Idiopathic Orbital Inflammation

Distribution, Clinical Features, and Treatment Outcome

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Objective: To evaluate the distribution and clinical as well as treatment outcome characteristics of idiopathic orbital inflammation with the aim of delineating a more systematic approach to diagnosis and treatment.

Methods: A 10-year retrospective review of patients with idiopathic orbital inflammation treated at one institution.

Results: Ninety eyes in 65 patients (22 men and 43 women) were studied. Diagnoses were isolated dacryoadenitis (n=21), isolated myositis (n=19), concurrent dacryoadenitis and myositis (n=5), orbital apex syndrome (n=6), and idiopathic inflammation involving the preseptal region, supraorbital region, sclera, Tenon capsule, orbital fat, or optic nerve (n=14). The mean age at presentation was 45 years. Pain and periorbital swelling were the most common clinical features and were observed in 45 (69%) and 49 (75%) patients, respectively. Seventeen patients (26%) had bilateral involvement. Biopsy was performed in 19 patients (29%) with atypical presentations or who failed to respond to the initial therapy. Patients were treated with steroids alone (n=45), steroids and subsequent radiation therapy (n=8), steroids and nonsteroidal anti-inflammatory agents (n=6), nonsteroidal anti-inflammatory agents alone in mild cases (n=2), and, rarely, radiation therapy without steroids (n=1) or surgical debulking alone (n=1). Of 65 patients, 41 (63%) represented treatment successes, with complete symptom relief at the time of the last follow-up, and 24 (37%) represented treatment failures, with partial or no relief of symptoms. Treatment failures were often characterized by recurrence of inflammation after a period of quiescence (58%) and unremitting, recalcitrant inflammation (38%); 1 patient ultimately required an exenteration.

Conclusion: Systemic steroid with a slow taper has been the established first-line treatment for idiopathic orbital inflammation, but refractory cases accounted for a significant portion of treatment failures in our study, reflecting the need for a more systematic approach to the study of this multifaceted disease and for therapeutic alternatives to systemic steroids.

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Idiopathic orbital inflammation, also known as orbital pseudotumor, is defined as a benign, noninfective clinical syndrome characterized by features of non-specific inflammatory conditions of the orbit without identifiable local or systemic causes. It was first described in 1903 by Gleason and by Busse and Hochheim and characterized as a specific clinicopathological entity in 1905 by Birch-Hirschfeld, who described it as an orbital mass that simulated a neoplasm but was histologically inflammatory. Since the initial description, many classification schemes have been applied to idiopathic orbital inflammation based on the location of the inflammatory process, the histopathological characteristics, and the stage of inflammation. Idiopathic orbital inflammation is the third most common orbital disease, following Graves orbitopathy and lymphoproliferative diseases. It accounts for 4.7% to 6.3% of orbital disorders.

Idiopathic orbital inflammation has highly variable clinical features, ranging from a diffuse to very focal process targeting specific orbital tissues, such as the lacrimal gland, extraocular muscles, and orbital fat. This space-occupying infiltrating orbital process is typically characterized by an abrupt onset of pain, proptosis, and inflammatory signs and symptoms, such as swelling and erythema. Presentations vary according to the specific location and the degree of inflammation, fibrosis, and mass effect. Posis, chemosis, motility dysfunction, and optic neuropathy may also be found. Entrapment, compression, and destruction of orbital tissues may occur in patients with extensive sclerosis. Unilateral presentation is typical, but bilateral presentations are not uncommon. Symptoms most commonly de-
velop acutely (hours to days) with patients reporting a
datable onset. In the minority of patients, presentation may
occur over weeks (subacute) or may occur insidiously over
a period of months (chronic). Pediatric idiopathic orbital
inflammation is characterized by a number of features that
differ from the adult presentation. Bilateral manifestation,
as well as uveitis, disc edema, and eosinophilia, appear to
be more common in the pediatric population.15-17

The pathogenesis of idiopathic orbital inflammation
has remained elusive. Idiopathic orbital inflammation
has been associated with several infectious pro-
cesses, including upper respiratory tract infections and
flu-like viral illness, but the exact nature of these asso-
ciations is not clear.15,16,18-20 Several lines of evidence point
to immune-mediated processes as the likely underlying
ocular mechanism. Associations of idiopathic orbital in-
flammation with a number of systemic immunologic dis-
orders, including Crohn disease, systemic lupus ery-
thematosus, rheumatoid arthritis, diabetes mellitus,
myasthenia gravis, and ankylosing spondylitis, have been
reported in several studies.9,21-26 Mombaerts and Koorn-
neef,27 for instance, found in their series that 10% of 58
patients with idiopathic orbital inflammation had con-
current autoimmune disease. In addition, idiopathic or-
bital inflammation typically responds favorably to sys-
temic corticosteroid treatment and successful outcomes
have been reported with other immunosuppressive agents,
such as cyclophosphamide,28 methotrexate,29 and cyclo-
sporine.30 Interestingly, 2 other disorders with a predi-
lection for the orbit, namely Graves orbitopathy and ocu-
lar myasthenia gravis, are also immune-mediated.

An autoimmune process has been suggested as the
ocular mechanism for idiopathic orbital inflammation by
Atabay et al,2,2 who reported the presence of circulating
autoantibodies against eye muscle antigens in patients
with orbital myositis. Although autoimmunity is a plau-
sible idea, it is not clear whether these autoantibodies are
specific to idiopathic orbital inflammation or are also pres-
ent in other forms of inflammation, such as scleritis and
uveitis. In addition, the typical unilateral presentation of
idiopathic orbital inflammation argues against the no-
tion that autoimmunity is the primary mechanism. Al-
ternatively, Mombaerts et al22 and Rootman et al23 pro-
posed aberrant immune-mediated production of fi-
brogenic cytokines leading to aberrant wound healing as
the ocular mechanism underlying the process of fi-
brosis in sclerosing orbital inflammation.

Although benign, idiopathic orbital inflammation
may have a clinically malignant course, with severe vi-
sion loss and ocular motor dysfunction. Spontaneous re-
mission may occur without any therapy, but systemic corti-
costeroids are the cornerstone of therapy in the acute
phase. Despite the generally favorable response to ste-
roid therapy, relapses and persistent inflammation com-
plicate the clinical course and treatment. Therefore, id-
iopathic orbital inflammation poses a considerable
diagnostic and therapeutic challenge.

METHODS

This study is a retrospective review of 79 patients with the di-
agnosis of idiopathic orbital inflammation who were treated
at the Massachusetts Eye and Ear Infirmary (MEEI), Boston, from
January 1991 to April 2001. The study protocol was approved
by the institutional review board at MEEI. The diagnosis of id-
iopathic orbital inflammation was made based on the follow-
ing clinical criteria: benign, noninfective, inflammatory con-
dition of the orbit without identifiable local or systemic causes.
Radiological workup was performed for many patients but was
not a necessary diagnostic criterion for the study. Likewise, his-
topathological confirmation was not a diagnostic requirement
for the study.

Of 79 patients, 6 with the eventual final diagnosis of We-
gen granulomatosis or Graves orbitopathy were excluded from
the analysis; an additional 8 patients with a follow-up period
of less than 5 weeks were also excluded from the study. A lower
limit for the follow-up period was set at 5 weeks because re-
source to treatment is usually evident by this time. All the re-
main 65 patients met the criteria for idiopathic orbital in-
flammation and had at least 5 weeks of follow-up.

These patients were managed according to the following
in treatment algorithm: at the initial manifestation, patients were
typically treated with a high-dose oral steroid (1.0-1.5 mg/kg
per day) for 1 to 2 weeks with taper during the ensuing 3 to 8
weeks. In the event of rebound of symptoms during steroid taper
or recurrence of symptoms after a period of quiescence, ste-
roid dosage was increased (with a slower taper) or restarted for
typically no longer than 10 to 12 weeks. Alternatively, when the
disease course was atypical or refractory to systemic ste-
roids, biopsy was performed for definitive diagnosis. Radia-
tion therapy typically reserved for patients who did not respond to
or were intolerant to systemic steroid therapy. Radia-
tion therapy typically consisted of low-dose irradiation (usu-
ally 15 to 20 Gy fractioned over 10 days). Treatment outcome
was considered a “success” if the patient had complete relief
of symptoms at the time of the last follow-up and a “failure” if
the patient had no or only partial relief of symptoms at the time
of the last follow-up.

RESULTS

Ninety eyes in 65 patients (22 men and 43 women) with a
final diagnosis of idiopathic orbital inflammation and
at least 5 weeks of follow-up were included in the data
analysis. Patients were followed for a mean of 20 months
(range, 1 month to 9 years). Each patient was evaluated
at least twice.

DISTRIBUTION OF SUBTYPES

The 65 patients had isolated dacryoanoditis (n=21), iso-
lated myositis (n=19), concurrent dacryoanoditis and
myositis (n=5), orbital apex syndrome (n=6), and idio-
pathic inflammation involving the preseptal region, su-
praorbital region, sclera, Tenon capsule, orbital fat, or
the optic nerve (n=14). The frequency of these sub-
types is given in the Table. The mean age at manifesta-
tion was 45 years (range, 2.5 weeks to 89 years).

CLINICAL FEATURES

Pain was the most common symptom and was evident
in at least 45 patients (69%). Diplopia was less frequent
but present in at least 20 patients (31%). Periorbital edema
was the most common sign and was present in at least
49 patients (75%), followed by red eye, proptosis, and
chemosis occurring in at least 31 (48%), 21 (32%), and
19 (29%) of patients, respectively (Figure 1). Seven-
Orbital fat bordering the muscle, blurring the margin of the muscle.

Extraocular muscles: enlargement of the extraocular muscles (single or multiple; with or without the involvement of the associated tendons) accompanied by some spillover of the inflammatory process into orbital fat bordering the muscle, blurring the margin of the muscle.

Orbital fat: diffuse infiltration in the orbital fat, enveloping the globe, that may involve the optic nerve sheath complex.

Preseptum, sclera, episclera, Tenon capsule, and uvea: inflammation and enlargement of the tissues.

Optic nerve: inflammation of the optic nerve sheath with thickening of the margin of the nerve and streaky densities in the contiguous orbital fat.

Orbital mass: orbital mass of heterogeneous composition, occasionally invading extraorbital structures, extending along the optic nerve sheath from the globe to the optic canal.

Orbital apex and cavernous sinus: inflammatory process at the apex may compress, obliterate, or displace the optic nerve and may have intracranial extension into the cavernous sinus.

Biopsy was performed in 19 patients (29%) with atypical presentations or who failed to respond to the initial therapy. Of the biopsy specimens, 14 showed a benign nonspecific inflammatory pattern, and the remaining 5 showed a sclerosing pattern, with dense fibrosis as the primary feature.

TREATMENT OUTCOME

Of 65 patients included in the study, 45 (69%) were treated with steroids alone, 8 (12%) with steroids and subsequent radiation therapy, 6 (9%) with steroids and nonsteroidal anti-inflammatory agents, 1 atypical case (2%) with radiation therapy and nonsteroidal anti-inflammatory agents, 2 mild cases (3%) with nonsteroidal anti-inflammatory agents alone, and 1 rare case (2%) with surgical debulking alone; treatment was deferred in the remaining 2 cases (per patient request or pending completion of workup). Of 65 patients studied, 41 (63%) represented treatment successes and had complete symptom relief; 24 (37%) represented treatment failures, with 23 patients experiencing only partial relief and 1 patient experiencing no relief. These treatment outcome results may reflect an overall higher rate of steroid failures than that generally observed in the community because MEEI serves as a referral center, which would introduce some degree of selection bias toward more complicated and recalcitrant disease. The stringent definition for treatment success used in our study, ie, complete relief of symptoms may also inflate the overall higher failure rate. Treatment outcomes are shown for different subtypes of idiopathic orbital inflammation (Figure 2) and treatment modes (Figure 3).

TREATMENT FAILURE ANALYSIS

The clinical course for many patients in our study was complicated by incomplete or no resolution of inflammation, ie, treatment failure. For 14 (58%) of 24 pa-
patients who failed to respond to treatment, inflammation recurred after a seemingly favorable response to treatment with a period of quiescence. For 9 (38%) of 24 patients, the disease course was characterized by unremitting, recalcitrant inflammation, with no real relief provided by treatment; 1 of these patients ultimately required an exenteration.

Systemic steroid therapy has traditionally been the mainstay of treatment for idiopathic orbital inflammation. However, many patients in our study, particularly those who ultimately failed to respond to treatment, had unsatisfactory outcomes from systemic steroids. Rebound of symptoms during steroid taper (ie, steroid dependence) and adverse reaction to steroid therapy (ie, steroid intolerance) occurred in 8 (33%) and 3 (13%), respectively, of the 24 patients who failed to respond to treatment. Steroid dependence and steroid intolerance also occurred in 12% and 2%, respectively, at some point in the clinical course of patients who ultimately had successful outcomes (Figure 4).

Age was not a predictor of treatment failure because the mean age of patients successfully treated (42 years) was comparable to that of patients who failed to respond to treatment (45 years). Likewise, sex was not significantly associated with treatment failure because the male-female ratio remained comparable for the treatment success group (13:28) and the treatment failure group (9:15). Inflammation involving the orbital apex was relatively uncommon in our study but was associated with the poorest treatment outcome; 4 (66%) of 6 patients with this subtype failed to respond to treatment. Sclerosing orbital inflammation also appeared to be associated with poor outcome because all 4 cases in our study failed to respond to treatment and 1 patient ultimately required an exenteration.

A more detailed characterization of treatment failure was beyond the primary scope of this study and remains to be further explored. Our study did not systematically address several questions that are important in defining more fully the pattern of recalcitrant disease and thereby improving treatment outcome, such as: Is there a particular window period of peak recurrence after the initial presentation, and would an aggressive treatment targeted at this window ultimately improve outcome? Does a more prompt initiation of treatment reduce the rate of recurrence and treatment failure? Is there an optimal course of steroid treatment or tapering for more difficult cases that would ultimately reduce the rate of recurrence?

In our study, idiopathic orbital inflammation occurred more frequently in middle-aged women. The true incidence of...
idiopathic orbital inflammation in the literature is difficult to assess, given the wide spectrum of manifestations and the lack of a universally accepted definition of the disease entity. However, the peak incidence reported in the literature appears to be predominantly in the adult population, typically in middle-aged persons, with pediatric cases accounting for only 6% to 17% of the total incidence. No strong sex predilection has been reported for idiopathic orbital inflammation. However, a 2:1 predominance in women, as well as a rare instance of familial occurrence, has been reported for orbital myositis. In our study, an overall 1:8:1 predominance in women was observed across the different subtypes; the highest predominance in women (5:1) was observed for the orbital apex syndrome group. Dacryoadenitis and myositis were the most common subtypes observed in our study.

Our patients typically had unilateral periorbital pain and edema at the initial visit, which is consistent with the clinical features reported in the literature. Other features such as diplopia, redness, chemosis, and proptosis occurred less frequently in our study. Restriction, compression, and destruction of orbital tissues occurred rarely in our study and only in patients with extensive sclerosis and poor treatment outcomes. Medial rectus was the most commonly involved extraocular muscle in our study, followed by superior rectus and lateral rectus; inferior rectus was the least frequently involved. In their studies of orbital myositis, Mombaerts and Koornneef and Siatkowski et al reported that medial and lateral rectus was the least frequently involved. In their studies followed by superior rectus and lateral rectus; inferior most commonly involved extraocular muscle in our study, medial rectus was the most commonly involved extraocular muscle in our study, followed by superior rectus and lateral rectus; inferior rectus was the least frequently involved. In their studies of orbital myositis, Mombaerts and Koornneef and Siatkowski et al reported that medial and lateral rectus were most commonly involved.

Radiological imaging studies allow tissue characterization and localization without surgical intervention and thereby have become invaluable diagnostic tools. Computed tomography is the preferred imaging mode for idiopathic orbital inflammation and was by far the most common imaging mode used in our study. Idiopathic orbital inflammation is typically seen on CT scans as a focal or diffuse mass, usually poorly demarcated and enhancing with contrast. Common CT findings include enhancement with contrast medium, infiltration of retrobulbar fat, proptosis, extraocular muscle enlargement, muscle tendon or sheath enlargement, apical fat edema, optic nerve thickening, uveal-scleral thickening, edema of the Tenon capsule, and lacrimal gland infiltration. Tendons of the extraocular muscles may be involved or spared. Magnetic resonance imaging is generally used, either alone or in combination with CT, in patients with extraorbital or intracranial extensions. Intracranial extension and bone destruction have been reported but are rare findings, usually occurring with the sclerosing process. Echography may be useful as an alternative if CT or MRI is not readily available.

The histopathological spectrum of idiopathic orbital inflammation is typically nondiagnostic, wide, and diverse, ranging from the typical diffuse polymorphous infiltrate to the atypical granulomatous inflammation, tissue eosinophilia, and infiltrative sclerosis. In the absence of systemic fibroinflammatory, granulomatous, and vasculitic disease, these atypical presentations are considered to be subclasses of idiopathic orbital inflammation. Histopathological confirmation was sought in our study for patients who had atypical presentations or who failed to respond to the initial therapy. A benign, non-specific inflammatory pattern was the general finding in our study, with the exception of 4 cases, which showed dense fibrous connective tissue as the predominating component with little inflammatory infiltrate (ie, the sclerosing form). The dense collagenization seen in the sclerosing form is considered by some authors to be the end stage of the histological continuum of idiopathic orbital inflammation, with the earlier stage characterized by greater lymphocytic component that then progresses toward fibrosis in the later chronic stage. Others, however, support the notion that idiopathic sclerosing inflammation of the orbit is a unique clinicopathological entity distinct from idiopathic orbital inflammation. In either case, the sclerosing form runs an insidious, frequently progressive course that replaces and damages orbital structures through cicatricial entrapment. It tends to be more aggressive than the nonsclerosing forms and appears to have a poor therapeutic outcome, consistent with the findings in our study.

Systemic steroid therapy with a slow taper has been the established first-line treatment, but refractory cases accounted for a significant portion of treatment failures in our study. Steroid dependence and intolerance were prominent features of the patients who failed to respond to treatment. Steroid therapy, in general, hastens clinical resolution in the acute phase. However, as observed in our study, there are serious shortcomings to steroid therapy. Although many patients with idiopathic orbital inflammation do have favorable responses to steroid therapy, incomplete resolution is common. Steroid resistance and dependence as well as potential adverse reactions, such as mood changes, hyperglycemia, dyspepsia, and weight gain, further complicate the clinical course and therapy. Mombaerts et al report a low cure rate (37%) and a high recurrence rate (52%) obtained with steroid therapy in their retrospective studies and question the value of steroids as the primary treatment modality. They propose that systemic steroid therapy not be used as the initial step but be reserved as therapy in selected patients who have associated optic neuropathy or who may benefit from rapid though possibly transient symptomatic relief. They point out the need for a controlled prospective study that compares the efficacy of different therapeutic modalities. However, until more information on the efficacy of these alternative treatment modalities becomes available, systemic steroid therapy appears to be the best-accepted first-line treatment for idiopathic orbital inflammation. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, may be used as an alternative to or in combination with steroid therapy. Mannor et al recommend a trial of nonsteroidal anti-inflammatory drugs for up to 3 weeks or until clinical resolution, with steroids reserved for refractory cases.

Reports of alternatives to steroid therapy, such as immunosuppressive chemotherapy, are fairly limited in the idiopathic orbital inflammation literature. Pulsed chemotherapy consisting of either cyclophosphamide or chlorambucil combined with prednisone has been reported to be effective in the treatment of idiopathic orbital inflammation refractory to both steroid and radiation.
therapy. Methotrexate and intravenous immunoglobulin have similarly been found to be effective in treating idiopathic orbital inflammation that did not respond to steroids. The role of chemotherapy in the treatment of idiopathic orbital inflammation remains to be further explored.

Radiation therapy was used in our study to treat patients with idiopathic orbital inflammation who were unresponsive to steroid therapy, became steroid dependent, or had intolerable adverse reactions to steroids. Radiation therapy was used as the initial treatment in only 1 atypical case in which Graves orbitopathy and atypical lymphoma were strongly considered in the differential diagnosis. Radiation therapy did not significantly affect the treatment of idiopathic orbital inflammation in our study, because 8 of 9 patients who underwent radiation therapy ultimately failed to respond to treatment. This is not surprising given that the patients who ultimately undergo radiation therapy tend to have more complicated or atypical disease. However, several studies have reported favorable outcomes with radiation therapy, indicating that radiation therapy remains a viable treatment option for idiopathic orbital inflammation. Radiation therapy is an attractive alternative to steroid therapy, particularly given the relatively few potential adverse effects of low-dose external-beam radiation treatment, which include increased soft tissue inflammation that is generally self-limited. At approximately 20 Gy of irradiation, the only ocular structure with a significant potential risk is the lens, because dry eye, retinopathy, and optic neuropathy are not generally observed with radiation doses of less than 30 to 40 Gy.

Surgical resection may be an effective alternative to medical and radiation therapy for more localized lesions. It is not a strong therapeutic option for diffuse, fibrotic orbital lesions that cannot be removed because of the involvement of vital structures. The ultimate surgical option of exenteration is indicated for idiopathic orbital inflammation in patients with irretrievable visual loss accompanied by pain inadequately controlled by medical or radiation therapy.

Idiopathic orbital inflammation is a clinical diagnosis of exclusion characterized by highly variable clinical, radiological, and histopathological presentations. A stepwise algorithm is presented in Figure 5 to provide a more systematic approach to the diagnosis and treatment of this disease.

By definition, idiopathic orbital inflammation excludes lesions with identifiable local or systemic etiology. Differential diagnosis includes the following: infections, inflammatory reaction to trauma or a foreign body, thyroid dysfunction, vasculitis (such as Wegener granulomatosis, polyarteritis nodosa, and giant cell arteritis), sarcoidosis, neoplasm, and arteriovenous fistulas and malformations. Because idiopathic orbital inflammation is a diagnosis of exclusion, meticulous physical examination and history taking are important initial steps. Particular attention to the following is essential: previous similar episodes, antecedent trauma or infection, chronicity and duration of symptoms, associated constitutional symptoms, systemic disorders (including cancer), and risk factors for potential immunological compromise.

Infection must be considered. The orbit may be the site of specific infections, most commonly by parasal sinusitis or contiguous spread from infections of the face, teeth, a penetrating foreign body in cases of trauma, and septicemia. Infection most commonly begins in the ethmoid sinus, with extension of the inflammatory infiltrate into the orbital space. In mild cases, the process may be limited to the preseptal space. In more severe cases, the inflammatory infiltrate may extend into the extraconal space with subperiosteal involvement. Extension into the intraconal space across the periorbita is rare but does occur and requires very aggressive and prompt treatment. It is important to be mindful of atypical microorganisms, including fungal infections such as mucormycosis and aspergillosis, in patients with diabetes and immunocompromised patients.

Other potential causes must be evaluated and ruled out according to clinical suspicion. Thyroid orbitopathy, also known as Graves orbitopathy, is the most common cause of exophthalmos and is an important consideration in the workup of patients with idiopathic orbital inflammation. Thyroid orbitopathy has characteristic manifestations such as eyelid retraction, eyelid lag, proptosis, restrictive extraocular myopathy, and optic neuropathy. Radiological findings include enlargement of extraocular muscles and an increase in
orbital fat volume. These findings may occur in the euthyroid setting in the absence of any objective thyroid dysfunction as the initial presentation of the disease process or after adequate control. A number of clinical and radiological features distinguish idiopathic orbital inflammation from thyroid orbitopathy. Abrupt onset of pain and inflammatory signs, such as periorbital erythema and swelling, are typical early manifestations of idiopathic orbital inflammation. In contrast, Graves disease has a slower, more insidious course, and extraocular motility dysfunction and visual disabilities tend to occur later in the disease process. In addition, pain is not a prominent feature of Graves orbitopathy. Radiological findings for idiopathic orbital inflammation are typically unilateral and may involve any of the orbital structures, including the extraocular muscles, muscle tendons, orbital fat, perineural connective tissues, Tenon capsule, and sclera. Graves orbitopathy, in contrast, has findings that are typically bilateral, and the primary focus is on the enlargement of extraocular muscles and increased orbital fat volume.

Wegener granulomatosis is a necrotizing, granulomatous inflammation and vasculitis that affects the respiratory and renal systems; there is ocular involvement in about 50% of cases. Wegener granulomatosis is a rare disease but an important differential diagnosis for idiopathic orbital inflammation because of its association with high morbidity and mortality. Bilateral eye pain, proptosis, redness, and ocular motility dysfunction are common clinical features. Ocular and orbital manifestations of Wegener granulomatosis include conjunctivitis, marginal ulcerative keratitis, scleritis, uveitis, retinal vasculitis and optic neuropathy, dacryoadenitis, and nasolacrimal duct obstruction. Histological findings consist of necrotizing, granulomatous inflammation and vasculitis. Serum levels of antineutrophil cytoplasmic antibodies that display a cytoplasmic immunofluorescent staining pattern (c-ANCA) are elevated in about 90% of patients with active Wegener granulomatosis and are very helpful in diagnosis and differential diagnosis. However, it is important to note that c-ANCA may not be a prominent feature of limited Wegener granulomatosis. Systemic workup including pulmonary and renal function assessment and radiological evaluation would be indicated if Wegener granulomatosis is suspected.

Sarcoidosis is characterized by systemic granulomatous inflammation involving the lungs, hilar lymph nodes, eyes, and skin. Ocular involvement occurs in 25% to 50% of patients and may include infiltration of the lacrimal gland, extraocular muscles, orbital fat, optic nerve, and uveal tract. Conjunctival granuloma or solitary orbital granuloma may also be found. Clinical features include pain, proptosis, oculomotor dysfunction, uveitis, and vision loss. Radiological findings include bilateral hilar adenopathy and parenchymal pulmonary involvement. Noncaseating granulomas are the classic histological finding. Angiotensin-converting enzyme and lysozyme levels can be useful as adjuncts to clinical, radiological, and histological findings but not as primary diagnostic tools because of their limited sensitivity and specificity.

Neoplasm is also an important consideration in the evaluation of idiopathic orbital inflammation, especially in patients with a solitary orbital lesion. Imaging studies may show mass lesions, bony changes, and intracranial extension. In the adult population, metastatic lesions and lymphoma are high in the differential diagnosis, and systemic workup would be indicated. Breast, lung, prostate, and kidney are common primary sites for metastatic orbital tumors. The possibility of chronic inflammatory reaction around a true neoplasm should also be considered.

Differential diagnosis of pediatric idiopathic orbital inflammation is somewhat different from that for the adult population and includes the following: orbital cellulitis, trauma, foreign body, dermoid and epidermoid cysts, capillary hemangioma, lymphangioma, and dacrocyoadenitis, as well as neoplasms such as rhabdomyosarcoma, retinoblastoma, and neuroblastoma and thyroid orbitopathy. The most serious consideration is neoplasia, and a low threshold for biopsy is indicated. Rhabdomyosarcoma is the most common pediatric primary orbital malignancy and is commonly accompanied by radiographically evident bony changes, which are very rare in idiopathic orbital inflammation. Retinoblastoma is also an important consideration because it is the most common intraocular tumor of children, with 10% of cases having orbital extension. Thyroid orbitopathy is exceedingly rare in children and is much lower in the differential diagnosis than it is for idiopathic orbital inflammation in an adult. Dermoid and epidermoid cysts and capillary hemangioma are not uncommon orbital lesions in newborns and infants. Ruptured dermoid cysts can provoke a significant granulomatous inflammatory reaction in the surrounding orbital tissue. Lymphangioma is usually slow growing but can also have a fulminating inflammatory presentation on rupture and hemorrhage.

After the local and systemic causes have been ruled out, treatment for presumed idiopathic orbital inflammation can be initiated. In patients with a mild clinical presentation, clinical progression may be monitored while awaiting test results, or nonsteroidal anti-inflammatory drug therapy may be initiated. In patients with a moderate to severe clinical presentation and a strong possibility of idiopathic orbital inflammation, systemic corticosteroid therapy may be initiated as long as suspicion for an infectious etiology is low and there is no other contraindication for steroid therapy. Systemic prednisone can be started with an initial dosage of 60 mg to 100 mg per day for 1 to 2 weeks and a taper typically over 5 to 6 weeks. Clinical progression and potential adverse reactions need to be closely monitored once systemic corticosteroid therapy has been initiated. In the event of persistent or recurrent episodes that are refractory to systemic steroid therapy, biopsy (open biopsy or, if applicable, fine needle aspiration) should be strongly considered for definitive diagnosis, particularly if the lesion is easily accessible (eg, lacrimal gland). If the biopsy findings are consistent with idiopathic orbital inflammation, consider the following options in patients with a disease course that is refractory to systemic steroid therapy: (1) if the patient had a favorable response to steroid therapy
initially, oral steroid therapy may be restarted or, if the patient is in the steroid taper phase, the dosage may be increased with a slower taper and (2) if the patient is steroid intolerant, nonresponsive, or dependent, low-dose external beam irradiation (typically 15 to 20 Gy fractioned over 10 days) may be considered.

For idiopathic orbital inflammation refractory to both systemic corticosteroid and radiation therapy, treatment options are limited. It would be reasonable to step back and repeat or expand the radiological evaluation, laboratory workup, and biopsy (of a different site if multiple sites are involved) to readdress the possibility of other causes. Alternatively, chemotherapeutic agents, such as cyclophosphamide, may be considered. Surgical debulking may be a consideration if the lesion is easily approachable or in patients with a severely progressive and disabling clinical course (eg, orbital apex syndrome with optic nerve compression).

CONCLUSIONS

Idiopathic orbital inflammation is a multifaceted disease with a wide spectrum of clinical, radiological, and histopathological presentations. In our study, idiopathic orbital inflammation occurred more frequently in middle-aged persons, affected more women than men, and typically manifested with unilateral periocular pain and edema. Dacryoadenitis and myositis were most common. Response to steroid therapy was generally favorable initially in our study, but persistent and recurrent cases accounted for a significant portion of the treatment failures. Steroid dependence and intolerance were prominent features of patients who failed to respond to treatment in our study.

Idiopathic orbital inflammation encompasses a broad spectrum of disease entities with a high degree of variability in clinical presentation and outcome. Many aspects of this disorder remain unknown. The pathogenesis of idiopathic orbital inflammation has remained elusive despite several lines of evidence for an immune-mediated etiology. Moreover, no satisfactory animal model has been developed to date to aid in the understanding of the disease process or to assist in determining optimal treatment protocols to limit sequelae from inflammation. Relapses are exceedingly frustrating to both patients and physicians because there are few treatment alternatives in these refractory cases. Factors predictive of these recurrent and refractory cases need to be further delineated. There is a great need for a more systematic and comprehensive characterization of this disease. This would provide a framework for a controlled prospective study comparing the efficacy of different treatment modalities for idiopathic orbital inflammation and thereby aid in further exploration of therapeutic alternatives to systemic corticosteroids.

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