Update in pathological diagnosis of orbital infections and inflammations

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Abstract
Orbital inflammations include a broad spectrum of orbital diseases that can be infectious, from a primary or secondary inflammatory process, or idiopathic. Being able to properly diagnose and manage these orbital diseases in a timely manner can avoid permanent visual loss and possibly save a patient’s life. When clinicians are faced with such patients, quite often the exact diagnosis cannot be made based on clinical examination; various laboratory tests and imaging are also needed. Often, orbital biopsies with histopathological analyses may also be required, especially for the atypical cases. Thus, it is important for the clinicians to be familiar with the pathological and other characteristics of these orbital diseases. This review provides a comprehensive update on the clinical and pathological diagnosis of these orbital infections and inflammations.

Key words: Anti-inflammatory agents; Diagnosis, differential; Inflammation; Orbital diseases

Introduction
Orbital inflammatory diseases encompass a broad spectrum of diseases. They are usually characterized by various cardinal features of inflammation, including: pain and tenderness, redness, swelling, and warmth. Orbital infection can have a similar presentation to other orbital inflammatory processes. Since the orbit is a confined space, swelling or edema secondary to any inflammatory process may lead to proptosis, as well as compression of the structures within. Typical presentations include red eye, proptosis, ophthalmoplegia and pain. In severe cases, the eyeball and optic nerve can be compressed leading to choroidal folds or compressive optic neuropathy. A comprehensive medical history detailing the timeline and acuity, along with a complete physical examination, as well as laboratory and radiologic testing, can help to narrow the differential diagnosis. Blood tests should be guided by clinical suspicions, as well as: complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein level, titres of anti-nuclear antibody, cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), rheumatoid factor, serum protein electrophoresis, angiotensin-converting enzyme (ACE), and thyroid function test results. Radiologic orbital evaluation commonly involves computed tomography scan (CT) or magnetic resonance imaging (MRI) with intravenous contrast and is very helpful to narrow differential diagnoses and assess the location and extent of the disease process. Patients with atypical presentations or those who are unresponsive to medical treatment should undergo orbital biopsy to obtain a pathological diagnosis.

Orbital infections
Infections constitute the first differential diagnosis, whenever we are faced with an orbital inflammatory process. Orbit infections or orbital cellulitis can be classified as preseptal or postseptal cellulitis. Preseptal cellulitis refers to infections localized to the eyelids and periorbital structures anterior to the orbital septum. The term postseptal cellulitis is used when the infectious process is located or has extended posterior to the orbital septum. Generally, postseptal cellulitis is more severe and can lead to visual loss. For patients with postseptal cellulitis, CT scan with contrast
infusion (with axial and coronal views) is essential. Axial views should include low narrow cuts of the frontal lobes to rule out peridural and parenchymal brain abscess formation. Coronal views are helpful in determining the presence and extent of any subperiosteal abscesses. An MRI may help in defining an orbital abscess and in evaluating the possibility of cavernous sinus disease. Patients may also have fever and elevated white blood counts.

Complications secondary to orbital cellulitis include subperiosteal abscess (SPA), orbital abscess, and cavernous sinus thrombosis. SPAs can expand rapidly causing more extensive complications such as orbital and cerebral abscesses. Visual loss can be due to central retinal artery occlusion, optic atrophy, septic optic neuritis, and thromboembolic lesions to the retina, choroid, or optic nerve.1 Indications to drain an orbital abscess include: patient age of 9 years or older, large SPA, frontal sinusitis, non-medial SPA, suspicion of anaerobic subperiosteal infection, recurrent SPA after drainage, chronic nerve or retinal compromise, or dental infection.2 A recent study suggests SPA volume as an important criterion; volumes of less than 1,250 mm3 do not require surgical management.3 If drainage of the orbital abscess is necessary, a Gram stain of the pus can be performed, which can be a useful guide for selecting appropriate antibiotic treatment. The exact pathogen can be identified by microbiological culture. When the infection spreads posteriorly into the cavernous sinus, a cavernous sinus thrombosis can develop and meningeal signs such as nausea, vomiting and sepsis become apparent. Palsies of the cranial nerve III, IV, and VI are common in cavernous sinus thrombosis. These cases require urgent administration of intravenous antibiotics and surgical drainage of the orbital abscess.4

Bacterial orbital cellulitis
Common pathogens
Orbital infection can be caused by a host of organisms, including: bacteria, fungi, and parasitic agents. Preseptal cellulitis is commonly caused by direct trauma to the skin or secondary infection often involving a chalazion of the eyelid, and is commonly due to Staphylococcus aureus, Streptococcus sp., and Haemophilus influenzae type B (HiB).5 Since the inception of the HiB vaccine for the pediatric population, HiB has decreased as the causative agent.6 Postseptal orbital infections commonly result from spread of paranasal sinusitis, mostly from the ethmoidal sinus.7,8 Orbital infections can also occur after trauma, skin infection, or bacteremia.9 The pathogens involved in postseptal orbital cellulitis are similar to those in preseptal cellulitis, but age can be a factor in the causative organisms. Patients with SPA younger than 9 years old mostly have sterile or single aerobe infections; in older patients a mixture of aerobes and anaerobes are increasingly encountered and indicate a more problematic pathology.2,10

Community-associated methicillin-resistant
Staphylococcus aureus
Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) should be considered in young children and infants who present with preseptal or orbital cellulitis. Once a nosocomial infection, MRSA now occurs in healthy immunocompetent patients who lack any associated health care environments.11 A retrospective review of pediatric orbital cellulitis found that Staphylococcus was the most common organism isolated (73% being MRSA), followed by the Streptococcus species.12 In another study, MRSA was found in 44% of cases.13 The predominance of MRSA can vary depending on the geographic location.

Streptococcus milleri and Pseudomonas aeruginosa
Although Staphylococcus aureus, Streptococcus sp., and HiB are the most commonly encountered pathogens in orbital cellulitis, uncommon bacteria should also be considered. Streptococcus milleri, a Gram-positive coccus occurring in pairs, is usually found in normal bacterial flora within sinuses and the nasopharynx, however it can spread extensively when there is an obstructed ostium.14,15 This pathogen can form multiple abscesses and is associated with fulminant orbital cellulitis complicated by intraorbital abscesses and cavernous sinus thrombosis (Figure 1).16-18 In patients with multiple orbital abscess, Streptococcus milleri should be considered and aggressive treatment initiated to prevent further complications. It is important to recognize that Pseudomonas aeruginosa (an aerobic Gram-negative rod) is another uncommon cause of preseptal and orbital cellulitis that should be identified in the early stages. It is reported to present with eyelid necrosis in the setting

Figure 1. (a) A clinical photograph demonstrating a left orbital cellulitis with redness and proptosis. (b) A computed tomographic scan of the same patient demonstrating opacification of left paranasal sinuses and left subperiosteal orbital abscesses of the orbital roof.
of neutropenia; delayed diagnosis can cause extensive soft tissue destruction and is life-threatening. Early recognition with reversal of neutropenia is crucial in the management of this infection.19

**Orbital tuberculosis**

Infection of the orbit with *Mycobacterium tuberculosis* is a rare form of extrapulmonary tuberculosis (TB), but more frequent human immunodeficiency virus (HIV) infection and drug-resistant TB has contributed to an increased incidence. Orbital TB can arise from hematogenous spread or direct extension from the paranasal sinuses. It is classified into five forms: classical periostitis; orbital soft tissue tuberculosis or cold abscess with no bony destruction; orbital TB with bony involvement; orbital TB spread from the paranasal sinuses; and tuberculosis dacryoadenitis. All patients with suspected orbital TB should have CT of the orbits followed by an open orbital biopsy to look for acid-fast bacilli (AFB) and chronic granulomatous inflammation. A work-up for systemic TB (chest radiograph and sputum microscopy) is also necessary. Polymerase chain reaction is considered due to its specificity for pulmonary (98% if AFB-positive, 40-77% if AFB-negative) and extrapulmonary TB (93.7-100%). In cases where biopsy is not confirmatory, the use of ancillary testing should be performed. These tests include the tuberculin skin testing and interferon-based immunological tests.20

**Fungal orbital infections**

The presentation of fungal infections of the orbit is similar to those of bacterial orbital infections and other inflammatory conditions, for which reason the diagnosis is often delayed. Fungal infections can cause extensive tissue damage, leading to permanent loss of vision and death if not treated. Fungi invade the orbit via the paranasal sinuses and mostly occur in the immunocompromised host.21 Those at risk of developing fungal orbital infection include: patients with diabetic ketoacidosis, neutropenia, recipients of desferrioxamine therapy, intravenous drug users, premature babies, bone marrow transplantation recipients, trauma victims, and persons receiving corticosteroids or chemotherapy.22,23 Rhino-orbital-cerebral-zygomyces (ROCZ) [also known as mucormycosis] is commonly caused by the non-septate filamentous fungus, *Rhizopus oryzae;*24 and causes an acute and rapidly progressive illness. Due to the ability of the fungus to invade blood vessels, vascular occlusion and tissue necrosis ensue and lead to the classic necrotic black eschar in the nasal mucosa or palate. Extension of the infection can cause central retinal artery occlusion, cerebral infarction, and cavernous sinus thrombosis.25 Imaging with CT or MRI can suggest the presence of invasive mucormycosis but is not diagnostic. Most commonly, CT reveals mucosal thickening of sinuses or thickening of the extraocular muscles, while MRI can show a variety of abnormalities.26 When ROCZ is suspected, empiric antifungal medications should be started and biopsy of the affected tissue should be performed immediately for detailed histopathological analysis. It is important to understand another fungal orbital infection, namely sino-orbital aspergillosis. Aspergillosis is caused by the species *Aspergillus,* which is a septate filamentous mould found in soil and decaying vegetation. Sino-orbital *Aspergillus* infection occurs acutely or chronically and can affect both the immunocompetent and immunocompromised. *Aspergillus flavus* infection is most common in the immunocompetent while *Aspergillus fumigatus* affects the immunocompromised. The risk factors are similar to those of ROCZ but also include prosthetic devices, alcoholism, HIV infection (CD4 <50 cells/mm³), living in an endemic area, excessive environmental exposure, and marijuana use.22,27 Invasive *Aspergillus* infection in the immunocompetent hosts usually presents as a relatively indolent but progressive condition. CT imaging can show heterogeneous soft tissue enhancement with focal bony destruction; intraluminal calcification is indicative of *Aspergillus* infection.28,29 Whenever fungal orbital infection is suspected, a biopsy is essential. The specimen should be sent fresh and stained with potassium hydroxide or calcofluor-white.30 Additional stains with Gomori’s methamine silver and periodic acid-Schiff can be helpful in determining mucosal invasion.30 Repeat biopsies are often necessary, as initial specimens may yield inconclusive results.31

**Parasitic orbital infections**

Parasitic infestations of the orbit are rare and have a relatively higher prevalence in developing countries. Cysticercosis (due to the larval form of *Taenia solium*) and Cysticercus cellulosae can be a cause of orbital cellulitis. A recent large case series of 171 patients found that orbital cysticercosis was the most common ocular manifestation in Southern India.32 Patients most often present with periocular swelling, proptosis, and ptosis. Both CT and contact B-scan ultrasonography are efficient means of confirming the diagnosis (by identifying a cystic lesion with a scolex).32 Echinococcosis or hydatid cyst (caused by *Echinococcus granulosus*) has been reported to occur in the orbit in endemic areas such as Argentina and Iraq.33,34 Patients present with slowly progressive, painless non-pulsatile proptosis, and CT or MRI can reveal unilocular or polycystic orbital cysts.35

**Non-infectious orbital inflammations**

**Thyroid-associated opthalmopathy**

Thyroid-associated ophthalmopathy (TAO) occurs in patients with hyperthyroidism but also occurs with euthyroid or hypothyroid chronic autoimmune thyroiditis. TAO is the most common form of orbital disease particularly among women; the annual incidence is 16 per 100,000 in women and 3 per 100,000 in men.36 TAO is also the most common cause of both unilateral and bilateral proptosis in adults. Although there have been numerous advances in the understanding of TAO, its exact cause is still unknown. Studies suggest that its pathogenesis involves infiltration of hyaluronan into extraocular muscle fibers and orbital adipose tissue.37 TAO typically starts with an initial active inflammatory phase, followed by a subsequent inactive fibrotic phase. Enlargement of extraocular muscles and
orbital adipose tissue ensues, with patients under 40 years old having predominantly fat expansion and those aged over 60 years have muscle enlargement. Common clinical features are: upper eyelid retraction, edema, erythema, diplopia, and chemosis (Figure 2a). Extensive IOID can result in ophthalmoplegia, compressive optic neuropathy, and destruction of orbital tissue.38 CT with contrast is the preferred imaging modality, which enhances any focal or diffuse mass. Common radiologic findings include: infiltration of orbital fat and the orbital apex, proptosis, extraocular muscle enlargement, muscle tendon or sheath enlargement, optic nerve thickening, uveal scleral thickening, edema of tenon’s capsule, and lacrimal gland infiltration (Figure 2b and 2c); tendons of extraocular muscle may be involved or spared, and the feature can help differentiation from TAO.32,43 In atypical cases and those not responding to initial corticosteroid therapy, an orbital biopsy should be performed. Histopathology typically shows a benign, non-specific inflammatory pattern ranging from diffuse lymphocytic and polymorphous infiltration to varying degrees of infiltrative fibrotic connective tissue (Figure 2d). No infectious agents or granuloma formation occurs. So IOID is a clinical diagnosis of exclusion; there being no clear local or systemic etiology such as infection, inflammation, trauma, or foreign body, TAO, Wegener’s granulomatosis (WG), polyarteritis nodosa, giant cell arteritis, sarcoidosis, neoplasm, and arteriovenous malformation should also be excluded. Idiopathic sclerosing orbital inflammation (ISOI) is a rare subgroup of IOID, accounting for 5 to 8% of inflammatory orbital lesions.42 There is a debate as to whether ISOI is a primary fibrosing

Idiopathic orbital inflammatory disease
Idiopathic orbital inflammatory disease (IOID) is the third most common orbital disease after TAO and lymphoproliferative diseases. It accounts for 4.7 to 6.3% of orbital disorders.4 It can affect the whole orbit as a diffuse process, or as a focal process affecting specific orbital tissues such as an extraocular muscle (myositis), lacrimal gland (dacryoadenitis), optic nerve sheath (optic perineuritis) or orbital apex (orbital apex syndrome). Due to its diffusely infiltrating nature, the presentation can vary depending on which orbital tissues are involved. This disease typically presents unilaterally with acute pain, proptosis, edema, erythema, diplopia, and chemosis (Figure 2a). Extensive IOID can result in ophthalmoplegia, compressive optic neuropathy, and destruction of orbital tissue.41 CT with contrast is the preferred imaging modality, which enhances any focal or diffuse mass. Common radiologic findings include: infiltration of orbital fat and the orbital apex, proptosis, extraocular muscle enlargement, muscle tendon or sheath enlargement, optic nerve thickening, uveal scleral thickening, edema of tenon’s capsule, and lacrimal gland infiltration (Figure 2b and 2c); tendons of extraocular muscle may be involved or spared, and the feature can help differentiation from TAO.32,43 In atypical cases and those not responding to initial corticosteroid therapy, an orbital biopsy should be performed. Histopathology typically shows a benign, non-specific inflammatory pattern ranging from diffuse lymphocytic and polymorphous infiltration to varying degrees of infiltrative fibrotic connective tissue (Figure 2d). No infectious agents or granuloma formation occurs. So IOID is a clinical diagnosis of exclusion; there being no clear local or systemic etiology such as infection, inflammation, trauma, or foreign body, TAO, Wegener’s granulomatosis (WG), polyarteritis nodosa, giant cell arteritis, sarcoidosis, neoplasm, and arteriovenous malformation should also be excluded. Idiopathic sclerosing orbital inflammation (ISOI) is a rare subgroup of IOID, accounting for 5 to 8% of inflammatory orbital lesions.42 There is a debate as to whether ISOI is a primary fibrosing
disease or represents end-stage IOID. Patients with ISOI differ from those with IOID in that they present with fewer inflammatory signs, have chronic/insidious onset, yet tend to be more aggressive. Histologically, ISOI shows marked fibrosis associated with few mixed chronic inflammatory cell infiltrates (Figure 3).

Specific orbital inflammation

Wegener's granulomatosis

WG is a necrotizing, granulomatous inflammation featuring vasculitis affecting any organ, but most commonly the respiratory and renal systems. Untreated it is associated with a high morbidity and mortality. Orbital involvement in WG may be the first or only manifestation; ocular manifestations occur in over 50% of patients. Orbital WG usually results from spread of adjacent sinus disease, presenting with orbital pain, proptosis, and ophthalmoplegia. Severe WG can result in orbital socket contraction (enophthalmos), optic nerve infiltration or compression, leading to permanent loss of vision and local destruction of the bony orbit.

Ocular complications include: conjunctivitis, scleritis, marginal ulcerative keratitis, uveitis, retinal vasculitis, optic neuropathy, dacyroadenitis, and nasolacrimal duct obstruction. Persons suspected to have active orbital WG should have a systemic work-up that includes renal and pulmonary assessment, testing for C-ANCA, and orbital imaging with CT or MRI. Serum C-ANCA levels are elevated in 80 to 90% of patients. In WG, the lesions appear hyperintense relative to nasal mucosa in contrast-enhanced CT, and sinus opacification with bony erosion may be visualized. In MRI, the lesions appear hypointense compared to orbital fat after both T1 and T2 weighting, but lesions enhance with IV gadolinium contrast. In circumstances where the diagnosis has not been confirmed following clinical, laboratory, and radiologic evaluation, an orbital biopsy is necessary. Classical histologic findings in WG consist of necrotizing granulomatous vasculitis with giant cells. A mixed inflammatory infiltrate with moderate numbers of neutrophils forming microabscesses may be seen. The vasculitis can cause vessel wall necrosis with infiltration by neutrophils, which degenerate and become surrounded by palisading histiocytes and multinucleated giant cells. In these cases, the pathologist needs to perform a Gram stain, and fungal and Ziehl Neelsen stains to rule out infection.

Sarcoidosis

Sarcoidosis is a multisystem inflammatory disease characterized by non-caseating granulomas. It typically affects the lungs, mediastinal lymph nodes, eyes, ocular adnexa, peripheral lymph nodes, skin, central nervous system, and heart. Ocular adnexal and orbital lesions have been reported in 8 to 28% of cases, with the lacrimal gland being affected the most followed by the orbit, eyelid, and lacrimal sac. Common orbital signs are erythema and edema of eyelids, followed by mass effects, infiltrative processes, and visual loss. Radiologic pulmonary findings include: bilateral hilar lymphadenopathy and parenchymal lung involvement. Work-up of patients suspected with sarcoidosis includes: chest X-ray, determination of ACE, lysozyme, and calcium levels, as well as gadolinium scans. Patients with negative results may still warrant a biopsy to look for characteristic histopathology (non-caseating granulomatous inflammation).

Adult orbital xanthogranuloma

Adult orbital xanthogranuloma is a rare orbital and ocular adnexal disease, classified as a type II non-Langerhans histiocytic disorder. Depending on its systemic involvement, this condition can be classified into four syndromes: adult-onset xanthogranuloma, adult-onset asthma with periocular xanthogranuloma, necrobiotic xanthogranuloma, and Erdheim-Chester disease. Adult-onset xanthogranuloma involves an isolated xanthogranulomatous lesion without other systemic manifestations and its course is often self-limited. Adult-onset asthma with periocular xanthogranuloma is associated with asthma, lymphadenopathy, and increased immunoglobulin G (IgG) levels, which present with eyelid xanthogranulomatous lesions and/or orbital masses. Necrobiotic xanthogranuloma is associated with subcutaneous skin lesions in the eyelids, orbit, and elsewhere on the body. Systemically it can be associated

Figure 3. (a) Histology of a case of idiopathic sclerosing orbital inflammation showing markedly diffuse fibrosis and a few polymorphous infiltrates (H&E stain, x 200). (b) Masson trichrome stain was used to highlight the fibrous tissue from the same specimen (x 200).
with paraproteinemia and multiple myeloma, and more often there may also be ulcerating and fibrosing skin lesions. Erdheim-Chester is the most severe form, with diffuse progressive, fibrosclerosis of the orbit and internal organs.52 These conditions are all characterized histopathologically by the presence of xanthoma cells, Touton giant cells, and fibrosis. Necrosis is most commonly found in necrobiotic xanthogranuloma.53

Mass-forming orbital inflammations

Langerhans cell histiocytosis

Langerhans cell histiocytosis is histopathologically characterized by proliferation of Langerhans cells.54 It occurs in children with peak incidence at around the age of 1 to 4 years, those with disease onset earlier than 1 year old have the worst prognosis.55 Its manifestations can range from a benign unifocal bone lesion to an aggressive multisystem disease. In its multisystem form, it can be complicated by diabetes insipidus. The most typical presentation is an osteolytic mass-like lesion, located in the superolateral orbit with variable degrees of proptosis and inflammation (Figure 4a and 4b). The diagnosis should be confirmed by histopathology showing the presence of Langerhans cells, characterized by a distinct cell margin and pink granular cytoplasm. Further confirmation can be provided by CD1a immunostaining or electron microscopy revealing the presence of birbeck granules (Figure 4c and 4d).56

Immunoglobulin G4–related sclerosing disease

This condition is an inflammatory disorder characterized by increased serum levels of IgG4 and presence of IgG4-positive plasma cells in the affected tissues.57 It was first described in autoimmune pancreatitis and subsequently in various internal organs such as retroperitoneal soft tissue, breast, biliary tract, liver, salivary glands, and elsewhere. Patients typically present with a mass-like lesion in the affected organs and the diagnosis depends on histology. The orbit is a possible site of involvement, where it can manifest with unilateral or bilateral mass-like lesions; the lacrimal gland being the most commonly involved site. Mikulicz disease (bilateral lacrimal, parotid, and submandibular gland swellings) was identified as a form of IgG4-related sclerosing disease (Figure 5a and 5b). Histopathologic orbital biopsy shows chronic inflammatory cell infiltrates with numerous IgG4-positive plasma cells and a variable degree of fibrosis (Figure 5c and 5d). A panel of lymphoid

Figure 4. (a) A clinical photograph of a patient with right Langerhans cell histiocytosis (LCH) showing proptosis, redness, and a mass-like lesion. (b) A coronal computed tomographic scan showing an osteolytic right superolateral orbit lesion. (c) Histopathology from the same patient showing the presence of numerous Langerhans cells suggesting LCH. A multinucleated giant cell is present (H&E stain, x 400). (d) The diagnosis of LCH was confirmed with CD1a immunostaining (x 400).
markers (immunostaining) should be used to exclude the possibility of lymphoma. A recent study comparing its histology to IOID and prominent lymphoid hyperplasia with IgG4-related systemic disease found that the IgG4-positive group had higher frequency of marked follicular hyperplasia, fibrosis, plasma cells, and eosinophils, all of which suggest an IgG4-associated systemic disease with distinct orbital manifestations.58

Rosai-Dorfman disease
Rosai-Dorfman disease (RDD) is a histiocytic proliferative disorder of unknown etiology, commonly presenting with large, painless, bilateral cervical lymphadenopathy, but can involve any organ.59 It is associated with fever, leukocytosis, elevated ESR, and hypergammaglobulinemia. The orbit is involved in 10% of cases, commonly as infiltration of soft tissues and the intraconal space. Clinical manifestations include: proptosis, diplopia, blurred vision, dry eye, epiphora, epibulbar masses, marginal corneal infiltrate, and uveitis (Figure 6a).60,61 If the patient presents with an orbital mass-like lesion, orbital biopsy for histopathologic analysis is necessary to make a diagnosis of RDD. Histology reveals multiple aggregates of large histiocytes, accompanied by a dense infiltrate of plasma cells, lymphocytes, and granulocytes, many of which show emperipolesis meaning engulfed lymphocytes within their cytoplasm (Figure 6b). The histiocytes stain positive for S-100 and CD-68, but negative for CD1a (Figure 6c). Extranodal RDD entails prominent fibrosis.62

Drug-related orbital inflammation
The bisphosphonates (zoledronic acid and pamidronate) inhibit osteoclastic bone resorption, and are used to treat osteolytic bone cancer, bony metastasis, Paget’s disease, and osteoporosis; they can also lead to orbital inflammation.63 Onset of ocular and orbital symptoms can vary from 1 to 6 days after drug administration. Patients report orbital pain, diplopia, and eyelid swelling. While examination may reveal periorcular edema, chemosis, episcleritis, scleritis, uveitis, proptosis, and ophthalmoplegia, MRI can show fat stranding, optic nerve sheath enhancement, scleral enhancement, and enlargement of extraocular muscles. The mechanism behind the cause of orbital inflammation from bisphosphonate is unknown, but release of acute-phase reactants and cytokine may play a role.63

Secondary orbital inflammations
Orbital inflammation can occur in response to another orbital condition rather than being a primary orbital inflammatory
Orbital lymphoproliferative lesions

Lymphoproliferative lesions are the most common primary orbital tumors in adults.64 Clinically, they are often confused with IOID because of similar clinical and radiologic features. Since they can lead to a variable degree of inflammation and respond partially to systemic steroid treatment, the diagnosis may be delayed unless a biopsy is performed. These tumors range from reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, to frank lymphomas, characterized by different histopathologic and immunophenotypic features. In general, B cell lymphomas are far more common than the T cell variety, but the latter tend to have a more aggressive clinical course. Low-grade orbital marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) are the most common subtype, and account for 40 to 70% of cases.55-67 According to a large case series, the most common presenting feature was eyelid swelling followed by a palpable eyelid mass, diplopia, blurred vision, proptosis, pain, and lid erythema.68 Orbital lymphoid tumors usually become evident on CT as diffuse, solid-enhancing masses with moulding of the globe.69 Occasionally, they can present as a circumscribed mass. Bony erosion is usually not seen except in large B-cell lymphomas.68 Histopathology of MALT lymphomas is characterized by poorly defined follicular areas composed of monocytoid B cells that feature large nuclei. A more aggressive and rare non–B-cell type lymphoma is the natural killer/T (NK/T) cell lymphoma, which is highly aggressive, and typically involves the nasal cavity and paranasal sinuses; initially it may present with orbital and adnexal symptoms.70 Patients can also present with orbital edema, ophthalmoplegia, and uveitis.71 Such NK/T cell lymphomas have been reported to present as orbital cellulitis that fails to improve with antibiotic therapy.72 Imaging often shows a soft tissue mass that obliterates the nasal and paranasal sinuses in association with bony erosion. Both CT and MRI with contrast enhancement may show heterogeneous enhancement of the tumor.71 Histologically the tumor exhibits variable cytology, with angiocentricity and angioinvasion. Immunophenotyping shows NK cell characteristics, including evidence of CD2+, CD4+, CD20-, CD56+ cell types and Epstein-Barr virus.73 These lymphomas are very aggressive disease and confer a poor prognosis once disseminated, notwithstanding radiotherapy and aggressive chemotheray.71

Orbital foreign bodies

Patients suffering from orbital foreign bodies typically have a history of injury. Occasionally, delayed presentation is possible, and the presentation may entail orbital inflammation or discharging sinus. The presence of most foreign bodies can be revealed by X-ray and/or CT; MRI can be useful for the non-metallic foreign bodies.

Orbital hemorrhages

Acute orbital hemorrhages cause acute proptosis, redness, orbital pain, and ophthalmoplegia, all of which can simulate orbital tumors and other inflammatory diseases. Moreover, orbital hemorrhage itself is often associated with a degree of inflammation. The various etiologies include: orbital venous malformations (orbital varix), and lymphangioma (a common cause of spontaneous orbital hemorrhages). Imaging by CT usually shows a diffuse reticular pattern. MRI can be used to help differentiate intraorbital hemorrhage from orbital inflammatory conditions, since T1- and T2-weighted images show enhancement of the former.74
Conclusion

A variety of infections and inflammatory conditions can be encountered in the orbit. When a clinician encounters a patient with clinical features suggesting an orbital process, it is important to consider, and work-up for, a wide range of differential diagnoses. Orbital imaging with CT or MRI should always be performed in these patients, and orbital biopsy is necessary for any atypical or doubtful diagnosis. Close collaboration between the clinician and pathologist is important in elucidating the correct diagnosis, as crucial information may direct the pathologist to use special stains and immunohistochemistry to establish a pathological diagnosis.

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