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Orbital inflammatory disease: a diagnostic and therapeutic challenge

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Abstract

The spectrum of orbital inflammatory disease (OID) ranges broadly from specific disease diagnoses, for example, Wegener's granulomatosis or sarcoidosis, to nonspecific inflammation which may involve one or multiple structures of the orbit. Mimics of idiopathic OID must be considered in a comprehensive differential diagnosis and include malignancies, congenital mass lesions, infectious diseases, and occult or distant trauma. Idiopathic OID may be secondary to an underlying systemic inflammatory disease, which must be diagnosed in order to develop a comprehensive therapeutic plan, or may represent localized pathologic processes without systemic involvement. Evaluation of the patient with suspected OID must include a careful history, physical examination, directed laboratory, and radiologic studies, and may sometimes require tissue for diagnostic studies. Therapeutic options for inflammatory diseases are expanding as biologically targeted agents become available that act on specific segments of the inflammatory cascades. The purpose of this paper is to provide a framework for the evaluation and management of patients with the spectrum of diseases known as OID and to discuss some of the new advances in immunologic monitoring and targeted immune therapies that will likely play an increasingly important role in the care of these patients.
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Introduction

Orbital inflammatory disease (OID) accounts for up to 6% of orbital diseases, affects all age groups of patients, and is a frequent cause for orbital biopsy.[1–13] Differential diagnosis of OID ranges from idiopathic inflammatory disease to systemic or local inflammatory conditions to other associated conditions such as neoplasm, infection, congenital malformation, or trauma.[14] Systemic inflammatory diseases associations of OID include autoimmune thyroid disease, sarcoidosis, Wegener's granulomatosis, Crohn's disease, systemic lupus erythematosis, and other connective tissue diseases, Churg–Strauss syndrome, Erdheim–Chester, histiocytosis X, and giant cell arteritis[2,5,15–48] (Table 1). Congenital lesions, in particular dermoid cysts but also lymphangiomas, may develop an inflammatory component or alternatively may create intermittent signs and symptoms that may mimic OID.[49] Primary tumours of the eye, for example, malignant melanoma, may develop extra-scleral extension eliciting a secondary orbital inflammatory process.[21,50] Both primary and metastatic tumours in the orbit may have inflammatory components and rhabdomyosarcoma in particular may mimic inflammatory disease. Infectious diseases secondary to bacteria, viruses, fungi, and parasites may produce significant inflammatory disease and must always be considered as a potential diagnosis in any patient with OID.[18,40,51–56] The key to developing a rational differential diagnosis and therapeutic plan is a comprehensive approach to patients with symptoms or signs of orbital inflammation.

Orbital involvement in OID

Inflammation of the orbit may diffusely involve multiple or all orbital structures or may be localized to a specific orbital tissue. Localized anterior OID may result from retained foreign body with local granuloma and the underlying etiology may be revealed only through a careful

Table 1 OID: differential diagnosis

Idiopathic Inflammatory Disease
Systemic inflammatory disease
Autoimmune thyroid disease: endocrine exophthalmos
Sarcoidosis
Wegener's granulomatosis
Crohn's disease
Systemic lupus erythematosis
Churg-Strauss syndrome
Erdheim-Chester syndrome
Histiocytosis X
Giant cell arteritis
Idiopathic fibrosclerotic disorders
Periarteritis nodosa
Scleroderma
Sclerosing cholangitis
Neoplasm
Lymphoma
Lymphoproliferative disorders
Rhabdomyosarcoma
Choroidal malignant melanoma with extrascleral spread
Metastatic disease
Congenital malformation
Dermoid cyst
Lymphangioma
Infectious disease
Trauma

history and diagnostic evaluation. Scleral involvement may be secondary to other orbital inflammation or may represent a primary inflammatory process; posterior scleritis may not be accompanied by anterior signs or symptoms of inflammation.[41,57,58] Associated ocular signs, such as anterior or posterior uveitis, exudative retinal detachment, or papillitis may be identified and are helpful in establishing a differential diagnosis.[14] The differential diagnosis of scleral inflammation includes systemic collagen-vascular disease or active infectious disease. Diffuse OID may present either acutely with an explosive inflammatory component or may occur insidiously with chronic disease.

Differential diagnosis of acute OID primarily includes infectious orbital cellulitis, tumour with acute inflammatory signs, and thyroid eye disease (Figure 1). Orbital cellulitis is a potentially life-threatening disease often associated with antecedent sinus disease, dental procedures, or trauma and is typically accompanied by fever and leukocytosis, features that are uncommon in noninfectious OID.[40,52,53,56,59,60] These patients are generally hospitalized for intensive, broad-spectrum intravenous antimicrobial therapy pending identification of the inciting organism. The correct diagnosis of OID may occur only after a lack of response to the presumptive treatment of an underlying infection and exquisite sensitivity to systemic corticosteroids.

Chronic forms of diffuse OID are often diagnostically challenging and the examiner must maintain a high suspicion for underlying diseases including thyroid eye disease, sarcoidosis, Wegener's granulomatosis, lymphoproliferative diseases, or vasculitis.[6,17,22,33,47,61,62] In the absence of thyroid orbitopathy, orbital biopsy and histopathology may be required before onset of therapeutic intervention. Although corticosteroids are typically used in initial therapy, some idiopathic chronic forms of OID may be poorly responsive and require other therapeutic modalities including radiation therapy or immune modulation.

Multiple syndromes of granulomatous inflammatory diseases, including sarcoidosis, Wegener's granulomatosis, Erdheim–Chester, Churg–Strauss, and Tolosa–Hunt, deserve specific consideration. Sarcoidosis is a multisystem granulomatous inflammatory disease that affects the respiratory tract, skin, and eyes.[17,33,47] Ocular involvement is reported in up to 50% of affected patients and is characterized by noncaseating granulomas of the conjunctiva, uveitis, optic neuropathy, or orbital involvement of the lacrimal gland, extraocular muscle, or fat. Hilar adenopathy or parenchymal lung disease is present in up to 90% of patients with sarcoidosis.[29,47] Serum-angiotensin converting enzyme (ACE), if elevated, may be helpful in diagnosing sarcoidosis.

Wegener's granulomatosis is a systemic vasculitis of small vessels that typically affects the renal and respiratory systems; however, a limited form may only involve the orbit and sinuses.[5,12] Histology reveals vasculitis and necrotizing, granulomatous inflammation. Ocular involvement is demonstrated in up to 50% of involved patients, and Wegener's granulomatosis is the diagnosis in 15% of scleritis patients. Although the c-ANCA autoantibody against proteinase 3 is present in more than 90% of patients with active systemic disease, one study documented positivity in only 32% of patients with the limited disease form.[63] Orbital involvement includes mass lesions, pain, epiphora, and diplopia. Clinical examination may reveal conjunctivitis, scleritis, keratitis, uveitis, retinal vasculitis, optic neuropathy, dacryoadenitis, obstruction of the nasolacrimal duct, and, rarely fistulas. In addition, orbital socket contraction may occur.[64] Wegener's granulomatosis may result in significant morbidity and mortality; hence, initiation of medical therapy generally requires both systemic corticosteroids and other systemic medication such as cyclophosphamide.

Erdheim–Chester is a systemic non-Langerhans histiocytic xanthogranulomatous inflammatory disease with variable orbital involvement ranging from mild impairment of function to devastating loss of visual acuity secondary to mass effect.[65,66] Systemic

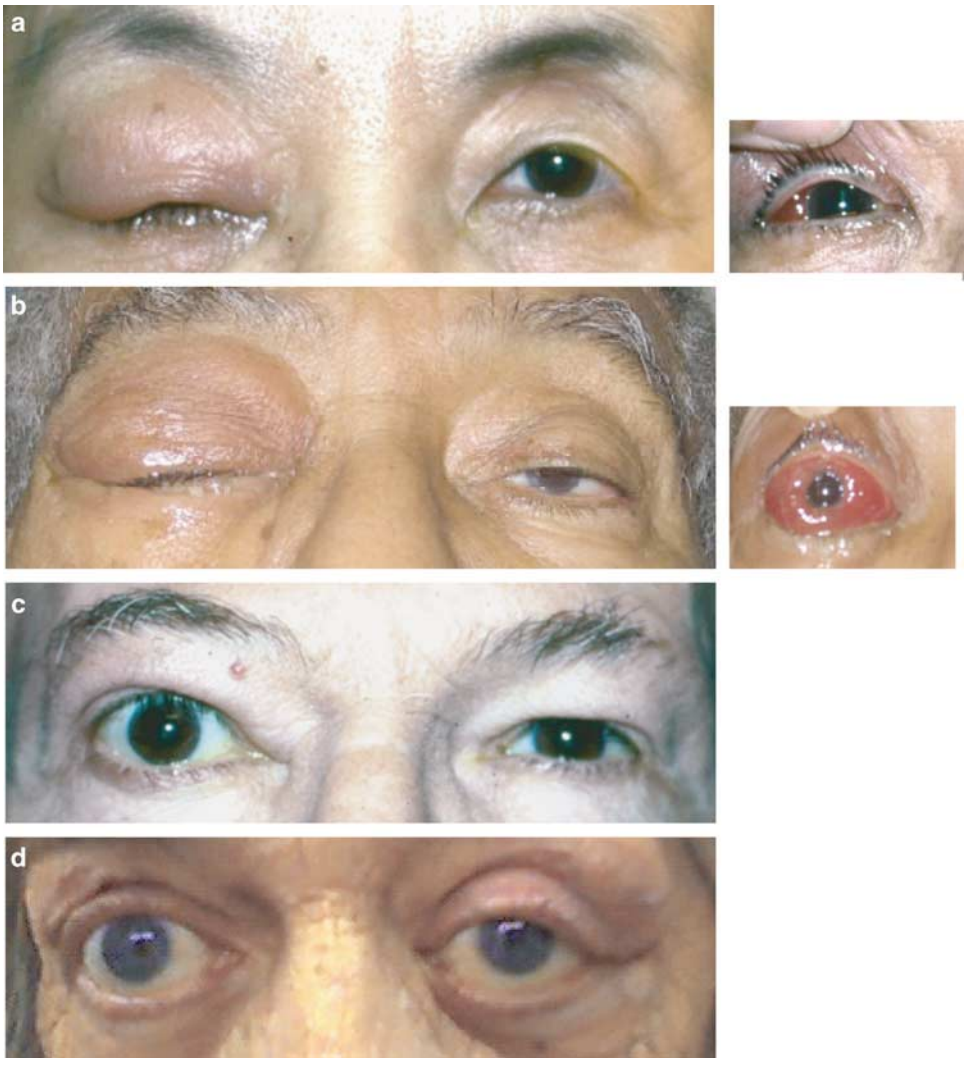

Figure 1 The differential diagnosis of OID includes infection, inflammation, and tumour. (**a**) Orbital cellulitis in patient who presented with acute onset orbital inflammation post-foreign body. (**b**) Idiopathic OID in patient who presented with acute onset of orbital inflammation. (**c**) Thyroid orbitopathy in patient who presented with a several months history of increasing proptosis. (**d**) Tumour in region of the lacrimal gland, note S-shaped ptosis.

involvement may be extensive and include the brain, heart, lung, liver, kidney, retroperitoneal space, and musculoskeletal system. Histologic evaluation reveals foamy cell infiltration and Touton giant cells, fibrosis, and immunologic staining confirms the diagnosis as these cells are positive for CD 68, a histiocytic marker.

Churg–Strauss syndrome, characterized by a necrotizing vasculitis, eosinophilic infiltration into involved tissues, and extravascular granulomas, often presents with clinical features of eosinophilia and asthma.[67,68] Multiple organ system involvement is common in this disease and may include the heart, central nervous system, liver, colon, gall bladder, kidney, peripheral nerves, brain, and musculoskeletal system. Laboratory evaluation may also reveal increased circulating IgE and identify the presence of p-ANCA antibodies. Evaluation of 17 reported orbital cases revealed that the presence of ANCA antibodies was associated with ischaemia and may have a poor visual prognosis. Relapses are common in Churg–Strauss, occurring in about 25% of affected individuals.

The Tolosa–Hunt syndrome is a painful ophthalmoplegia with variable cranial nerve involvement including motor, sensory, and oculosympathetic pathways localizing to the region of the cavernous sinus or superior orbital fissure.[69–72] Rarely, involvement of the orbital apex or extension of the pathologic process may produce an optic neuropathy, cause a facial paralysis, or involve the mandibular or maxillary branches of the trigeminal nerve. Although

unilateral involvement is typical, patients may experience bilateral disease and may develop recurrences. This condition may appear at any age and equally affects males and females. Cases with histopathologic diagnosis demonstrate a granulomatosis inflammation characterized by epithelioid cells and giant cells. Exquisite relief of pain characteristically occurs within several days of initiation of high-dose corticosteroids. Magnetic resonance imaging (MRI) may reveal soft tissue inflammatory changes.[73] The differential diagnosis includes trauma, primary or metastatic tumours, lymphoproliferative disease, sarcoidosis, Wegener's granulomatosis, vasculitis, and infectious diseases (bacterial, fungal, viral, and parasitic).

The sclerosing variant of orbital inflammation is uncommon, but produces serious morbidity with a severe, chronic, progressive syndrome often characterized by proptosis, mild external inflammatory signs, restricted motility, diplopia, and dull, chronic pain.[42,74,75] Diagnosis is typically made by orbital biopsy in which there is evidence for scarring and fibrosis. Sclerosing OID shares some features with and may be related to systemic fibrosclerotic diseases involving the retroperitoneum, mediastinum, biliary tract, and thyroid.[27,38] Sclerosing OID must be considered in all age groups, even as early as the first decade of life. Loss of vision may occur in up to 30% of affected individuals because of the blunted response to conventional therapies; some authors advocate early, aggressive immunosuppressive therapy in an endeavour to retain function.

In contrast to the diffuse forms of OID, localized OID may occur in the lacrimal gland, extraocular muscles, or optic nerve sheath. The typical acute presentation of dacryoadenitis includes pain, enlargement of the lacrimal gland, an S-shaped ptosis of the upper eyelid, and tenderness to palpation. Inflammatory disease of the lacrimal gland may also present in a subacute or chronic form in which a painless mass appears in the region of the lacrimal fossa.[7,23,35] Differential diagnosis of dacryoadenitis primarily includes idiopathic inflammation, infection, Sjogren's syndrome, sarcoidosis, lymphoma, and primary tumour of the lacrimal gland. Neuro-radiologic imaging may be helpful in that longitudinal enlargement and variable enhancement of the gland, with adjacent soft tissue inflammation, is observed in idiopathic inflammatory dacryoadenitis.[76] If the differential diagnosis includes pleomorphic adenoma, then incisional biopsy is contraindicated and either an en bloc resection or fine-needle aspiration biopsy is required for diagnosis.

Myositis, defined by inflammation primarily involving extraocular muscles, is typically either due to thyroid-associated orbitopathy (TAO) or due to idiopathic myositis.[12,15,18,20,34,39,77–81] TAO, often identified by clinical features of lid retraction and sparing of the tendon insertion, is the major cause of inflammatory orbital disease, and may present in a severe inflammatory phase, mimicking idiopathic OID.[82] Imaging studies, generally indicated in TAO for surgical planning and evaluation of the orbital apex, may be helpful in differentiating idiopathic myositis from TAO. Other potential diagnoses that must be considered include lymphoma, metastasis, carotid-cavernous fistula, and infiltrative myopathies.[1,76,83,84]

Orbital myositis occurs in multiple forms and may be recurrent, unilateral or bilateral, acute or chronic, and may involve one or multiple extraocular muscles.[84] In contrast to other forms of OID that equally affect males and females, myositis has a female predilection. Diplopia, pain, proptosis, and external signs of inflammation are common complaints in the acute inflammatory phase. The typical examination reveals proptosis and restrictive strabismus with variable external inflammatory signs such as chemosis. Although the distinction between OID and TAO may be challenging, involvement of the insertions and irregular borders of the extraocular muscles is usually a sign of myositis.[85] Orbital ultrasonography is a quick and cost-effective modality for evaluation of the muscle insertion. Biopsy is rarely required, but in cases of atypical muscle involvement, may be indicated to look for infiltrative or metastatic lesions. In the inflammatory phase, orbital myositis usually responds dramatically to systemic steroids; however, the clinical response does not allow a definitive diagnosis of idiopathic OID. The frequency of recurrent disease is believed to be decreased by a slow taper of corticosteroids. Patients who are refractory or intolerant of steroids may require additional therapeutic modalities for effective disease control. Granulomatous myositis is an uncommon but serious cause of extraocular muscle involvement in orbital inflammation.[39] This may involve multiple muscles as a bilateral process, and may be associated with systemic malignancy or giant cell myocarditis.[39,86]

Local inflammation of the trochlea may produce a chronic orbital pain syndrome and is often overlooked; associated conditions include migraine and systemic rheumatologic conditions.[87,88] Although some affected orbits demonstrate localized erythema near the superior oblique insertion, complaints of diplopia or pain accentuated by eye movement are unusual. Abnormal thickening of the superior oblique tendon may be observed on imaging studies or alternatively, there may be no formal clinical or radiographic evidence for localized disease. Orbital palpation produces a localized increase in pain over the region of the trochlea. Although oral nonsteroidal inflammatory medications sometimes

produce pain relief, local injections of long-acting corticosteroids are often beneficial.

Optic perineuritis is a category of OID in which there is preferential involvement of the optic nerve sheath with associated pain and loss of vision.[89–92] Optic perineuritis occurs more commonly in females during the adult years and may recur. The major differential diagnoses include typical optic neuritis, in which there is pain on eye movement and decreased vision, sarcoidosis, or primary tumours of the optic nerve sheath.

Examination of the OID patient

Evaluation of patients with inflammatory disease of the orbit begins with the history and physical examination.[1–3,5,7,9–12,93–96] In particular, the tempo of disease onset and duration must be evaluated. For example, an acute, explosive disease onset may be part of an infectious process, idiopathic inflammatory disease, or may result from the sudden change in a pre-existing lesion such as a tumour or retained foreign body. An insidious onset may arise from a more chronic progressive disease such as idiopathic sclerosing orbital inflammation.[42,74,75] Patients are not always cognizant of slow, progressive lesions and for that reason the 'family album scan' of dated photographs may help in determining both disease onset and progression. The patient or family members should be asked about alterations in appearance with valsalva or positional change.

Characterization of symptoms should be performed including erythema, pain, exophthalmos, diplopia, blurred vision, acquired colour vision abnormalities, or perceived changes in the visual field. Past medical history, including sinus disease, diabetes, thyroid disease, collagen-vascular disease, and cancer, must be documented as they can add clues to develop the differential diagnosis. Family history of immune-mediated diseases may also be relevant to the differential diagnosis of OID.

The typical ophthalmologic evaluation forms the cornerstone of physical diagnosis for patients with suspected OID.[6,14,95] Careful refraction should be performed to detect induced astigmatism from orbital mass lesions or secondary amblyopia in the paediatric age group. Evaluation of the optic nerve function includes formal colour testing and careful observation for an objective or subjective relative afferent pupillary defect. Pupil testing also is performed to evaluate sympathetic and oculomotor innervation. Corneal sensation should be tested before instillation of any topical medications in order to detect involvement of the trigeminal nerve. Slit-lamp biomicroscopy is performed to evaluate the ocular surface and anterior segment and use of topical neosynephrine helps identify the location of inflamed vasculature, for example, conjunctiva, episclera, or sclera. In cases of extraocular muscle involvement, intraocular pressure measurements should be performed in primary and vertical gaze directions. Dilated examination of the fundus is performed to evaluate the retina and optic nerve and to specifically identify choroidal folds or abnormal retinal vasculature. Formal visual field testing is required if the patient notices decreased central or peripheral vision or if there is concern about a potential for compressive optic neuropathy.

A standard approach to the physical examination of the orbit includes inspection, measurement of exophthalmos, palpation, determination of motility, and may require auscultation. Dynamic observation during voluntary valsalva may suggest potential for vascular or bone malformations. Measurement of globe position is important and, in some cases of cicatrizing orbital disease, the enophthalmic side may be abnormal. Exophthalmometry is performed in a standard way and direction of globe displacement should be quantified using facial landmarks or the fellow eye. Auscultation, if a bruit is perceived, may be helpful in diagnosis of specific vascular lesions. Quantification of ocular motility, using a technique such as the lateral version reflex, and forced duction testing is helpful in cases of paralytic or restrictive strabismus. Orbital palpation may reveal orbital mass lesions or define areas of point tenderness.

At the conclusion of the clinical evaluation, a differential diagnosis is formulated and decisions made about subsequent testing. Classification of orbital disease by location and involvement of specific orbital structures may help direct this evaluation phase by determining the appropriate laboratory evaluations, best imaging technique, and necessity for biopsy.

Diagnostic testing

Once a differential diagnosis is formed, laboratory and radiologic investigations help in identifying underlying or associated systemic diseases and define the pathologic involvement. Appropriate laboratory studies must be guided by clinical suspicion.[9,11,70,93,95,97] These may include a complete blood count, erythrocyte sedimentation rate, C-reactive protein, anti-nuclear antibody screen, ANCA, rheumatoid factor, serum protein electrophoresis, ACE, and thyroid function studies including TSH and anti-thyroid antibodies. Chest radiographs or computed tomography (CT) should be performed in patients with suspected sarcoidosis.

Although most radiographic orbital evaluations use CT or MRI, there is still a role for orbital ultrasonography in select patients.[52,58,84] Orbital ultrasonography is

helpful in evaluating the insertions of extraocular muscles, determining extrascleral expansion of intraocular tumours, and identifying enlargement and internal reflectivity of lacrimal gland tumours. In addition, scleritis is often identified by increased lucency of posterior Tenon's producing the characteristic 'T' sign on ultrasonography. Pathognomonic changes observed by ultrasonography define lymphangiomas which may mimic OID.

MRI or CT are frequently used in evaluation of acute orbital diseases.[10,37,61,73,76,83,90,91,95,98] The radiologic findings may be variable and highly dependent on the anatomic location and underlying pathology. Lacrimal gland involvement is often observed as enlargement with ill-defined borders and may occur in isolation or in combination with changes in other orbital structures. Orbital fat, when involved, exhibits diffuse or ill-defined infiltration. Extraocular muscle typically shows enlargement of the insertion, a feature that aids in differentiation from thyroid-associated orbitopathy. Orbital apex inflammation may exhibit either infiltrate or mass effect. The optic nerve may show enlargement of the optic nerve sheath with associated changes in contiguous orbital fat.

Although extracranial extension of OID is uncommon, about 37 reported cases, more than half involving the intracranial space, have been reported in the literature, eight of which were reported within the last 18 months.[99,100] In a series of four patients from the Mayo Clinic, three had associated intracranial extension and one demonstrated maxillary sinus involvement. Notably, neuroimaging revealed the disease extension, pain was not a unified feature of the disease, all had a non-specific inflammatory pattern, and none of these four patients required non-steroidal immunosuppressive or radiotherapeutic regimens.[99] In contrast, all four patients reported from Australia reported pain as part of their symptom complex, sclerosing inflammation was observed in three patients, and all required radiotherapy or immunosuppression.[100]

The choice of MRI or CT is determined both by the clinical features of disease and suspected tissue involvement. In evaluations of the optic nerve and nerve sheath, identification of extraorbital extension, or if there is concern about radiation dose, MRI is superior to CT. Contrast agents should typically be used in conjunction with techniques to diminish the fat signal in order to maximize the view of orbital anatomy. Special surface coils may also refine the technique to increase specificity of the study. Inflammatory infiltrates generally show a low signal intensity on T1, variable intensity on T2, and gadolinium enhancement. In contrast, the sclerosing variant of OID typically shows decreased signal intensity on T2 weighted images. In order to evaluate cases for possible abscess formation, or in patients in whom a detailed analysis of orbital bone and adjacent sinuses is desired, CT is the imaging modality of choice.

Orbital biopsy is generally not required in most cases of OID. However, diagnostic concern or unresponsiveness to therapeutic interventions may require sampling for pathologic analysis. Fine-needle aspiration biopsies (FNAB) are most useful in cases of possible orbital metastasis and have been used in evaluating some lesions of lymphoid origin, although special immunologic staining usually requires the availability of sufficient specimen quantity, a challenge in FNAB.[19,101,102] Incisional or excisional biopsies may be performed in the setting of OID. In cases of suspected lymphoproliferative diseases, the pathologist should be alerted and consulted before biopsy in order to optimally handle and deliver the specimen. In many cases of OID, special processing of specimens is required for microbial identification, immunologic testing, and retrieval of genetic information.

Therapeutic intervention

Therapy is directed toward preservation of vision and orbital function and at reducing the acute inflammatory process. Antimicrobial or antifungal therapy is indicated if an infectious organism is suspected, and these cases may require advice from infectious disease specialists. Diagnosis of other associated diseases, for example, Wegener's granulomatosis, leads to the development of specific comprehensive therapeutic plans. High-dose corticosteroids, the adult daily dose typically in the range of 60–80 mg of prednisone, is the mainstay initial therapy for acute or subacute idiopathic OID[3,8,33,95,103–105] (Table 2). A dramatic initial clinical response helps confirm the diagnosis in acute or granulomatous disease groups, but steroid taper must be performed slowly over period of weeks to months in order to prevent exacerbation or recurrence of inflammation. Long term steroid therapy is complicated by adverse events including mood or weight changes, hyperglycaemia, dyspepsia, or accelerated bone changes in patients who are at risk for osteoporosis. It is recommended that bone density evaluations be performed in patients who require long-term steroid therapy in order to determine who might benefit from concomitant medical therapy for osteoporosis. In the event that steroid therapy fails or if dose reduction is inadequate then other modalities must be considered.

Radiation therapy plays an important role in the treatment of metastatic lesions to the orbit or lymphoproliferative disorders but is not an initial therapy for idiopathic OID.[98,106–108] Although low-dose radiotherapy has been successful in multiple cases of

Table 2 OID: medical therapy

Agent	*Comments*
Systemic corticosteroid	Monitor bone density on long-term therapy Adverse effects include mood or weight change, hyperglycaemia, GI distress, accelerated loss of bone density
Methotrexate	Useful steroid sparing agent Folate helps minimize side effects Adverse effects include fatigue, GI distress, liver toxicity, hair loss, headaches, arthralgias
Cyclophosphamide	Cytotoxicity with haemorrhagic cyctitis, bone marrow suppression, malignancy potential
Azathioprine	Adverse effects include bone marrow suppression, GI distress, myalgias, and there is malignancy potential
Cyclosporine	Adverse effects include renal dysfunction, hyptertension, liver toxicity
Mycophenolate mofetil	Potential steroid sparing Adverse effects include haematuria, constitutional symptoms, cough, peripheral oedema, arthralgias, GI distress, haematologic abnormalities
Anti-TNF-α	Adverse effects include demyelinating disease, reactivation of infectious disease, bone marrow suppression, dermatitis, liver toxicity, potential for malignancy induction
IFN-α	Adverse events include bone marrow toxicity, fatigue, flu-like symptoms, diarrhoea, skin rash, hair loss

recurrent myositis, recurrences have also been documented.[98] In the course of TAO, radiation therapy may improve optic nerve functioning in compressive optic neuropathies; however, its use typical TAO remains controversial.[108]

Several classes of immunomodulatory agents have been variably useful in OID.[80,109–118] Methotrexate acts on rapidly proliferating cells and suppresses both T and B lymphocyte function; however, it is also known to enhance release of adenosine, which has potent anti-inflammatory effects. It has a long history of successful use as a steroid-sparing therapy or as an adjunct to steroids in patients of all age groups who have rheumatoid arthritis or uveitis syndromes.[95,109] A recent study of 11 patients with Churg–Strauss syndrome also demonstrated efficacy of this agent in the majority of patients when treated for remission induction at the initial diagnosis.[68] A separate study of 14 OID patients showed a therapeutic benefit in about 64% of treated individuals using methotrexate at a dose of 15–20 mg per week.[109] Prominent side effects of this medication include fatigue, gastrointestinal (GI) disturbances, and elevation of liver enzymes. Headaches, arthralgias, and hair loss may also occur. Dietary supplements of folate help alleviate adverse reactions and parenteral administration of methotrexate may also decrease side effects.

Cyclophosphamide, a derivative of nitrogen mustard, has long been the primary therapy for patients with Wegener's granulomatosis and has been used in several series of patients with severe vasculitic OID.[70,95,104,115] This agent may be used in conjunction with corticosteroids to improve the clinical response in OID patients. The toxicity profile is high with haemorrhagic cystitis, bone marrow suppression, and potential for malignancy induction. Despite the toxicity, cyclophosphamide remains an important agent for use in select patients under conditions of intense and thorough monitoring. There have been several case reports of therapeutic success with azathioprine, which produces T-cell cytotoxicity and decreased antibody production.[115] This also has a significant toxicity profile for bone marrow suppression, GI irritation, and induction of malignancy. Some evidence supports use of cyclosporine, an inhibitor of early T lymphocytes, in patients who are refractory to steroids and in diabetic patients, cyclosporine may improve glucose control. Serious adverse effects include renal dysfunction, hypertension, liver toxicity, and lymphoproliferative diseases. Mycophenolate mofetil (MMF), an antimetabolite with immunosuppressive activity, has been used as a steroid sparing agent in uveitis and scleritis and there is increasing interest in its use in OID.[110,111,117,118] A recent review detailing the experience of MMF in 84 patients with inflammatory ocular disease was recently published.[117] Although more than 80% of their patients achieved therapeutic success, the subset of patients with OID was small and success with MMF was poor in these patients.

Multiple other immune-modulating agents are currently available for therapy in refractory cases of OID or in the pharmaceutical pipeline for use in inflammatory diseases. The success and safety of these designer pharmaceuticals in the therapy of OID is not fully understood but the future availability of targeted biologic therapy is an exciting prospect. Two classes of agents used in case series of patients with OID include agents that interfere with tumour necrosis factor alpha (TNF-α), anti-TNF-α agents, and interferon alpha (IFN-α). In addition to these agents, compounds that produce blockade of interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 15 (IL-15), or IFN-γ are being explored for

therapeutic use in human inflammatory diseases.[119] IFN-α has been reported to have beneficial therapeutic effects in some patients with the Churg–Strauss syndrome and Erdheim–Chester disease.[120] Use of this agent is rooted in the disease biology as IFN-α induces differentiation of histiocytes and dendritic cells.

Anti-TNF-α therapy is now in widespread use for rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, and new indications for its use are emerging including sarcoidosis and inflammatory eye disease.[87,121–123] In the eye, these agents are variably efficacious in inflammatory diseases including uveitis, scleritis, and OID. There are three currently available agents in this class, two of which are monoclonal antibodies, infliximab and adalimumab, and one is a soluble TNF receptor fusion protein, etanercept. Adverse events include exacerbation of demyelinating disease, increased risk of infectious disease such as tuberculosis reactivation, severe dermatitis, induction of systemic lupus erythematosis, worsening of pre-existing congestive heart failure, promotion of lymphoma, induction of significant haematologic cytopenias, and elevated liver function studies. The three forms of anti-TNF therapy vary in their route of administration, subcutaneous for adalimumab and etanercept and intravenous for infliximab, which is typically used in combination with methotrexate. A recent report of seven patients with recalcitrant orbital myositis, previously treated with steroids and either radiotherapy or other anti-inflammatory medications, documented clinical response in all patients to infliximab therapy.[112] Underlying disease associations in these patients included Crohn's disease ($n=2$), Behcet's disease ($n=1$), and psoriasis ($n=1$) and the mean follow-up for response was 15.7 months, with a range of 4–31 months. Other case reports have documented therapeutic responses in Churg–Strauss syndrome and myositis.[114] However, complications of therapy and development of new inflammatory diseases while on therapy may occur. There is a pending case report on development of demyelinating optic neuropathy on anti-TNF therapy in an adolescent and at least one case report of a female patient on etanercept therapy for rheumatoid arthritis who developed orbital myositis.[80]

Conclusions

OID encompasses a group of heterogeneous inflammatory diseases of the orbit. The challenges in OID include diagnosis through careful history, physical examination, laboratory and radiologic investigations, and development of a comprehensive therapeutic plan. Future directions of experimental work require detailed real-time immunologic monitoring in order to determine the pathophysiology of disease and formulate increasingly sophisticated options for targeted therapy. It is likely that sophisticated understandings of the underlying immune pathology will allow optimization of biologic therapies for OID and other inflammatory disorders.

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