Idiopathic Orbital Inflammation

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2.1 Background

Idiopathic orbital inflammation is a noninfectious, inflammatory process of the extraocular orbit and adnexa without underlying local or systemic etiology. It is a diagnosis of exclusion after neoplasm, infection, and systemic inflammatory disorders have been ruled out. It was first described by Gleason in 1903 and characterized as a distinct entity with the name of orbital pseudotumor by Birch-Hirschfeld in 1905 [1, 2]. Over the years, besides orbital pseudotumor other names such as nonspecific orbital inflammation, orbital inflammatory pseudotumor, and orbital inflammatory syndrome have also been used.

Depending on the origin of the study, idiopathic orbital inflammation constitutes 5–18 % of all orbital space-occupying lesions [3–5]. A review of 1,795 consecutive orbital tumors from Mayo Clinic showed that 8 % of all orbital tumors were inflammatory [6]. It was the third common orbital tumor followed by carcinoma and lymphoid tumors [6]. Similarly, in a review of 1,264 orbital tumors and simulating lesions that presented to Wills Eye Hospital over a 30-year period, 11 % of tumors were inflammatory lesions [3]. It was the second most common orbital lesion followed by lymphoid tumor.

2.2 Clinical Features

Idiopathic orbital inflammation mostly involves middle-aged people although it can affect any race, age, and sex. The only exception is that myositis and trochleitis, subtypes of idiopathic orbital inflammation, were found to be more common in females [7–10]. Pediatric cases make up 6–17 % of all cases of idiopathic orbital inflammation [4, 5]. Idiopathic orbital inflammation is usually a unilateral disease with almost equal involvement of the right and left orbits [11]. About a quarter of patients have bilateral disease [11]. A review of 209 patients from China showed that the mean age of the patients was 44 years (range 4–80 years). The right orbit was involved in 43 % of patients and the left orbit in 39 %, and both orbits were involved in 19 % of patients [12]. Clinical presentation of idiopathic orbital inflammation differs between children and adults. In children, bilateral involvement and associated systemic symptoms such as fever, malaise, lymphadenopathy, optic disk edema, uveitis, and tissue and peripheral blood eosinophilia are more common [13, 14]. Lacrimal gland enlargement or dacryoadenitis is the most common form of orbital inflammation in children [15].

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Idiopathic orbital inflammation can have acute, subacute, or chronic presentation based on the onset and duration of symptoms [16]. Although presenting signs may change depending on the involved orbital structure(s), patients often present with periocular pain, periorbital edema and erythema, conjunctival injection, chemosis, proptosis, ptosis, diplopia, and pain with eye movements [16–19]. Pain is the most common symptom seen in 58–69 % of patients, followed by diplopia in 31–38 % of patients [4, 20]. Periorbital swelling is the most common sign seen in 75–79 % of patients, followed by proptosis in 32–63 %, restriction in extraocular motility in 54 %, conjunctival hyperemia in 48 %, chemosis in 29 %, decreased vision in 21 %, and ptosis in 17 % of patients [4, 20]. So, the patients with idiopathic orbital inflammation should evaluate a detailed eye examination, including visual acuity, orbital and external eye examinations, slit lamp examination, and detailed eye examination.

Patients with acute presentation have predominantly inflammatory signs such as pain, periorbital edema, and erythema. Patients with subacute and chronic presentation have predominantly mass effect such as proptosis, limitation in extraocular motility, and vertical globe displacement. The amount of proptosis might change according to the degree of inflammation, fibrosis, and mass effect. Idiopathic orbital inflammation can affect the orbit, as local, encapsulated mass or diffuse inflammation, or any tissue in the orbit including the lacrimal gland, extraocular muscle, sclera, or trochlea or around the optic nerve. In Tolosa-Hunt syndrome or orbital apex syndrome when the inflammation involves the orbital apex as well as cavernous sinus and superior orbital fissure, patients present with severe, unilateral headache with extraocular palsies, involving the third, fourth, fifth, and sixth cranial nerves. A review of 132 patients with idiopathic orbital inflammation showed that diffuse inflammatory process was the most frequent presentation in 40 patients (30 %) followed by myositis in 21 patients (16 %), dacryoadenitis in 14 patients (11 %), focal encapsulated inflammatory process in 5 patients (4 %), Tolosa-Hunt syndrome in 2 patients (2 %), perineuritis in 1 patient (1 %), and scleritis in 1 patient (1 %) [21]. Extraorbital extension of inflammation is rare but has been reported to occur into the intracranial cavity, paranasal sinuses, and pterygopalatine fossa and is best evaluated with an imaging study like computed tomography or magnetic resonance imaging [21–29].

2.3 Classification

Several classifications have been used for idiopathic orbital inflammation based on the onset of inflammation, involved orbital structures, and pathologic features [30]. Idiopathic orbital inflammation is classified into acute, subacute, and chronic forms based on the onset of the inflammation [30]. If the onset of symptoms is less than 2 weeks, it is classified as acute idiopathic orbital inflammation. If it is between 2 and 4 weeks, it is subacute idiopathic orbital inflammation, and if it is more than 4 weeks, then it is chronic idiopathic orbital inflammation. Idiopathic orbital inflammation is classified as dacryoadenitis when it involved the lacrimal gland, myositis when it involved the extraocular muscle or muscles, scleritis when it involved the sclera, optic neuritis when it involved the optic nerve, Tolosa-Hunt syndrome when it involved the superior orbital fissure, and cavernous sinus or diffuse orbital inflammation when it diffusely involved the orbital tissue [30]. Depending on the pathologic features, it is classified as predominantly lymphoid, granulomatous, sclerosing, eosinophilic, and vasculitic inflammation [30]. Bijlsma et al. [31] evaluated the classification systems of IOI in 84 patients and concluded that classification systems based on histopathology and localization showed good reliability, were easy to apply, and described the biologic process.

2.4 Pathophysiology

The etiology and pathogenesis of idiopathic orbital inflammation is unknown. Orbital myositis and dacryoadenitis have been reported to start simultaneously or within several weeks of streptococcal pharyngitis, Lyme disease, and herpes

zoster ophthalmicus in several case reports [32–35]. Mollicutes are cell wall-deficient bacteria and found in cases with chronic uveitis. Wirostko et al. [36] proposed that parasitizing followed by destruction of orbital leukocytes by mollicute-like organisms led to vasculitis, tissue lysis, lymphoid infiltrates, and granuloma formation.

Orbital inflammation has been observed in rheumatologic conditions like Crohn's disease, systemic lupus erythematous, rheumatoid arthritis, myasthenia gravis, and ankylosing spondylitis. In a series of idiopathic orbital inflammation and refractory ocular inflammation, coinciding rheumatologic or autoimmune disease has been present between 10 and 78 % of cases [37, 38]. Similarly, circulating autoantibodies against eye muscle membrane proteins of 55 and 64 kilodaltons were seen in 63 % of orbital myositis patients compared to 16–20 % of healthy people [39]. However, unilateral presentation and limited muscle involvement argue against the role of circulating autoantibodies in idiopathic orbital inflammation. Mottow-Lippe et al. [14] suggested that the release of circulating antigens caused by local vascular permeability triggered an inflammatory response in the orbit. They proposed that the network of connective tissue and capillaries in the orbit played a role in delivering antigenic agents to different orbital structures and hence different clinical presentations.

Studies evaluating molecular biologic environment of idiopathic orbital inflammation showed that interleukin-2, interleukin-8, interleukin-10, interleukin-12, gamma interferon, and tumor necrosis factor alpha were significantly elevated in the orbital tissue of idiopathic orbital inflammation patients compared to normal orbital tissue [40]. Among these, gamma interferon and interleukin-12 were expressed ten times higher concentrations than normal controls. Interleukin-12, produced by antigen-producing cells, promotes the production of Th1 cells and induces the production of interferon gamma, the chief product of Th1 cells. TNF-alpha is a critical mediator of induction of Th1 response. These suggest that Th1 pathway plays an important role in the pathogenesis of idiopathic orbital inflammation. Later, same authors reported that Toll-like receptors (TLR) especially TLR2 were markedly expressed in idiopathic orbital inflammation [41]. TLRs are receptors that are usually expressed in macrophages and dendritic cells, which are part of the innate immune system.

2.5 Diagnosis

By definition, idiopathic orbital inflammation is a diagnosis of exclusion. The patients with idiopathic orbital inflammation need systemic evaluation to exclude the other local and systemic causes of orbital inflammation. In the history, the presence of similar previous episodes, trauma, infection, systemic or immunocompromised conditions, and duration of symptoms need to be evaluated. As a part of systemic work-up, imaging of the orbit with computed tomography or magnetic resonance imaging, chest X-ray, complete blood count, angiotensin-converting enzyme and lysozyme levels, cytoplasmic and perinuclear antineutrophil cytoplasmic antibody, rapid plasma regain test, and thyroid function studies – T3, T4, thyroid-stimulating hormone, thyroid-stimulating immunoglobulin, and thyrotropin receptor antibody – should be ordered [4].

Computed imaging (CT) is the first choice of orbital imaging. On CT, idiopathic orbital inflammation shows diffuse homogenous involvement of the orbital soft tissue or homogenous enlargement of the involved orbital tissue such as the extraocular muscles, lacrimal gland, sclera, optic nerve sheath, or trochlea. The involved tissue demonstrates enhancement with contrast in computed tomography and has irregular borders. CT features might change from subtle infiltrative changes affecting specific orbital structures to almost complete orbit involvement [42]. There is usually no bony erosion, and if any bony erosion is seen, alternative etiologies should be in the differential diagnosis. Magnetic resonance imaging (MRI) and orbital ultrasonography may also be used as adjunct diagnostic imaging tools. On MRI, orbital inflammation appears as homogenous orbital mass that is isointense to extraocular muscles on T1- and T2-weighted images, while orbital cellulitis

appears hyperintense to extraocular muscles [18]. There is homogenous enhancement of the involved tissue with gadolinium. Diffusion-weighted imaging of MRI showed significant difference in image intensity and apparent diffusion coefficients between orbital lymphoid lesions, orbital cellulitis, and idiopathic orbital inflammation [43]. Orbital lymphoid lesions were the brightest followed by idiopathic orbital inflammation and orbital cellulitis. Traditionally, homogenous enlargement of the extraocular muscle with tendon involvement on imaging studies has been used to differentiate idiopathic orbital inflammation from Graves' eye disease because the tendon is typically spared in Graves' eye disease [44]. However, occasional tendon involvement was reported in Graves' eye disease, especially in the patients with primary gaze diplopia [44]. Ultrasonography is helpful in the evaluation of swelling around the sclera and optic nerve that appears as a "T sign" in scleritis or at the tendon of extraocular muscles [18].

The diagnosis of idiopathic orbital inflammation is usually based on clinical and radiologic findings; however, biopsy is required to confirm the diagnosis histopathologically and to exclude other possible diseases. In the past, some authors proposed that biopsy was not required for the diagnosis of idiopathic orbital inflammation [45, 46]. The relief of signs and symptoms by systemic corticosteroids was used to confirm the initial clinical diagnosis. However, the clinical and radiologic features of idiopathic orbital inflammation are not specific. Orbital tumors such as lymphoma or orbital involvement in systemic inflammatory disorders may have similar clinical and radiologic features, and they can regress in response to systemic corticosteroid. The biopsy should be performed before any therapy, because any form of immunosuppressive treatment might change the histopathologic features, making the diagnosis difficult.

2.6 Histopathology

On histopathologic examination, idiopathic orbital inflammation shows an infiltrate of inflammatory cells mainly of small, well-differentiated mature lymphocytes, admixed with plasma cells, neutrophils, eosinophils, and occasionally macrophages and histiocytes [30, 47]. When infiltrated lymphocytes are assessed, T lymphocytes outnumber the B lymphocytes, and T-helper cells are predominant over T-suppressor cells [30, 48]. B and T lymphocytes are immunophenotypically polyclonal. On immunohistochemistry, orbital inflammation tissue showed strong expression of B-cell marker CD20 in 5–25 % of lymphocytes, moderate expression of another B-cell marker CD22 in 2–70 % of lymphocytes, strong expression of a B-cell and dendritic cell marker CD23 in 5 % of dendritic cells, strong expression of an interleukin-2 receptor marker CD25 found on the activated T and B cells in 10–60 % of lymphocytes, and moderate expression of T-cell marker CD3 in 60 % of lymphocytes [49].

Histopathologic features vary depending on the stages of inflammation. In acute stages of inflammation, lymphocytes, plasma cells, and eosinophils are more numerous, while with chronic disease, lymphocytes, plasma cells, and occasionally macrophages predominate with increasing fibrosis among cells and along the septa, radiating into the orbital fat [50]. There are always associated stromal changes, including edema in acute inflammation and proliferative fibrosis, sclerosis, and hyalinization in chronic inflammation. Previously, fibrosis/sclerosis was thought to be the result of severe and long-standing inflammation; however, the sclerosing form of idiopathic orbital inflammation showed that fibrosis is an immune-mediated process with fibrosis in early stages of inflammation [51]. The presence of eosinophils and its cytotoxic contents in the fibrosis areas suggest that they play a role in the formation of fibrosis [52]. Orbital fat is infiltrated by lymphocytes and plasma cells, appearing as a mixed inflammatory infiltrate with increased fibrous tissue, and the orbital septa are thickened because of the increased fibroblastic tissue. Lymphoid follicles with reactive germinal center can be seen in varying amounts. Perivasculitis or angiocentric lymphocytic cuffing is the most common vascular change due to concentration of lymphocytes, occasionally plasma cells and eosinophils in the immediate

adventitial area of the capillaries and postcapillary venules [30, 50].

Histopathologically, subtypes of idiopathic orbital inflammation include lymphocytic, granulomatous, sclerosing, and vasculitic or eosinophilic. Granulomatous idiopathic orbital inflammation is rare and presents in a spectrum of histopathologic spectrum, including non-necrotizing foreign body type granulomas, lipogranulomatous inflammation and variable sclerosis [53, 54]. In idiopathic sclerosing orbital inflammation, sclerosis and hyalinization predominate with paucity of inflammatory cells consisting of predominantly T lymphocytes, few eosinophils, histiocytes, and plasma cells [51, 55]. It is a distinct clinical entity and represents about 8 % of all inflammatory lesions of the orbit [51]. Idiopathic sclerosing orbital inflammation might be associated with other fibrosclerosing disorders such as retroperitoneal fibrosis, Riedel's thyroiditis, mesenteritis, sclerosing cholangitis, and mediastinal fibrosis [48, 56–59]. It has a slow progression and may result in worse visual outcome due to response to conventional treatment [16, 60, 61]. It usually requires more aggressive and prolonged treatment [16, 55]. In these patients, an immunosuppressive agent might be needed in addition to the systemic corticosteroid. A review of the literature showed that 67 % of cases with idiopathic sclerosing orbital pseudotumor involved the anterior orbital and lacrimal gland, 56 % midorbit, and 51 % posterior orbit and extraocular muscles [55]. The most commonly involved quadrant was lateral and/or superior in 54 % of cases. Corticosteroid alone or in combination with other modalities was the most common choice of treatment. Treatment outcome for steroid alone was good in 43 % of cases, partial in 24 %, and poor in 33 % of cases. The overall response, regardless of treatment regimen, was good in 31 %, partial in 39 %, and poor in 21 % of cases.

When the lacrimal gland is involved, focal aggregates and follicles of lymphocytes and plasma cells are observed. Periductal and periacinar fibrosis, ductal dilatation, acinar atrophy, and thickened interlobular tissue septa separating the lobules are the features of lacrimal gland involvement. In myositis, the muscle fibers are swollen and infiltrated with lymphocytes and plasma cells in a diffuse or multifocal pattern and separated by edema and fibrosis.

2.7 Differential Diagnosis

The differential diagnosis of idiopathic orbital inflammation includes orbital cellulitis, Graves' eye disease, lymphoproliferative disorders, arteriovenous malformation and lymphangioma, metastatic carcinoma, retained foreign body, and ruptured dermoid cyst. Orbital cellulitis is usually associated with sinusitis, facial or eyelid infection, and trauma. Patients with orbital cellulitis present with fever, elevated white blood cell count, proptosis, chemosis, ptosis, and restriction of motility [62, 63]. Orbital imaging might show decreased orbital fat signal, concurrent sinus disease, bony erosion, and subperiosteal abscess. Graves' eye disease is an autoimmune inflammatory disorder that is commonly associated with hyperthyroidism but may occur in the euthyroid setting [64, 65]. It presents with eyelid retraction, eyelid lag, proptosis, restriction in motility, and compressive optic neuropathy. In contrast to the abrupt onset of pain and inflammatory signs in idiopathic orbital inflammation, Graves' eye disease usually has a slower, more insidious course. Graves' eye disease usually involves both orbits but can be asymmetric. The distinction between lymphoproliferative disorders and idiopathic orbital inflammation is based on clinical and mostly histopathologic findings. Clinically, lymphoproliferative disorders are seen in elder patients, have an insidious onset, and show slow progression. They are associated with symptoms and signs related to mass effect rather than inflammation [66]. Histopathologically, lymphoproliferative disorders demonstrate a homogenous monoclonal lymphocyte cell population with high lambda-kappa ratio. Other disorders that may be accompanied by a significant inflammatory reaction and present similar clinical picture include orbital arteriovenous malformation, lymphangioma, and ruptured dermoid cysts. Orbital imaging might be helpful in differentiation of these problems. A history of orbital

trauma and potential retained intraorbital foreign body causing inflammation should also be investigated. Metastatic orbital tumors, primary ocular tumors with extrascleral extension such as uveal melanoma, or necrotic retinoblastoma might present with similar clinical pictures and should be excluded.

2.8 Treatment of Idiopathic Orbital Inflammation

Management of idiopathic orbital inflammation includes observation, nonsteroidal anti-inflammatory agents, corticosteroids, immunosuppressive agents, immunotherapy, and external beam radiotherapy. Asymptomatic cases with mild inflammation and in whom vision was not threatened might be observed. In their review of 24 cases with idiopathic orbital inflammation, Swamy et al. [47] reported that 21 % of them were observed without any therapy and did not have any recurrence after a median of 23 months of follow-up. Nonsteroidal anti-inflammatory therapy has been used in the management of idiopathic orbital inflammation, especially for orbital myositis. Manor et al. [67] suggested to treat orbital myositis initially with a nonsteroidal anti-inflammatory therapy and observed that 65 % of their cases responded to this therapy without any recurrence. They used systemic corticosteroid therapy for cases refractory to this therapy.

Systemic corticosteroids are the main therapy for idiopathic orbital inflammation. They usually produce rapid and dramatic improvement of signs and symptoms. In an earlier study, Mombaerts et al. [68] reported that 78 % of patients with idiopathic orbital inflammation had a positive initial response to systemic corticosteroids, but only 37 % of them were cured and 52 % showed recurrence. While 95 % of patients with optic neuropathy recovered following systemic corticosteroids, patients with sclerosing and vasculitis subtype had a poor response. Yuen and Rubin [4] reported that 47 % of patients with idiopathic orbital inflammation showed treatment success with systemic corticosteroids, 33 % developed steroid dependence, and 13 % had steroid intolerance. Systemic steroids can be administered orally or pulsed intravenously. In non-vision threatening cases and those without optic nerve compression, oral steroids are initiated. The typical starting dose is between 1–1.5 mg/kg and 60–100 mg of oral prednisone, and a slow taper is recommended over weeks to months to prevent recurrence [69]. Intravenous treatment can be used in atypical cases, those with associated vision loss, or in cases refractory to oral administration [70]. Recurrent disease during or after steroid taper is common in adults, though rarely reported in the pediatric population [14]. When intravenous methylprednisolone plus oral prednisone with oral prednisone alone was compared in the treatment of idiopathic orbital inflammation, no difference in duration of therapy, symptom-free outcome, or recurrence rate was noted [71]. The only difference was the faster symptom relief and recovery from optic nerve symptoms. Localized intraorbital injection of corticosteroids has been used in the management of idiopathic orbital inflammation [70]. Localized intraorbital injection has been reported to have efficacy in patients with anterior idiopathic orbital inflammation and in a case of biopsy-proven idiopathic orbital inflammation unresponsive to systemic steroid administration [72, 73]. In addition, it may be used in children or diabetics to reduce the systemic side effects of corticosteroid use.

External beam radiotherapy has been used for patients who are resistant or intolerant to systemic corticosteroid therapy. Radiation dose varying from 1,000 to 3,000 cGy over 10–15 days has been used in the treatment of idiopathic orbital inflammation [74–76]. A review of 24 patients showed improvement in 87 % of patients with soft tissue swelling, in 82 % of patients with proptosis, in 78 % of patients with restriction of extraocular motility, and in 75 % of patients with pain [77]. Response to external beam radiotherapy varies depending on the subtype of idiopathic orbital inflammation. The patients with myositis variant respond well to external beam radiotherapy, while patients with sclerosing or granulomatous variant have a poor response, and patients

with the vasculitis variant show variable response [51, 68, 78, 79].

The use of steroid-sparing agents including antimetabolites, T-cell inhibitors, and alkylating agents has been reported in patients who are not responsive to steroid treatment, have a chronic progressive course, and require long-term immunosuppression or in combination with steroids as first-line treatment in patients with idiopathic sclerosing inflammation [22, 80–82]. Medications that have been used in idiopathic orbital inflammation patients include methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, tacrolimus, and cyclosporine [80, 82–85]. Among these agents, methotrexate is a commonly used one. It has been used 15–25 mg/week for the duration of ranging from 4 to 34 weeks. It has been reported that 57–73 % of patients showed reduction of inflammatory activity. In a review of 22 patients who used low dose of 12.5 mg/week systemic corticosteroid therapy, Shah et al. [85] observed that 64 % of patients were able to taper or discontinue corticosteroid therapy and 23 % of patients showed complete remission. Biologic agents like monoclonal antibody against tumor necrosis factor alpha and CD20 receptors have been used in the treatment of idiopathic orbital inflammation. There are case reports that show response to adalimumab, daclizumab, and rituximab therapy. Garrity et al. [38] reported favorable response in all seven patients with chronic and refractory orbital myositis after a dosing schedule of 3–5 mg/kg given at weeks 0, 2, and 6 with treatments every 4–8 weeks afterward.

Surgical debulking is rarely performed, but may have a role in the treatment of sclerosing forms of idiopathic orbital inflammation with significant mass effect, fibrosis, and scarring. Orbital exenteration may be indicated in select cases where diffuse orbital involvement results in vision loss and pain unresponsive to other medical or radiation therapy [4].

Compliance with Ethical Requirements Hakan Demirci declares that he has no conflict of interest.

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