Update in Pathological Diagnosis of Orbital Infections and Inflammations

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ABSTRACT

Orbital infections and inflammations include a broad spectrum of orbital diseases that can be idiopathic, infectious, from primary or secondary inflammatory processes. Being able to properly diagnose and manage these orbital diseases in a timely manner can avoid permanent vision loss and possibly save a patient's life. When clinicians are faced with such patients, quite often the exact diagnosis cannot be made just based on clinical examination, various laboratory tests and imaging are needed. Moreover, orbital biopsies with histopathological analyses are often required, especially for the atypical cases. Thus, it is important for the clinicians to be familiar with the pathological features and 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: Infection, Inflammation, Orbit

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INTRODUCTION

Orbital inflammatory diseases encompass a board spectrum of diseases. They are usually characterized by various cardinal signs of inflammation including pain, redness, swelling, and warmth. Orbital infection is a form of inflammation caused by infective agents and, therefore, orbital infection and other orbital inflammatory processes can have similar presentation. Since the orbit is a confined space, swelling or edema secondary to any inflammatory process can lead to proptosis, as well as compression of the structures within the orbit. Typical presentations include red eye, proptosis, ophthalmoplegia, and pain.[1] In severe cases, the eyeball and optic nerve can be compressed leading to choroidal folds or compressive optic neuropathy. Performing a complete medical history detailing the timeline and acuity, along with complete physical examination, and laboratory and radiologic testing will help narrow the differential diagnosis. Blood tests should be guided by clinical suspicion, these include complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, anti-nuclear antibody (ANA), cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), rheumatoid factor (RF), serum protein electrophoresis, angiotensin converting enzyme (ACE), and thyroid function studies. Radiologic orbital evaluation commonly involves computerized tomography scan (CT) or magnetic resonance imaging (MRI) with intravenous contrast and is very helpful to narrow down the differential diagnoses and assess the location and extent of the disease process.[2] Patients with atypical presentation or those who are unresponsive to medical treatment should have an orbital biopsy for pathological diagnosis.[2]

ORBITAL INFECTIONS

Infections should be the first differential diagnosis whenever one is faced with orbital inflammatory process. Historically, Chandler classified orbital cellulitis into 5 different stages. Stage 1, being inflammation localized anterior to the orbital septum, without orbital signs. In stage 2, there is infection extending posterior to the orbital septum leading to diffuse orbital edema. Stage 3 is defined by the presence of subperiosteal abcess, while stage 4

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represents intraorbital abcess within the orbit. With further extension of the infection posterior to the orbit, cavernous sinus thombosis develops which is what defines stage 5.[1] In more practical approach, orbital infections can be classified as preseptal or postseptal cellulitis. Preseptal cellulitis refers to those infections localized to the eyelids and periocular 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. In general, postseptal cellulitis is more severe and can lead to visual loss. For patients with postseptal cellulitis, CT scan with contrast infusion, including 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 subperiorbital abscesses. MRI may be helpful in defining orbital abscesses and in evaluating the possibility of cavernous sinus disease. Patients may also have fever and elevated WBC count in their complete blood count.

Complications secondary to orbital cellulitis include subperiosteal abcess (SPA), orbital abcess, and cavernous sinus thombosis. Subperiosteal abcesses can expand rapidly causing more extensive complications such as orbital and cerebral abcesses. Vision loss can result due to central retinal artery occlusion, optic atropy, septic optic neuritis, or thromboembolic lesions to the retina, choroid, or optic nerve.[3] Surgical indications to drain an orbital abcess include patients ≥ 9 years age, large SPA, frontal sinusitis, nonmedial SPA, suspicion of anerobic subperiosteal infection, recurrent SPA after drainage, chronic sinusitis, acute optic nerve or retinal compromise, or dental infection.[4] A recent study suggests SPA volume as an important criteria and those whose SPA volumes are less than 1,250 mm^3 do not require surgical management.[5] If drainage of the orbial abscess is required, a gram stain of the pus can be performed, and this can be a useful guide in terms of selecting appropriate antibiotics for treatment. The exact pathogen can be identified by microbiological culture tests. When the infection spreads posteriorly into the cavernous sinus, a cavernous sinus thrombosis can develop and meningeal signs such as nausea, vomiting, and sepsis will appear. Palsies of the cranial nerve III, IV, and VI are common presentations in cavenous sinus thrombosis. These cases require urgent administration of intravenous antibiotics and surgical drainage of orbital abscess.[6]

BACTERIAL ORBITAL CELLULITIS

Common pathogens

Orbital infection can be caused by a host of organisms and these include bacteria, fungi, and parasitic agents. Preseptal cellulitis is commonly caused by direct trauma to the skin or secondary infection of chalazion of the eyelid commonly by organisms such as *Staphylococcus aureus*, Streptococcus, and Hemophilus influenzae type B (HiB).[7] Since the inception of the HiB vaccine in the pediatric population, HiB has decreased as the causative agent.[8] Postseptal orbital infections commonly result from spread of paranasal sinusitis, mostly from the ethmoidal sinus.[9,10] Orbital infections also can occur after trauma, skin infection, or bactermia.[11] The pathogens involved in postseptal orbital cellulitis are similar to those in preseptal cellulitis, but age can be a factor in the composition of the organisms. Patients with subperiosteal abcess younger than nine years old mostly have sterile or single aerobe infections, while older age patients have increasing mixture of aerobe and anarobes indicating a more virulent infection[4,12]

Community associated methicillin-resistant *Staphlycoccus aureus*

Community associated methicillin-resistant *Staphlycoccus aureus* (CA-MRSA) should be considered in young children and infants who present with preseptal or orbital cellulitis. MRSA, once considered as a nosocomial infection, is now seen to occur in healthy immunocompetent patients who lack the risk factors associated with the contact of the health care environment.[13] A retrospective review of pediatric orbital cellulitis found that Staphylococcus species was the most common organism isolated followed by the Streptococcus species. This study found 73% of the S. aureus isolates were MRSA.[14] In another study, MRSA was found in 44.4% of cases.[15] The predominance of MRSA can vary by geographical location.

Streptococcus milleri and *Pseudomonas aeruginosa*

Although *Staphylococcus aureus*, Streptococcus, and Hemophilus influenzae type B are the most commonly encountered pathogens in orbital cellulits, uncommon bacterial organisms should be considered. *Streptococcus milleri*, a Gram positive cocci in pairs, is usually found in normal bacterial flora in the sinus and nasopharynx; however, it can grow extensively when there is an obstructed ostia.[16,17] This pathogen can form multiple abscesses and is associated with fulminant orbital cellulitis complicated by intraorbital abscesses and cavernous sinus thrombosis [Figure 1a and b].[18-20] In patients with multiple orbital abscess, *Streptococcus milleri* should be considered and aggressive treatment should be initiated to prevent further complications. *Pseudomonas aeruginosa* is another uncommon cause of preseptal and orbital cellulitis and is important to recognize. *Pseudomonas aeruginosa*, an aerobic Gram negative rod, is an uncommon cause of preseptal and orbital cellulites and it is important to recognize this in the early stages. It has been reported to present with eyelid necrosis in the setting of neutropenia. Unrecognized, this infection can cause extensive soft tissue destruction and be life threatning. Early recognition with reversal of neutropenia is crucial in the management of this infection.[21]

Orbital tuberculosis

Infection of the orbit with *Mycobacterium tuberculosis* (TB) is a rare form of extrapulmonary tuberculosis, but the rise in HIV infection and drug-resistant tuberculosis has contributed to the increase in incidence of TB infection. Orbital TB can arise from hematogenous spread or from direct extension from the paranasal sinuses. Orbital TB is classified into five forms: classical periostitis, orbital soft tissue tuberculoma or cold abcess with no bony destruction, orbital TB with bony involvement, orbital TB spread from the paranasal sinuses, and tuberculous dacryoadenitis. All patients with suspected orbital TB should have a computerized tomography of the orbits followed by an open orbital biopsy to look for acid fast bacilli and chronic inflammation with granuloma formation (granulomatous inflammation). A work up of systemic TB with a chest radiograph and sputum microscopy is required. PCR 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 the interferon-based immunological tests.[22]

ORBITAL FUNGAL INFECTIONS

The initial presentation of fungal infections of the orbit is similar to those bacterial orbital infections or other inflammatory conditions and the diagnosis is often delayed. Fungal infections can cause extensive tissue damage potentially leading to permanent vision loss and death if not treated. Fungal orbital infections invade the orbit via the paranasal sinuses and occur mostly in the immunocompromised host.[23] Those patients who are at risk of developing orbital fungal infection include diabetic ketoacidosis, neutropenia, deferoxamine therapy, intravenous drug use, prematurity, bone marrow transplantation, use of corticosteroid or chemotherapy, and trauma.[24,25] Rhino-orbital-cerebral-zygomycosis (ROCZ), also known as mucormycosis, is commonly caused by the non-septate filamentous fungus, *Rhizopus oryzae*.[26] Patients with ROCZ present acutely and progress rapidly. Due to the affinity of the fungus to invade blood vessels, vascular occlusion and tissue necrosis occur leading 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.[27] Imaging with CT or MRI can suggest invasive mucormycosis but is not diagnostic. Most common CT finding is mucosal sinus thickening or thickening of the extraocular muscles, while MRI can show a variety of findings.[28] When ROCZ is suspected, empiric treatment with antifungal medications should be started and biopsy of the affected tissue should be performed immediately for detailed histopathological analysis. Another fungal orbital infection important to understand is sino-orbital aspergillosis. Aspergillosis is caused by the fungal species Aspergillus, which is a septate filamentous mould found in the soil and decaying vegetation. Sino-orbital Aspergillus infection can occur 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 ROCZ with the addition of prothetic devices, alcoholism, HIV infection (CD-4 $<$ 50 cells/mm^3), living in endemic area, excessive environmental exposure, and marijuana use.[25,29] Invasive Aspergillus infection in the immunocompetent host usually presents in a more indolent but progressive course. CT imaging can show heterogenous soft tissue enhancement with focal bony destruction with intraluminal calcification being indicative of an Aspergillus infection.[30,31] When there is suspicion of fungal orbital infection, a biopsy is essential. The specimen should be sent fresh and stained with potassium hydroxide or calcoflour white.[25] Additional stains with Gomori's methenamine silver (GMS) and periodic acid Schiff (PAS) can be helpful in detemining mucosal invasion.[32] Repeat biopsies are often necessary due to frequent inconclusive results.[33]

ORBITAL PARASITIC INFESTATIONS

Parasitic infestations of the orbit are rare and have highest prevalence in developing countries. Cysticercosis is a parasitic infestation by 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.[34] Patients most commonly present with periocular swelling, proptosis, and ptosis. Both computer tomography and contact B-scan ultrasonography are efficient ways to confirm the diagnosis by identifying a cystic lesion with a scolex.[34] Echinococcosis or hydatid cyst caused by E. granulosus, has been reported to occur in the orbit in endemic areas such as Argentina and Iraq.[35,36] Reported cases present with slowly progresssive, painless non-pulsitle proptosis. CT or MRI can reveal unilocular or polycystic cyst in the orbit.[37]

NON INFECTIOUS ORBITAL INFLAMMATIONS

Thyroid-associated ophthalmopathy

Thyroid-associated ophthalmopathy (TAO) occurs in patients with hyperthyroidsim but also occurs with euthyroid or hypothyroid chronic autoimmune thyroiditis. TAO is the most common form of orbital disease and is more common in women with an incidence rate of 16 per 100,000 and 3 per 100,000 in men.[38] TAO is also the most common cause of both unilateral and bilateral proptosis in adults. Though there has been numerous recent advances in the understanding of TAO, the exact cause is still unknown. Studies do suggest that the pathogesis of the disease is due to infiltration of hyaluronan in extraocular muscle

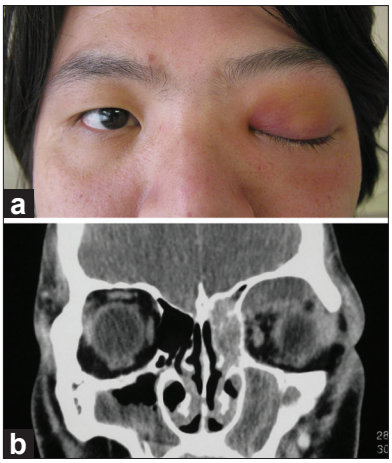

Figure 1: (a) A clinical photograph demonstrating a left orbital cellulitis with redness and proptosis. (b) CT scan of the same patient demonstrating opacification of left paranasal sinuses and left subperiosteal orbital abcesses of the orbital roof

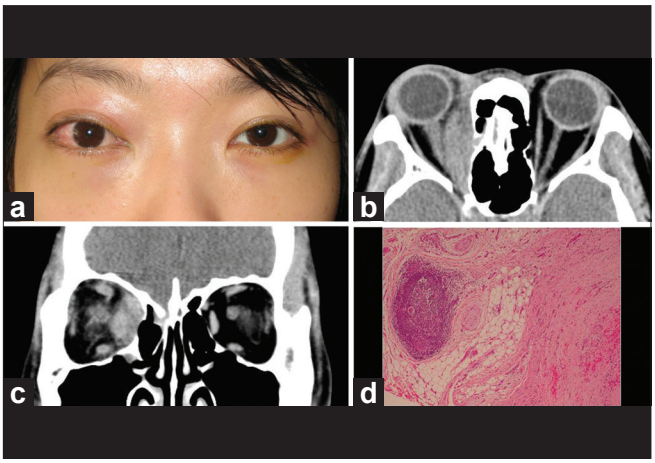

Figure 2: (a) A patient with right IOID with proptosis and redness of the right eye. (b) Axial computer tomographic scan of the same patient demonstrating enlargement of medial rectus with surrounding orbital fat intensities suggesting orbital inflammatory process. (c) Coronal computer tomographic scan of the same patient demonstrating enlargement of medial rectus with surrounding orbital fat intensities suggesting orbital inflammatory process. (d) Histology of a case of IOID showing diffuse polymorphous infiltrate with surrouding fibrous tissue and orbital adipose tissue (H and E, ×100)

fibers and orbital adipose tissue.[39] TAO typically starts with an initial active inflammatory phase, followed by a subsequent inactive fibrotic phase. Enlargement of extraocular muscles and orbital adipose tissue occur, with patients under 40 years of age having predominantly fat expansion and those over 60 years having muscle enlargement. Common clinical features are upper eyelid retraction, edema, erythema of the periorbital tissues and conjunctiva, and proptosis. 3 to 5% of patients will suffer from intense pain, inflammation, corneal ulceration, or compressive optic neuropathy.[40] Orbital imaging with CT or MRI will show extraocular muscle enlargement in 70% of affected patients and presence of asymmetric bilateral disease is usually detected despite unilateral presentation.[41,42] The diagnosis can be made based on clinical and radiological features, orbital biopsy is seldom required except for atypical cases. The histologic features of the extraocular muscles in TAO is composed of clusters focal and perivascular interstitial inflammatory mononuclear cell infiltrates with striated extraocular muscle fibers separated by amorphous granular material muscle fibres known as 'lymphorrhages'.[39]

Idiopathic orbital inflammatory disease

Idiopathic orbital inflammatory disease (IOID) is the third most common orbital disease after TAO and lymphoproliferative diseases. IOID accounts for 4.7% to 6.3% of orbital disorders.[2] This disorder 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 (darcyoadenitis), optic nerve sheath (optic perineuritis) or orbital apex (orbital apex syndrome). Due to the diffusely infiltrating nature of the disease, the presentation can vary depending on which orbital tissues 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.[2] CT with contrast is the preferred imaging modality, enhancing the focal or diffuse mass. Common radiological findings include infiltration of orbital fat and orbital apex, proptosis, extraocular muscle enlargement, muscle tendon or sheath enlargement, optic nerve thickening, uveal scleral thickening, edema of tenon capsule, and lacrimal gland infiltration [Figure 2b and c], the tendons of extraocular muscle may be involved or spared and this feature helps differenciation from TAO.[43,44] 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 that can range from diffuse lymphocytic and polymorphous infiltrate to varying degrees of infiltrative fibrotic connective tissue [Figure 2d]. There will be no infectious agents and no granuloma formation. IOID is a clinical diagnosis of exclusion; therefore lesions that have a clear local or systemic etiology such as infection, inflammation from trauma or foreign body, TAO, Wegener granulomatosis, polyarteritis nodosa, giant cell arteritis, sarcoidosis, neoplasm, and arteriovenous malformation should be excluded. Idiopathic sclerosing orbital inflammation (ISOI) is a rare subgroup of IOID, composing 5–7.8% of the inflammatory orbital lesions.[43] There is a debate whether ISOI is a primary fibrosing disease or a disease representing end-stage IOID.[45] Differing from IOID, patients with ISOI presents with fewer inflammatory signs, have chronic onset and tend to be more aggressive. Histologically, ISOI shows marked fibrosis associated with few mixed chronic inflammatory cell infiltrates [Figure 3a and b].[46]

Specific orbital inflammation

Wegener's granulomatosis

WG is a necrotizing, granulomatous inflammation featuring vasculitis affecting any organ system, most commonly the

respiratory and renal systems. If untreated, it is associated with a high morbidity and mortality. Orbital involvement in WG may be the first or only manifestation, with ocular manifestations occuring in over 50% of patients.[47] 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 vision loss and local destruction of the bony orbit.[48] Ocular complications include conjunctivitis, scleritis, marginal ulcerative keratitis, uveitis, retinal vasculitis, optic neuropathy, dacryoadenitis, and nasolacrimal duct obstruction.[49] Those suspected to have active orbital WG should have systemic work-up including renal and pulmonary assessment, C-ANCA, and orbital imaging with CT or MRI. Serum C-ANCA will be elevated in 80–90% of patients.[47] The lesions in wegener's granulomatosis appear hyperintense relative to nasal mucosa in contrast enhanced CT, and sinus opacification with bony erosion will be visualized. In MRI, the lesions appear hypointense compared to orbital fat in both T1 and T2, but lesions enhance with IV gadolinium contrast.[50] In circumstances where diagnosis has not been confirmed following clinical, laboratory, and radiologic evaluation, an orbital biopsy needs to be performed. Classic histological findings in WG consists of necrotizing granulomatous vasculitis with giant cells. Mixed inflammatory infiltrate with moderate number of neutrophils forming microabscess will be seen. The vasculitis will 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 will perform Gram stain, fungal and Zeihl–Neelson 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 has been reported to occur in 8–28% of cases with 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 effect, infiltrative process, and vision loss.[51,52] Radiologic pulmonary findings include bilateral hilar adenopathy and parenchymal lung invovlement. Work-up of patients suspected with sarcoidosis include chest X-ray, ACE converting enzyme, lysozyme levels, serum calcium assay, and gadolinium scan. Patients with negative results should warrant a biopsy. Histopathology will show non-caseating granulomatous inflammation.[52]

Adult orbital xanthogranuloma

Adult orbital xanthogranuloma is a rare orbital and ocular adnexal disease classified as a type II non-Langerhan histiocytic disorder. Depending on the 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 systemic lesions and is often self limited. Adult onset asthma with periocular xanthogranuloma is associated with asthma, lymphadenopathy, and increased IgG levels presenting with eyelid xanthogranulomatous lesions and or orbital masses. Necrobiotic xanthogranuloma is associated with subcutaneous skin lesions in the eyelids, orbit, and body. Systemically, necrobiotic xanthogranuloma can be associated with paraproteinemia and multiple myeloma with skin lesions ulcerating and fibrosing more often. Erdheim-Chester is the most severe form of the xanthogranulomas, with diffuse progressive, fibrosclerosis of the orbit and the internal organs.[53] 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.[54]

Mass forming orbital inflammations

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is histopathologically chararacterized by proliferation of Langerhans cells.[55] This disease occurs in children with peak incidence at age 1 and 4, those with onset of disease earlier than 1 year of age have worst prognosis.[56] Severity can range from a benign unifocal bone lesion to aggressive multisystem disease. In multisystem form, this can be complicated by diabetes insipidus. The most typical presentation is a osteolytic mass like lesion, located in the superolateral orbit in pediatric patients with varibale degree of proptosis and inflammatory signs [Figure 4a and b]. The diagnosis should be confirmed by histopathology and this will show the presence of langerhans cells, characterized by distinct cell margin and pink granular cytoplasm. The diagnosis can be confirmed by CD1a immunstaining or the presence of birbeck granules in electron microscopy [Figure 4c and 4d].[57]

IgG4-related sclersoing disease

IgG4-related sclerosing disease is an inflammatory disorder characterized by increased serum levels of IgG4 and presence of IgG4-positive plasma cells in the affected tissues.[58] It was first described in autoimmune pancreatitis and subsequently in various internal organs such as retroperitoneal soft tissue, breast, biliary tract, liver, salivary glands etc. Patients typically presented with a mass-like lesion in the affected organs and the diagnosis is made histologically. Orbit is a possible site of involvement, and orbital manifestations can be unilateral or bilateral mass like lesions. The lacrimal gland is the most commonly involved site. Mikulicz disease (bilateral lacrimal glands, parotid glands and submandibular glands swelling) was idenitifed as a form of IgG4-related sclerosing disease [Figure 5a and b]. Histopathology of orbital biopsy will show chronic inflammatory cell infiltrates with numerous IgG4 positive plasma cells and a variable degree

of fibrosis [Figure 5c and d]. A panel of lymphoid makers (immunostaining) should be done to exclude the possibility of lymphoma. A recent study compared the histology between IOID and prominent lymphoid hyperplasia with IgG4 related systemic disease and found that the IgG4 positive group had higher incidence of marked follicular hyperplasia, fibrosis, plasma cells, and eosinophils, suggesting IgG4 systemic disease to be a distinct orbital manifestation to IOID.[59]

Rosai Dorfman disease

Rosai Dorfman disease (RDD) is a histiocytic proliferative disorder of unknown etiology, presenting commonly with large, painless, bilateral cervical lymphadenopathy, but able to involve any organ.[60] It is associated with fever, leukocytosis, elevated ESR, and hypergammaglobulinemia. The orbit is involved in 10% of the cases, commonly by soft tissue infiltration and infiltration of the intraconal space. Clinical manifestations include proptosis, diplopia, blurry vision, dry eye, epiphora, epibulbar masses, marginal corneal infiltrate, and uveitis [Figure 6a].[61,62] Orbital biopsy for histopathological analysis is needed for a diagnosis of RDD if the patient presents with an orbital mass-like lesion. Histologic examination reveals multiple aggregates of large histiocytes, accompanied by a dense infiltrate of plasma cells, lymphocytes, and granulocytes. Many of these histiocytes have engulfed lymphocytes within their cytoplasm (emperipolesis) [Figure 6b]. The histiocytes stain positive for S-100 and CD-68, but negative for CD1a [Figure 6c]. Extranodal RDD will show prominent fibrosis.[63]

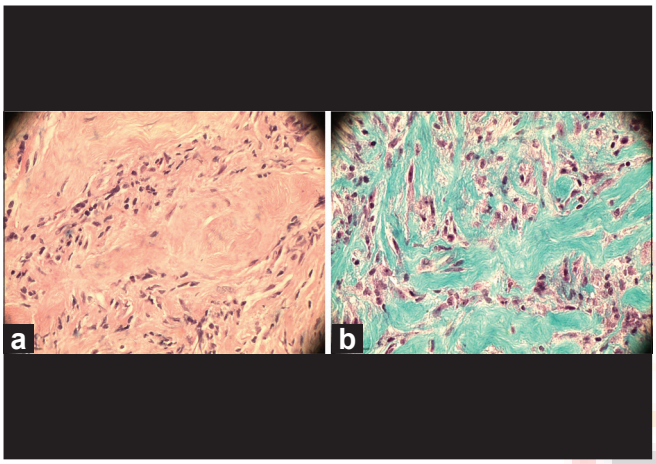

Figure 3: (a) Histology of a case of ISOI showing marked diffuse fibrosis and few polymophous infiltrate (H and E, ×200). (b) Masson trichrome stain was used to highlight the fibrous tissue for the same case (×200)

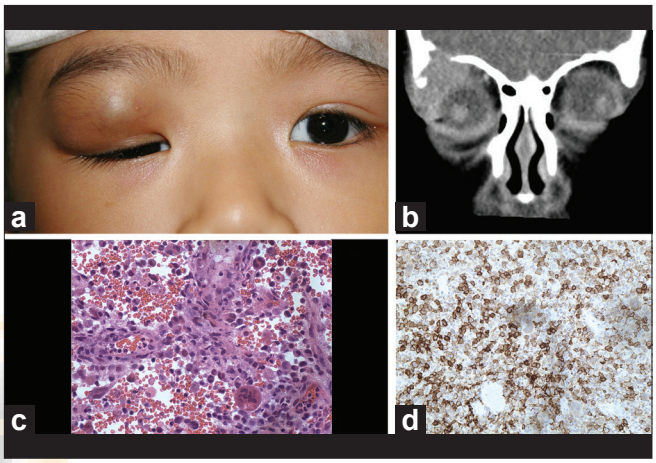

Figure 4: (a) Clinical photograph of a patient with right Langerhans cell histiocytosis showing right eye proptosis, redness and a mass-like lesion. (b) Coronal CT scan showing an osteolytic right superolateral orbit lesion. (c) Histopathology of the same patients showing the presence of numeorus Langerhans cells suggesting Langerhans cell histiocytosis. A multinucleated giant cell is present (H and E, ×200). (d) The diagnosis of Langerhans cell histiocytosis was confimed with CD1a immunostaining (×200)

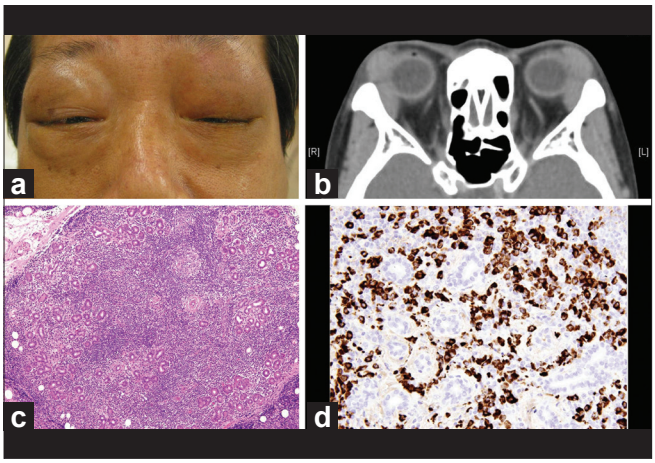

Figure 5: (a) Clinical photograph of a patient with Mikulicz disease demonstrating bilateral lacrimal gland enlargement with proptosis and secondary ptosis. (b) Computer tomographic scan of the same patient demonstrating bilateral lacrimal gland infiltration. (c) Histology of lacrimal gland biopsy showing diffuse infiltration of polymorphonuclear cells with loss of acinar and periductal fibrosis (H and E, ×100). (d) IgG4 immunostaining showing the presence of numeorus IgG4 positive plasma cells (×200)

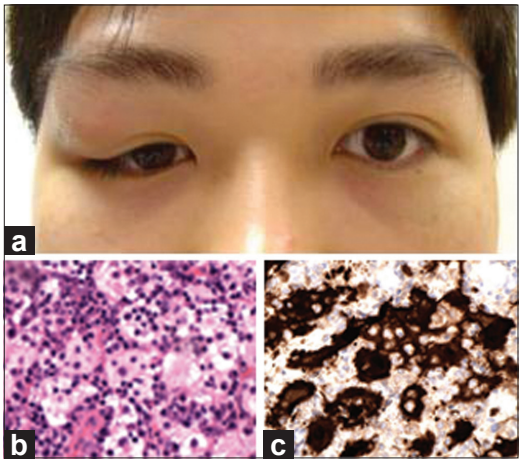

Figure 6: (a) Clinical photograph demonstrating right upper eyelid and brow swelling. (b) Histologic examination revealing numerous large histiocytes with some plasma cells and lymphocytes. Many of the histiocytes have engulfed intact lymphocytes within their cytoplasm (emperipolesis) (H and E, ×200). (c) The histiocytes are positive for S 100 immunostaining (×200)

Drug related orbital inflammation

It has been reported that the use of bisphosphanate (zoledronic acid and pamidronate), which inhibits osteoclastic bone resorption, in treating osteolytic bone cancer, bony metastasis, Paget disease, and osteoporosis can lead to orbital inflammation induced by its administration.[64] Onset of ocular and orbital symptoms can vary from 1 to 6 days after drug administration. Patients have reported orbital pain, diplopia, and eyelid swelling. While observed signs have included periocular 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.[64]

SECONDARY ORBITAL INFLAMMATIONS

Orbital inflammation can occur from response to an orbital condition rather than being a primary orbital inflammatory disease. Such triggering conditions include orbital tumors, especially lymphoproliferative lesions, ruptured orbital dermoids, orbital hemorrahages, mucoceles, or orbital foreign bodies.

Orbital lymphoproliferative lesions

Lymphoproliferative lesions are the most common primary orbital tumors in adults.[65] Clincially, these lesions are often confused with IOID because of similar clinical and radiological features. Since these lesions can have a variable degree of inflammatory signs and a partial response with systemic steroid treatment, the diagnosis may be delayed if a biopsy is not performed. These tumors range from reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, and lymphoma, characterized by different histopathologic and immunophenotypic features. In general, B cell lymphoma is far more common than T cell lymphoma, but the latter tends to have a more aggressive clincial course. Orbital lymphoma of low-grade marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) type is the most common orbital lymphoma subtype, accounting for 40-70% of cases.[66-68] The most common presenting symptom, according to a large case series, is eyelid swelling followed by palpable eyelid mass, diplopia or blury vision, proptosis, pain, and lid erythema.[69] Orbital lymphoid tumors usually present in CT as a diffuse, solid, enhancing mass with moulding of the globe.[70] Occasionally, orbital lymphoid tumors can present as a circumscribed mass. Bony erosion is usually not seen except in large B-cell lymphoma.[69] Histopathology of MALT lymphoma 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 NK/T cell lymphoma. NK/T cell lymphoma is highly aggressive, typically involving the nasal cavity and paranasal sinuses, and can present initially with orbital and adnexal symptoms.[71] Patients can present with orbital edema, ophthalmoplegia, and uveitis.[72] There have been resported cases of NK/T cell lymphoma presenting as orbital cellulitis that failed to improve with antibiotic therapy.[73] Imaging often shows a soft tissue mass that obliterates the nasal and paranasal sinuses with bone erosion being a common finding. Both CT and MRI with contrast enhancement will show heterogeneous enhancement of the tumor.[72] Histologically, the tumor shows a variable cytologic appearance, with angiocentricity and angioinvasion. Immunophenotypic characteristics will show NK cell characteristic which include CD2+, CD4+, CD20- , CD56+ and evidence of Epstein-Barr virus infection.[74] NK/T cell lymphoma is a very aggressive disease and has a poor prognosis once disseminated despite radiodiotherapy and aggressive chemotherapy.[72]

Orbital foreign bodies

Patients suffering from orbital foreign bodies typically have a history of injury. Occasionally, delayed presentation is possible, and the patient can present with orbital inflammation or discharge from the sinus. For most of the foreign bodies, the diagnosis can be made by using X-ray and CT scan. MRI can be useful for the non metallic foreign bodies.

Orbital hemorrahges

Acute orbital hemorrhages cause acute proptosis, redness, orbital pain, and ophthalmoplegia which can simulate orbital tumors and other inflammatory orbital diseases. Moreover, orbital hemorrhage itself is often associated with a certain degree of orbital inflammation. There are various causes of orbital hemorrhages and bleeding from orbital venous malformation such as orbital varix. Lymphangioma is one of the most common causes of spontaneous orbital hemorrhages. CT imaging usually shows a diffuse reticular pattern. MRI can be used to help differentiate intraorbital hemorrahage from orbital inflammatory conditions, since T1 and T2 weighted MRI will show enhancement of the intraorbital hemorrahge.[75]

Summary

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 should be performed for any atypical or doubful diagnosis. A close collaboration between the clinician and pathologist is important in elucidating the correct diagnosis as crucial information may direct the pathologist in conducting special stains and immunohistochemistry to establish a pathological diagnosis.

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