

Idiopathic Orbital Inflammation: Diagnosis and Management

Nonspecific orbital inflammation (NSOI), formerly known as orbital pseudotumor, is a benign, noninfectious, space-occupying inflammatory lesion of the orbit.¹ The name *pseudotumor* was initially coined to indicate the condition's propensity for mimicking neoplastic processes. NSOI describes orbital inflammation in the absence of a known systemic or local etiology.

Presentation

The majority of cases occur in adults, and the average age of presentation is in the mid-40s.² Pediatric cases are rarer, comprising 6% to 17% of all NSOI cases.³ Up to 13% of cases are bilateral.

NSOI can affect various types of orbital tissue. It may be categorized by location within the orbit (anterior, diffuse, apical) or by the tissue affected (dacryoadenitis, myositis, posterior scleritis, optic perineuritis). The lacrimal gland is affected most frequently (32%), with extraocular muscles a close second (29%).⁴ Although the symptoms depend on which tissues are affected, the typical presentation includes pain, periorbital edema, erythema, and blepharoptosis, with proptosis, uveitis, papillitis, and exudative retinal detachments being less common.

Diagnosis and Workup

NSOI is a diagnosis of exclusion. Therefore, inflammatory, infectious,

and neoplastic causes must be ruled out. The differential diagnosis for orbital inflammation is broad, but it can be narrowed based on the region of inflammation, for example:

Anterior lesions

- retained foreign body
- orbital cellulitis
- posterior scleritis
- ruptured dermoid cyst

Diffuse inflammation

- orbital lymphoma
- granulomatosis with polyangiitis

Apical lesions

- Tolosa-Hunt syndrome
- orbital lymphoma
- glioma
- metastases

The tissue involved can also help to focus the differential, for example:

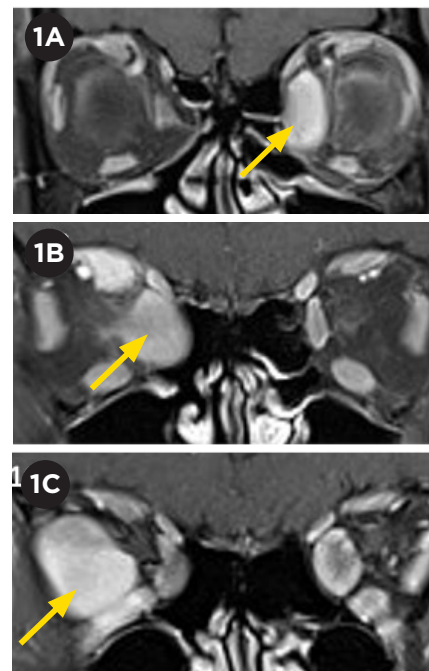
Dacryoadenitis (the most common subtype of NSOI)

- orbital lymphoma
- benign lymphoid hyperplasia
- sarcoidosis
- granulomatosis with polyangiitis
- epithelial neoplasms

Myositis

- thyroid orbitopathy
- vasculitis
- metastatic lesions
- orbital lymphoma
- carotid-cavernous fistula

History. The clinician should focus on factors that could help determine the origin of the inflammation. For example, recent infectious processes such



MRI SCAN. Images of a patient who had recurrent NSOI in three different muscles over five years. (1A) Left medial rectus; (1B) right medial rectus; (1C) right lateral rectus.

as upper respiratory infections, streptococcal pharyngitis, or viral illnesses can occasionally be linked temporally to NSOI.⁵ A history of autoimmune disorders such as granulomatosis with polyangiitis, sarcoidosis, giant cell arteritis, systemic lupus erythematosus, or rheumatoid arthritis can also help point toward an underlying cause of the inflammation. Finally, a history of thyroid conditions may be relevant, as thyroid-associated orbitopathy can often mimic idiopathic myositis.

Examination. A thorough ophthal-

mologic exam should evaluate the eyelids (for retraction, lid lag, lagophthalmos), orbit (proptosis, globe displacement), extraocular muscles (restriction), and globe (injection, chemosis, scleritis). Assessment of optic nerve function includes testing visual acuity and color vision, as well as checking the pupils for relative afferent pupillary defect.

Imaging. The use of computed tomography or magnetic resonance imaging (MRI) can help localize and potentially differentiate the lesion.

- On MRI, the lesion will show a low signal intensity on T1- and T2-weighted imaging, with lower signal intensity corresponding with higher degrees of sclerosis.

- Dacryoadenitis will exhibit diffuse enlargement of the gland with preservation of the shape of the gland, along with associated inflammatory reaction of the periglandular tissue and poor marginal definition adjacent to the lateral rectus muscle.

- Idiopathic myositis may involve single or multiple muscles. The tendons are often enlarged, in contrast to thyroid ophthalmopathy, which features spindle-shaped muscles with normal tendons.

- Sinus involvement on imaging can suggest infectious causes or granulomatosis with polyangiitis.

- Orbital fat infiltration is often present and can mimic a lymphoproliferative process.

Laboratory testing. Findings from systemic tests should be used as supporting, rather than diagnostic, evidence. Initial lab workup typically evaluates for markers of infection, inflammation, or thyroid disease: complete blood count, erythrocyte sedimentation rate, C-reactive protein, and thyroid-function testing should be performed.

There is a common association between rheumatologic disease and orbital inflammation, so if the initial workup is negative, further testing should be done for autoimmune disease. Studies include antinuclear antibodies, antineutrophil cytoplasmic antibodies, angiotensin-converting enzyme levels, rapid plasma reagin, serum IgG4 levels, and rheumatoid factor.

Biopsy. If clinical and radiological findings are not diagnostic, biopsy of the lesion is the gold standard for diagnosis. Inflammatory lesions usually appear gray-white and solid.⁶ NSOI will demonstrate lymphoplasmacytic infiltration, fibrosis, eosinophilia, and lymphoid aggregates with germinal centers. Extensive fibrosis that replaces all normal tissue is more likely to be caused by sclerosing NSOI or IgG4-related orbital disease (IgG4-ROD). Quantitative immunohistochemical assessment can further suggest IgG4-ROD if the ratio of IgG4+ to IgG+ cells is elevated. (See “IgG4-Related Disease.”)

The method of biopsy depends on the location of the lesion. In the anterior two-thirds of the orbit, superior lesions can be accessed through an upper eyelid crease incision, while lower lesions can be accessed transconjunctivally.⁶ If the patient is being treated with oral or intravenous steroids, these drugs should, if possible, be discontinued prior to biopsy to avoid confounding the results.

IgG4-Related Disease

Increasingly frequently, biopsies of inflammatory masses are showing IgG4-related disease (IgG4-RD), formerly known as autoimmune-related sclerosing pancreatitis. This condition causes tumorlike masses consisting of fibrosis, obliterative phlebitis, and IgG4-rich lymphocytic plasmacytic infiltration that can occur in various organs throughout the body. When it occurs in the orbit, it is called IgG4-ROD. Similar to NSOI, IgG4-ROD typically presents with eyelid and periocular swelling, followed by proptosis and diplopia.

IgG4-ROD, however, dictates some differences from NSOI in workup and management. Because IgG4-RD can affect numerous organ systems throughout the body, the patient should be examined for salivary gland enlargement and diffuse lymphadenopathy. In addition, liver and renal function should be biochemically assessed, as IgG4-RD can lead to bile duct stenosis or obstruction; and retroperitoneal fibrosis can lead to ureteral obstruction and hydronephrosis.¹

Serum IgG4 levels can be monitored for treatment response. More importantly, patients with IgG4-ROD are thought to be at increased risk of lymphoma,² possibly secondary to the increased inflammatory response. Therefore, clinicians should have a low threshold to biopsy if the initial lesion recurs.

Similar to NSOI, IgG4-ROD is treated with steroids. However, IgG4-ROD has been shown in some studies to have higher recurrence rates, and patients may benefit from maintenance steroid therapy.³ Alternative therapies such as rituximab or surgical removal should be considered if initial steroid therapy fails.

1 McNab AA, McKelvie P. *Ophthalmic Plast Reconstr Surg*. 2015;31(3):167-178.

2 Andron A et al. *Orbit*. 2017;36(6):359-364.

3 Min HK et al. *Korean J Intern Med*. 2019;34(1):220-226.

Treatment

Observation is appropriate for mild cases of inflammation that do not threaten vision. Systemic corticosteroids are the first-line treatment, with over 75% of patients showing rapid improvement. High-dose oral steroids (1 mg/kg/day) are given for one week, followed by a slow 2-3 month taper. However, long-term steroids have well-documented adverse effects, and recurrence rates have been reported to be as high as 58%.⁷ Intralesional corticosteroid injections can be effective as well, and they are often performed in conjunction with orbital biopsies.

Recurrence is more common in patients younger than 16 years old, as well as in those with bilateral disease, optic disc edema, presence of a T-sign on B-scan ultrasonography, or a sclerosing histopathology variant. Other factors associated with recurrence are an incomplete response to initial steroids, a history of autoimmune diseases, or an episode of NSOI within three months of the original episode.

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In cases of recurrence, steroid-sparing therapy is often needed. Medications include immunomodulatory agents, lymphocyte inhibitors, and tumor necrosis factor- α inhibitors. Other modalities include external beam radiation therapy and surgical debulking.¹ Notably, surgery is a viable option only when the lesion is localized and not adjacent to any vital structures. Focal debulking, with or without intralesional steroid injections, has been reported to have lasting results in cases of localized dacryoadenitis and is associated with lower recurrence rates than pulse steroids alone.⁸

Conclusion

NSOI is a term for orbital inflammation for which an etiology cannot be determined. As underlying causes of the inflammatory changes are identified, fewer cases may be classified as NSOI. For now, it is useful to think of NSOI as a clinical entity on the basis of several unifying features. Clinicians should focus the differential diagnosis based on the location and distribution of the inflammation. Biopsy may be needed for definitive diagnosis. Treatment generally begins with pulse steroid therapy; and the disease may warrant surgery, radiation, and nonsteroid immunosuppressive therapy if it recurs.

1 Yeşiltaş YS, Gündüz AK. *Middle East Afr J Ophthalmol.* 2018;25(2):71-80.

2 Shields JA et al. *Ophthalmology.* 2004;111(5):997-1008.

3 Belanger C et al. *Am J Ophthalmol.* 2010;150(4):460-463.

4 Berry-Brincat A, Rose GE. *Curr Opin Ophthalmol.* 2012;23(5):415-419.

5 Espinoza GM. *Curr Rheumatol Rep.* 2010;12(6):443-447.

6 Mombaerts I et al. *Surv Ophthalmol.* 2016;61(5):664-669.

7 Braich PS et al. *Int Ophthalmol.* 2018;38(4):1485-1495.

8 Mombaerts I et al. *Ophthalmology.* 2014;121(2):603-609.

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