Inflammatory diseases of the orbit.
Highlights

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CONCEPTUAL MODEL – DEFINITION & CATEGORIZATION

The last 20 years of our experience in managing over 3,000 orbital cases has led to a paradigm shift in terms of nonthyroidal orbital inflammatory disease. This shift reflects the historical trends in medical understanding, which have been characterized by the clinical definition of disease giving way in this century to specific diagnoses based on pathologic, anatomic (imaging), and systemic associations of disease. The final decades of this millennium have seen increasing diagnostic specificity brought about by immunopathologic and molecular genetic techniques, which will link prevention and specific treatment based on the ultimate pathogenesis of disease.

With regard to inflammations of the orbit, our own experience has shifted towards the exclusion of lymphoproliferative processes from the discussion of inflammatory disease, since they are clinically and pathologically distinct from inflammatory disorders. There are however some transitional lesions. The orbital inflammatory processes can be viewed as either nonspecific or specific. The frequency of diagnosis of nonspecific orbital inflammatory syndromes is decreasing as we improve our understanding of the pathogenetic and clinical constellations of the specific orbital inflammations.

The definition of nonspecific inflammations remains clinical and consists of processes that are acute and subacute, and have characteristic locations in the orbit. In contrast, the specific inflammations represent three possible types of processes:

– those due to a specific pathogen (i.e., infections and infestations);
– those that have specific local and/or systemic constellations of findings that identify them as distinct entities, including such diseases as vasculitis;
– those disorders which have a specific histopathology that identifies them, such as some of the granulomatous diseases.

NONSPECIFIC INFLAMMATION OF THE ORBIT [1-11] (table I)

Traditionally, acute and subacute idiopathic inflammatory syndromes have been included with the polyglot of orbital “pseudotumours”, a clinically and histologically confusing category of lesions. The described pathologic substrate for these myriad diseases ranges from nonspecific polymorphous lymphocytic and plasmacytic infiltrates to granulomatous disorders, depending on the source in the literature. The full histologic spectrum, from truly inflammatory to pseudoneoplastic disease, has been described within this rubric. The histologic studies are confusing and may not correlate with the clinical features of the disease. Yet with improved orbital imaging and careful clinical analysis, more specificity is possible in defining the presentation and character of these diseases. The patterns of orbital involvement may not point to pathogenesis, but do provide a clinical framework for diagnosis and management. They are a heterogeneous group etiologically but in our opinion, their inclusion as inflammatory syndromes is more rational than a broader traditional framework. These entities probably include a number of different organ-specific immunologic disorders and more specific etiologies yet to be defined.

The common feature of these syndromes is that they have the clinical hallmarks of inflammation, are generally acute or subacute in onset, and histologically are composed of polymorphous infiltrations of inflammatory cells. They contrast to chronic or progressive infiltrative inflammations and granulomatous disease, which are usually characterized by mass effect associated with insidious destruction and desmoplasia and therefore frequently require biopsy to define them.

The clinical categories are defined by the location of the inflammation which on imaging have a characteristic feature of an irregular margin adjacent to the primary focus, with tissue swelling and enhancement with contrast media. The nonspecific acute and subacute inflammatory syndromes can be divided in order of oc-
ocurrence as myositic, lacrimal, anterior, apical, and diffuse on the basis of differences in presentation and clinical findings. Although this is an arbitrary subdivision, it parallels the clinical situation and allows a framework for diagnosis, categorization, and management. In effect, most patients with nonspecific acute and subacute idiopathic inflammatory syndromes are categorized as outlined and managed with nonspecific anti-inflammatory medications (table I).

**Specific inflammation of the Orbit**

**Infections and Infestations**

Infective cellulitis may develop from contiguous inflammatory disease of the sinuses, face, and oropharynx. In addition it may result from foreign bodies or be secondary to pyemic deposition. Causes include a wide variety of bacterial, viral, fungal, and parasitic pathogens that vary with regional epidemiology. In our experience, the most significant category of orbital cellulitis arise from bacterial infections of the sinuses. It is particularly important to take into account the nature of the local infectious disease profile (epidemiology) and to be suspicious of unusual pathogens in patients who are immunosuppressed.

**Microbial**

*Orbital cellulitis and sinusitis [12-23]*

Important advances in our understanding and management of these lesions have led to more conservative approaches using imaging and clinical criteria. Other sources of microbial orbital cellulitis:

- Contiguous spread,
- Orbital foreign bodies,
- Pyemic cellulitis,
- Intraorbital sources of cellulitis.

**Fungus Infections**

*Rhino-orbital mucormycosis [24-28]*

Recognition of localised forms, especially in mucormycosis and aspergillosis, have allowed for more conservative treatment.

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**Table I**

Comparative features of acute and subacute nonspecific idiopathic inflammatory syndromes of the orbit, University of British Columbia Orbital Clinic, 1976-98.

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>MYOSITIC</th>
<th>LACRIMAL</th>
<th>ANTERIOR</th>
<th>DIFFUSE</th>
<th>APICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>51</td>
<td>25</td>
<td>23</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Pain</td>
<td>On movement</td>
<td>With tenderness</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Ocular and Orbital Features</td>
<td>Painful Decreased extraocular movement Normal vision Localized injection and chemosis</td>
<td>Lateral swelling S-shaped lid deformity Tenderness Pouting of lacrimal ducts Chemosis and injection localized</td>
<td>Uveitis Retinal detachment Decreased extraocular movement Decreased vision Anterior inflammation Chemosis Diffuse injection and swelling of lid</td>
<td>Uveitis Retinal detachment Decreased extraocular movement Decreased vision Anterior inflammation Chemosis Diffuse injection and swelling of lid</td>
<td>Decreased vision Decreased extraocular movement Mild proptosis and chemosis</td>
</tr>
<tr>
<td>Visual Outcome</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Imaging (CT &amp; MR)</td>
<td>Muscle irregularly enlarged Swelling of tendon Local scleral and Tenon’s capsule swelling Fusiform enlargement of whole muscle</td>
<td>Irregular swelling of lacrimal gland and adjacent tissues</td>
<td>Anterior: enhancing with irregular margins intime to scleral envelope Variable extension along optic nerve Decreased fat density</td>
<td>Diffuse: enhancing with decreased fat density</td>
<td>Apical irregular infiltration Extends along muscle and optic nerve</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Increased extraocular muscle size</td>
<td>Local swelling with increased Tenon’s space</td>
<td>Sclerotenonitis with T sign</td>
<td>T sign</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Aspergillosis [29-32]
Other mycotic infections

Tuberculosis and Syphilis

Parasitic Infestations

Echinococcosis [33-35]
Cysticercosis [36, 37]

With echinococcosis and cysticercosis, new drugs can control many of these infestations without surgery.

Trichinosis
Other parasitoses

Other Infestations

OTHER SPECIFIC ORBITAL INFLAMMATIONS

The specific inflammatory disorders imply a combination of pathologically identifiable infiltrates often associated with systemic constellations of findings that make them specifically identifiable. They can be broadly divided into vasculitides, granulomatous disorders, and idiopathic sclerosing inflammation.

Vasculitis (Angiitides)

Vasculitis includes a wide range of inflammatory angiodestructive processes, which involve varying calibres of vessels and different types of infiltrates ranging from polymorphonuclear leucocytic with leucocyteclasis (periarteritis nodosa, hypersensitivity angitis) to necrotizing granulomatous disease (Wegener’s granulomatosis). Blood vessel damage is characterized by any or all of endothelial damage, vessel wall necrosis, fibrin deposition within and around vessels, or indirect evidence of tissue necrosis. Most are thought to have an immunologic basis varying from immune-complex deposition to delayed hypersensitivity. The majority are thought to have an immune-complex-mediated basis.

Clinically, angiitides express a continuum of inflammatory features from acute and subacute onset to chronic inflammation with vaso-obstructive signs and symptoms. The various entities are classified on the basis of symptoms related to the organs or tissues affected, as well as their principal histopathologic features. It should however be noted that some vascular inflammatory syndromes defy classification and may not fit neatly into a category. A wide range of disorders are included but the major ophthalmic or orbital diseases include Wegener’s granulomatosis, hypersensitivity angiitis, and polyarteritis nodosa. Connective tissue disease – including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and polymyositis – may have a significant vasculitic component.

Vasculitis deserves a special place as a specific orbital inflammation because it reminds us of the protean nature of clinical inflammatory diseases and the importance of systemic associations. Although many of these disorders have relatively distinct systemic symptoms and signs, in the early stages many are restricted to the orbit, making it difficult to diagnose and to differentiate them from nonspecific inflammatory diseases. Because they may have serious or even life-threatening consequences, we must be particularly careful in diagnosing and ruling them out in the face of nonspecific inflammations of the orbit. The major categories of orbital vasculitis include Wegener’s granulomatosis, hypersensitivity vasculitis (with the subclasses of orbital vasculitis, vasculitis associated with connective disease, and Cogan’s syndrome), periarteritis nodosa, and other rare forms of vasculitis.

Wegener’s granulomatosis

Wegener’s granulomatosis may occur as a systemic or localized (limited) disease. When systemic, it is characterized by widespread inflammatory effects suggestive of connective tissue disease. The dominant features are rapidly progressive multisystem damage with upper and lower respiratory tract involvement followed by renal failure from necrotizing glomerulonephritis. Untreated, the generalized form is fatal, usually within two years.

In cases involving the orbit, patients typically present without systemic evidence as part of the limited form of Wegener’s that spares the kidneys and may have a chronic remitting course associated with ear, nose, and throat ailments and chest disease [38-40]. Ocular and orbital involvement is common in both systemic and limited Wegener’s granulomatosis and is seen in about 50 % of cases. The limited form tends to be more indolent whereas the generalized disorder may follow a course from rapid progression to long-term intermittent activity.

The major orbital findings are proptosis associated with a destructive orbital inflammatory mass, ocular inflammation with necrotizing scleritis, and optic neuropathy [40-46]. These are often bilateral and usually cause an irreversible morbidity if they are not treated. The disease is best treated with systemic steroids combined with an alkylating agent, preferably cyclophosphamide, which usually halts local and systemic disease. A specific diagnosis is essential before instituting the necessarily aggressive treatment and in the case of the orbit, can be confirmed by biopsy.

The diagnosis of orbital Wegener’s should be based on a constellation of clinical, radiologic, and pathologic features. Clinically, the important features that should raise an index of suspicion are bilaterality, involvement of the respiratory tract or sinuses including the mastoids (which are often missed), scleritis at the time of onset particularly when associated with the classical features of limbal corneal infiltrates, and systemic associations [41]. Some of the more subtle aspects include hearing
loss or draining ears. In addition, previous episodes of orbital or sinus disease of unknown cause may be recognized historically since the disorder can progress in an episodic and regressing fashion.

A wide age range is associated with Wegener’s and it is particularly important to recognize that it can occur in young people.

Major clinical and CT findings tend to form three relatively distinct patterns: diffuse orbital involvement (which may be bilateral), lacrimal involvement, or midline involvement associated with visual deterioration [47-51]. Lid swelling with brawny discoloration is particularly notable in those with lacrimal gland involvement. Lacrimal involvement may not have contiguous orbital or mid-line disease. Extensive orbital infiltration may be associated with yellowing of the lids [52].

The CT features that are suggestive include involvement of the sinus (including mastoids) and a tendency for the orbital masses to be associated with infiltration and obliteration of the adjacent fat planes. Mid-line orbital involvement is associated with bone erosion. Optic neuropathy is the result of intraorbital involvement and is not infrequent [53].

Another important finding is the potential for acute progression of the chronic disease. We noted this in our patients in which the majority had a relatively mild prodromal disease followed by episodes of dramatic deterioration. Orbital biopsy may be difficult to interpret and should be studied in light of the constellation of clinical features, which include careful clinical systemic study, c-ANCA testing (not often positive initially in “limited” form), and imaging of the orbit, paranasal, and mastoid sinuses [49, 54]. The suggestive histopathologic features include mixed inflammation with lymphocytes, eosinophils, polymorphonuclear leukocytes (often cuffing vessels), areas of fat necrosis and lipid-laden macrophages, mixed granulomatous stellate or focal microabscesses, and fibroplasia [49]. These histopathologic features are characteristic of Wegener’s in other extravascular soft tissue sites.

It is important to recognize this disorder within this constellation of clinical and biopsy findings since treatment can be dramatically effective using the combination of cyclophosphamide and corticosteroids [55, 56]. The use of Septra (trimethoprim/sulfamethoxazole) has been advocated in some cases. A nonrestrictive clinical and pathologic definition can lead to earlier diagnosis, rapid treatment, and prevention of sometimes catastrophic local or systemic outcome.

Other respiratory vasculitides

Churg-Strauss syndrome

Polyarteritis nodosa

Hypersensitivity (leucocytoclastic) angiitis

Hypersensitivity angiitis resembles periarteritis nodosa microscopically but affects smaller vessels and is more widely uniform in involvement. Pathologically the arterioles, venules, and capillaries are usually, but not necessarily, necrotic or may simply have perivascular infiltration with neutrophils undergoing karyolysis (leucocytoclasia). This is a frequent form of vasculitis and typically involves the skin, lungs, mucous membranes, heart, gastrointestinal tract, kidney, and muscle. In most instances drugs, microorganisms, or tumour antigens have been identified as precipitating the vasculitis. The angiitides associated with the collagen diseases and essential cryoglobulinemia are examples in this category. Because smaller vessels are involved, the signs and symptoms relate to haemorrhagic and microinfarctive lesions. The spectrum of disease varies from widespread multisystem involvement to primary dermatologic lesions. Many patients may have a history of recent respiratory infection or drug ingestion. Patients may have arthralgia, arthritis, myalgia, pulmonary lesions with effusion, pericarditis, myocarditis, peripheral neuropathy, and encephalopathy. Gastrointestinal and renal involvement may also be noted.

Specific diagnosis is established by biopsy. The prognosis is difficult to predict for the group overall because of heterogeneity. Removal of the inciting cause, if related to drugs or toxins, will lead to reversal of the process. The signs and symptoms of the disease can be abated with corticosteroid therapy. It is important to rule out the possibility of underlying collagen diseases. We have divided our personal experience with leucocytoclastic vasculitis into three different groups: orbital vasculitis, vasculitis associated with connective tissue disorders, and Cogan’s syndrome. All of these have similar histologic features consistent with hypersensitivity angiitis, but have different associations.

Orbital vasculitis

Vasculitis associated with connective tissue disorders

Cogan’s syndrome

Temporal arteritis

Idiopathic Sclerosing Inflammation of the Orbit

Idiopathic sclerosing inflammation is an unique clinicopathologic entity that shares histopathologic similarities to retroperitoneal fibrosis. It is characterized by primary, chronic, immunologically mediated fibrosis and a poor response to corticosteroid treatment and radiotherapy leading to frequent visual disability. This entity accounted for about 5% of nontyroid inflammatory lesions seen in our institution [57, 58].

The clinical features are dominated by scarring associated with mass effect and mild inflammation. Patients present with pain, proptosis, mild lid swelling, injection, restriction of ocular movements, and ptosis, and a significant number have visual deterioration. The disease may be bilateral, in which case it is usually asymmetrical. Three anatomical subgroups have been noted: diffuse, lacrimal, and apical. Most commonly, the process
develops in the anterior superolateral orbit involving the lacrimal gland. Twenty percent begin as an apical lesion. We have also experienced several cases beginning as a myotic disorder. With progression, diffuse orbital involvement is common and may go on to intracranial and bone involvement, affecting the cavernous sinus region and even the pterygopalatine fossa. This disorder may be associated with similar fibrosclerosis in the retroperitoneum and elsewhere [59-61].

The characteristic imaging findings are a homogeneously enhancing mass with irregular margins, which obliterate the adjacent extraocular muscles, lacrimal gland, or orbital structures [57, 58, 62].

The differential diagnosis includes conditions characterized by orbital desmoplasia and pain with mild inflammation. These include thyroid orbitopathy, sarcoid, Wegener’s granulomatosis, sinus disease, tuberculosis, Erdheim-Chester disease, primary and secondary neoplasms (especially breast, bowel, or prostatic carcinoma), meningioma, and more rarely lymphoma.

The characteristic histopathologic feature is fibrosis with a paucicellular inflammatory infiltrate that has the immunopathologic profile of retroperitoneal fibrosis.

Historically, the treatment of nonspecific sclerosing inflammation of the orbit has been associated with poor outcome in up to 30% of cases [63]. Since our description of the immunopathologic profile of this disorder, we have developed a more aggressive approach to sclerosing inflammation that consists of biopsy for prompt, early diagnosis, and early intervention [57, 58]. Such intervention involves a combination of corticosteroids with other drugs directed against T-cells (cyclosporine) and B-cells (methotrexate, cyclophosphamide, azathioprine depending on age). Since instituting this regimen, we have had 6 cases which have been abruptly arrested without progression. This management profile requires multidisciplinary involvement of a rheumatologist.

**Granulomatous Inflammation** [64, 65]

Nonvasculitic granulomatous disorders have been grouped together based on their fundamental underlying histopathologic infiltration by histiocytes. As the clinical picture often involves a low grade infiltrative process with mild inflammatory features and varying clinical constellations, they almost universally come to biopsy. Thus from a practical point of view, they can be grouped histologically and clinically. The granulomatous inflammations of note in the orbit include foreign body granulomas, ruptured dermoid cysts, sarcoid and sarcoïd reactions, xanthogranulomatous disorders, and fibro-osseous processes.

**Foreign body granulomas**

**Sarcoïd and sarcoïdal reactions**

**Xanthogranulomatous disorders of the orbit [66-68]**

**Fibro-osseous processes**

**Idiopathic lipogranuloma**

**GUIDE TO ANALYSIS OF NONINFECTIOUS INFLAMMATION (fig. 1)**

Persistent or low-grade orbital inflammatory conditions often go to biopsy. It is this group of lesions that constitute the majority of diseases included in the differential diagnosis of specific noninfectious orbital inflammatory conditions. We recommend that the differential diagnosis is aided by imaging that allows for definition of location and associated orbital and periorbital findings. Once a biopsy is obtained, the type
of infiltration gives some guidance with regard to categorization of the lesions, and falls basically into types and focus of infiltrate.

RÉFÉRENCES