 | 2003 | Charles and Turbin54 | 36 | F | O.S. | Blindness, proptosis, immobile left eye, disc pallor | Diffuse | Left skull base (middle cranial fossa), right orbit/2 years | Fibrous tissue with scant, patchy infiltrate of lymphocytes and plasma cells | No progression with combined steroids and radiotherapy |
| 19 | 2003 | Cruz et al.45 | 56 | F | O.D. | Diplopia, pain, proptosis, limited adduction and abduction, painful mass in right temporal fossa | Lateral | Inferior orbital fissure, inferotemporal and temporal fossae/5 months | Dense collagenous tissue, lymphocytes, occasional lymphoid follicles | Reduced pain, improved ocular motility, and reduced size of orbital and temporal fossa masses on steroids. |
| 20 | 2004 | Mahr et al.55 | 40 | M | O.D. | Pain, proptosis, diplopia | Medial rectus muscle, orbital apex | Tip of right temporal lobe dura/15 months | Dense fibrous connective tissue with chronic inflammation and polyclonal lymphocytes | Symptomatic relief with intramuscular steroids followed by recurrence. Then symptom free and normal CT scan after 9 years. |
| 21 | 2004 | Mahr et al.55 | 41 | M | O.S. | proptosis, no light perception, afferent pupillary block, abduction weakness, optic nerve pallor | Orbital apex | Optic foramen, medial to left anterior clinoid process/8 months | Lymphocytes and plasma cells | No non-surgical treatment, but patient asymptomatic 4 months later with decreased proptosis. |
| 22 | 2004 | Mahr et al.55 | 60 | M | O.D. | Horizontal diplopia, proptosis, hyperglobus, lateral displacement of globe, mild edema of upper and lower eyelids, limited duction in downgaze | Inferior orbit centered in periorbita | Right maxillary sinus/1 month | “Mixed chronic inflammation and fibrosis”, polyclonal lymphocytes  | No treatment but patient with 4-prism diopter exotropia and decreased proptosis 4 months later |
| 23 | 2004 | Mahr et al.55 | 73 | F | O.D. | Right-sided facial pain, blurry vision in right eye 5 years later, afferent pupillary defect, slightly decreased ductions in all directions of gaze except laterally, slight ptosis, severe swelling of optic disc | Lacrimal gland | (Inflammatory pseudotumor of Meckel’s cave 5 years before vision blurring), optic nerve sheath, perineural and perivascular areas of upper portion of cavernous sinus/5 years  | Polyclonal chronic lymphocytic infiltrate | Relief of facial pain with steroids, but MRI unchanged. |
| 24 | 2005 | Lee et al.56 | 58 | M | O.S. | Facial pain, diplopia, decreased vision | Diffuse | Superior orbital fissure, cavernous sinus, middle cranial fossa/”chronic” | Not reported | “Yes” for response to steroids. |
| 25 | 2005 | Lee et al.56 | 63 | M | O.D., O.S. | Facial pain, decreased vision, proptosis | Diffuse | Inferior and superior orbital fissures, foramen rotundum, pterygopalatine fossa, inferotemporal fossa, infraorbital foramen/“chronic” | Chronic inflammatory cells with fibrosis | “Yes” for response to steroids. |
| 26 | 2005 | Lee et al.56 | 55 | M | O.S. | Diplopia, decreased vision, proptosis | Orbital apex | Inferior and superior orbital fissures, optic canal, cavernous sinus, middle cranial fossa, pterygopalatine fossa, inferotemporal fossa, paranasal sinus, petrous apex, clivus, Meckel’s cave/“chronic” | Not reported | “Yes” for response to steroids. |
| 27 | 2005 | Lee et al.56 | 32 | M | O.S. | Headache, diplopia, decreased vision | Orbital apex | Superior orbital fissure, cavernous sinus, middle cranial fossa/“chronic” |  Not reported | “Yes” for response to steroids. |
| 28 | 2005 | Lee et al.56 | 46 | M | O.D. | Facial pain, diplopia, proptosis | Orbital apex, myositis | Superior orbital fissure, cavernous sinus, middle cranial fossa, petrous apex, clivus, Meckel’s cave/“chronic” | Chronic inflammatory cells with fibrosis | “Yes” for response to steroids. |
| 29 | 2006 | Zborowska et al.46 | 45 | F | O.S. | Retroorbital pain, facial numbness 6 months later | Lateral wall | Infratemporal fossa, pterygopalatine fossa, lateral cavernous sinus, Meckel’s cave, dura of temporal lobe/6 months | Sclerotic fibrous tissue with patchy infiltrate of polyclonal lymphocytes and plasms cells | Relief of retroorbital pain with recurrence on steroid taper, then regression of symptoms on prednisone + azathioprine. Patient free of symptoms at 2 years. |
| 30 | 2006 | Zborowska et al.46 | 30 | F | O.D. | chemotic and injected eye, proptosis, ptosis, and diffuse scleritis 4 weeks later, subsequent right eye paresis | Lacrimal gland, right superior-temporal sclera, lateral rectus muscle | Inferior orbital fissure/4 weeks | Lymphocytes, neutrophils, occasional eosinophils and histiocytes, lymphoid follicles | No improvement on steroids alone. Relief of pain with azathioprine + prednisolone. Gradual symptom relief with decreased size of lacrimal mass using radiotherapy. Proptosis regressed but no recovery of vision or eye movement. |
| 31 | 2010 | Orgaz et al.57 | 37 | M | O.D. | Epiphora, upper eyelid swelling, ptosis, mild orbital pain, ptosis, upper eyelid edema, mechanical ptosis | Inferior-nasal, medial and inferior rectus muscles | Nasal cavity up to inferior nasal concha, maxillary sinus, ethmoid sinus/­­6 months | Dense collagenous tissue with sparse infiltrate of lymphocytes, neutrophils, occasional eosinophils, and histiocytes | No recurrence after surgical debulking and oral prednisolone. No clinical evidence of recurrence at 1 year |
| 32 | 2012 | Shinder at al.47 | 35 | F | O.S. | Periorbital pain and erythema, proptosis, hyperglobus | Inferior to inferior and middle rectus muscles | Maxillary sinus/5 months | Chronic inflammation and fibrosis | Complete resolution of signs and symptoms on prednisone with radiographic resolution of mass at 26 months. |

Note: \* indicates the interval between onset of symptoms or signs and the diagnosis of extraorbital extension

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