Nonspecific Orbital Inflammation

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Roberta E. Gausas, M.R. Damani,
and Kimberly P. Cockerham

Contents

R.E. Gausas, MD (✉) • M.R. Damani
Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania,
51 North 39th Street, Philadelphia, PA 19104, USA
e-mail: roberta.gausas@uphs.upenn.edu

K.P. Cockerham, MD, FACS
Department of Ophthalmology,
Stanford University, 2452 Watson Court, MC 5353,
Palo Alto, CA 94303, USA

6.1 Introduction

Nonspecific orbital inflammation (NSOI) is a term used to describe nonmalignant inflammation of the orbit characterized by a polymorphous lymphoid infiltrate with varying degrees of fibrosis, without a known local or systemic cause [1]. The emphasis is on lack of finding a known cause. Orbital inflammation itself is not a diagnosis, but rather a description of a tissue response to some underlying problem, such as infection, irritation, or injury, which has triggered the immune system. The injured cells release chemical factors stimulating the inflammatory response which is characterized by symptoms of pain, redness, swelling, warmth, and possible dysfunction of the tissues involved. In the case of the orbit, it is infiltration of orbital soft tissues by chronic inflammatory cells that causes findings such as proptosis, eyelid swelling, chemosis, pain, diplopia, or visual loss. Every effort must first be made to identify a specific cause of the inflammation. Navigating through the differential diagnosis of diseases that can cause or simulate orbital inflammation is challenging; however, adhering to a methodical history and exam will help facilitate the process (Table 6.1). Only once all other specific etiologies have been eliminated can one conclude with the diagnosis of nonspecific orbital inflammation, which only means that the causative pathogen or trigger could not be identified.

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Table 6.1 Differential diagnosis of orbital inflammation

Specific etiology	
Thyroid-associated	Thyroid-associated orbitopathy (TAO)
Infectious	Bacterial: tuberculosis, syphilis Fungal: mucormycosis, aspergillosis Parasitic: echinococcosis, cysticercosis
Vasculitic	Wegener's granulomatosis Polyarteritis nodosa Hypersensitivity angiitis Systemic lupus erythematosus Giant cell arteritis
Granulomatous	Sarcoidosis Xanthogranulomatous Foreign body granuloma Erdheim–Chester disease
Sjögren's syndrome	
Noninflammatory disorders with secondary inflammation	
Neoplasia	Lymphoproliferative disorders
Vascular disorders	Dural fistula Cavernous sinus arteriovenous fistula Cavernous sinus thrombosis
Nonspecific etiology	
Other diagnoses excluded	Nonspecific orbital inflammation (NSOI)

6.2 Historical Perspective

Recognition of this entity dates to the late 1800s and early 1900s, when several authors reported patients with all the findings consistent with a presumed tumor of the orbit, but either who were subsequently noted to experience unexpected, spontaneous improvement or who, upon surgical exploration and biopsy of the orbit, were found to have benign inflammation rather than malignancy. Hence, the term "orbital pseudotumor" was coined [2]. The clinical description of a benign process masquerading as a malignant one was appropriate for that era, but, unfortunately, the term has become entrenched in medical literature despite modern breakthroughs in imaging, immunopathology, and molecular techniques that allow for ever-increasing diagnostic specificity. The modern term nonspecific orbital inflammation (NSOI), or alternatively idiopathic orbital inflammation, more accurately reflects both our current understanding of this disease process and the acknowledgement that known causes were otherwise excluded [3].

6.3 Pathogenesis

Although the exact pathogenesis of NSOI remains unknown, it is generally believed to be an immune-mediated process. Wladis documented the molecular differences between normal orbits and those of patients affected by NSOI, showing that six cytokines are upregulated in NSOI, in particular IL-12, TNF-alpha, and IFN-gamma [4]. Furthermore, in comparing orbital biopsy specimens from patients with suspected NSOI to control orbital adipose specimens from those with noninflamed orbits, Wladis identified toll-like receptors (TLRs), a class of proteins that play a key role in the innate immune system [5]. The presence of TLRs has been associated with other inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis. NSOI has been associated with a number of systemic immunologic disorders including Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, and ankylosing spondylitis. Some authors have proposed a post-infectious etiology since NSOI has been reported following viral illness in both adult and pediatric studies [6].

6.4 Clinical Features

Rapid onset of pain associated with periorbital swelling and chemosis is the most common clinical presentation. However, recognizing that there is high variability in the symptoms and clinical findings of NSOI, which are very much dictated by the degree and anatomic location of the inflammation present, is important in the clinician's ability to recognize this disease [7]. If acute in nature, NSOI may mimic infectious orbital cellulitis. Anterior orbital inflammation

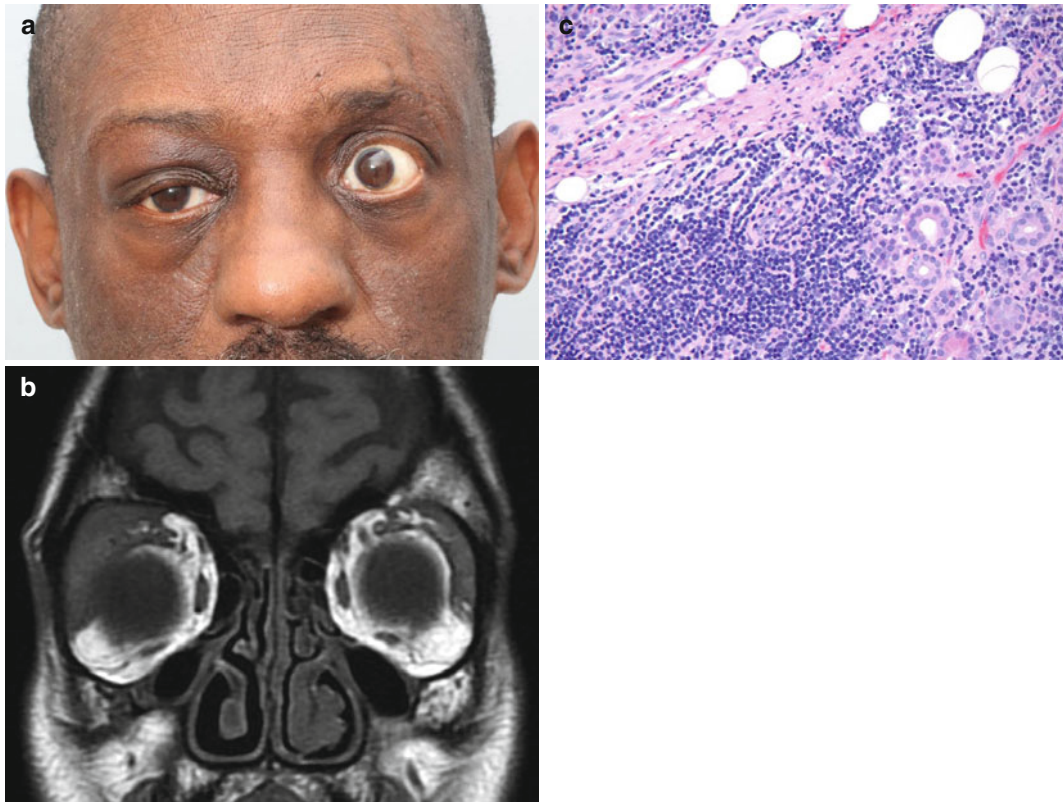

Fig. 6.1 Anterior orbital inflammation with S-shaped lid deformity (**a**). MRI reveals marked enlargement of lacrimal gland (**b**). Orbital biopsy shows lacrimal gland with focally dense chronic inflammatory cells, both lymphocytes and plasma cells, and with focal periductal fibrosis (**c**). Note absence of giant cells or lymphoepithelial lesions. No overt evidence of lymphoproliferative disorder was shown by flow cytometry

localized to the lacrimal gland may present with an S-shaped lid deformity and chemosis (Fig. 6.1). The swelling in anterior orbital inflammation may be dramatic, but vision is often spared. Conversely, inflammation localized to the orbital apex may present more insidiously with optic neuropathy and motility deficits despite a quiet anterior orbit, mimicking a neoplasm or cranial nerve palsy (Fig. 6.2). Widespread orbital inflammation may also manifest as uveitis or papillitis (Fig. 6.3). While pain or discomfort is commonly thought to be the hallmark feature of this disease, atypical cases may occur in which pain is absent.

Nonspecific orbital inflammation may be subclassified by onset: acute (within hours or days), subacute (days to weeks), chronic (weeks to months), relapsing, or recurrent.

Nonspecific orbital inflammation may be subclassified by anatomic location, with any number or amount of orbital tissues affected. The most common anatomic patterns may involve (1) one or more extraocular muscles, (2) one or both lacrimal glands, (3) anterior orbit, (4) apical orbital and perineural involvement, or (5) diffuse orbital inflammation. Inflammation localized to a specific anatomical site may acquire its own name, such as *dacryoadenitis* (inflammation localized to the lacrimal gland) or *orbital myositis* (inflammation localized to one or more extraocular muscles).

Compared to the adult population, NSOI in the pediatric population tends to manifest bilaterally more commonly and with elevated ESR, eosinophilia, and uveitis. The latter of which appears to portend a poor outcome [8].

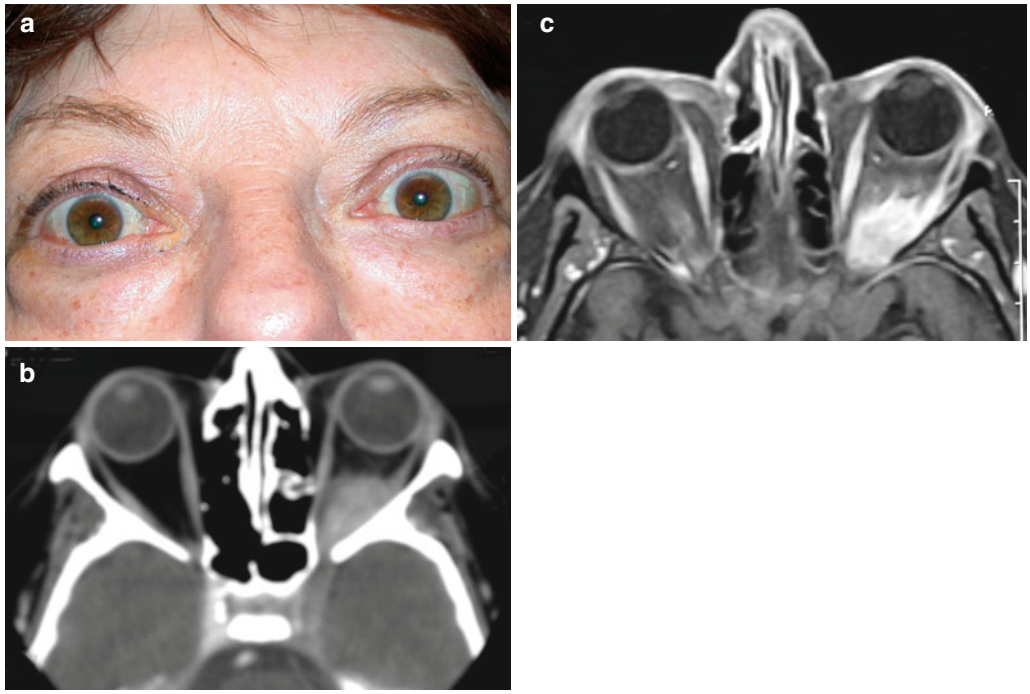

Fig. 6.2 Apical orbital inflammation. Patient with painful proptosis and optic neuropathy. Although the periorbital area and anterior segment are quiet (**a**), neuroimaging reveals an infiltrating lesion involving the orbital apex on a CT scan (**b**) and MRI (**c**)

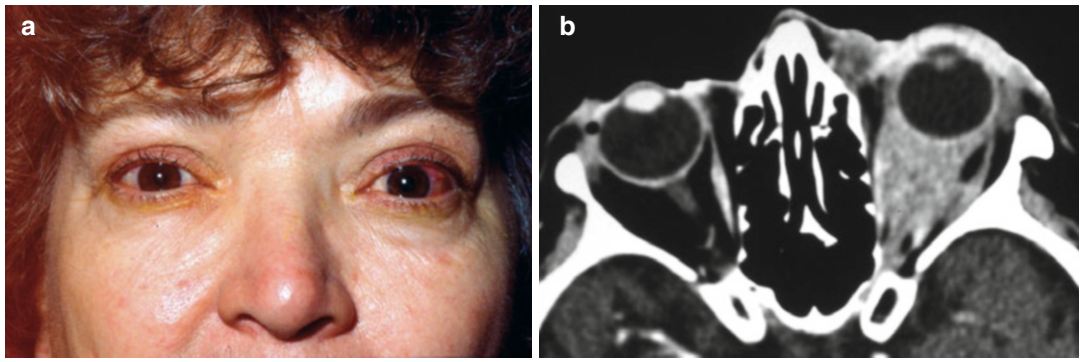

Fig. 6.3 Diffuse orbital inflammation. Patient with painful proptosis and limited motility of left eye (**a**). Orbital CT reveals periocular and retrobulbar involvement of multiple tissues (**b**)

6.5 Clinical Subtypes

6.5.1 Orbital Myositis

Orbital myositis consists of inflammation involving one or more extraocular muscles in one or both orbits. Diplopia and pain exacerbated by eye movement are the presenting signs. Examination may reveal restriction of motility and positive forced ductions. Recurrence of orbital myositis is not uncommon and may involve the same or different extraocular muscles in the same orbit or in the contralateral orbit [9].

6.5.2 Orbital Apex Syndrome

Inflammation centered in the posterior orbit may appear as an orbital apex syndrome, with ophthalmoplegia, optic neuropathy, and proptosis. The patient may present with visual loss and cranial nerve deficits, while the anterior orbit may or may not be involved. Imaging reveals a diffuse, infiltrative lesion in the apex surrounding the optic nerve (Fig. 6.2). It is crucial to eliminate other causes in such cases, because the differential diagnosis includes neoplasm, such as lymphoma, or infection, such as aspergillosis or mucormycosis.

6.5.3 Sclerosing Orbital Inflammation

A distinct sclerosing form of orbital inflammation has been identified which is characterized by dense fibrous replacement. Long believed to represent the chronic end stage of the disease, it is now thought to represent a distinct clinicopathologic entity. This sclerosing form has been shown to be histologically similar to other fibroproliferative disorders such as multifocal fibrosclerosis, a systemic disseminated fibrosing process that includes Riedel's thyroiditis, mediastinal fibrosis, sclerosing cholangitis, and fibrosis of the parotid gland, lacrimal gland, and lung [10]. Kovacs suggests that fibrosis formation in these disorders is mediated by the aberrant production of fibrogenic cytokines such as platelet-derived growth factor (PDGF) and transforming growth factor-B (TGF-B), which ultimately results in permanent alteration in tissue structure [11].

6.5.4 Nonsarcoid Granulomatous Inflammation

Another distinct form of NSOI is one which displays granulomatous inflammation similar to sarcoidosis but is not associated with systemic sarcoidosis [12].

6.5.5 Immunoglobulin G4-Related Disease and Orbital Inflammation

Since 2003, IgG4-related disease (IgG4-RD) has been recognized as a systemic fibroinflammatory condition characterized by mass-forming inflammatory reactions involving almost any organ system, in which the tissues are infiltrated by IgG4-positive plasma cells. It is usually, but not always, associated with elevated serum IgG4 concentrations. In the orbit, chronic sclerosing dacryoadenitis, characterized by bilateral lacrimal gland involvement and a dense lymphoplasmacytic infiltration, has been suggested to be an IgG4-related disease [13, 14].

Stone explains that although IgG4 is traditionally thought of as an anti-inflammatory immunoglobulin, it appears to actually play a significant role in certain immune-mediated conditions and that the identification of IgG4-RD has unified a large number of medical conditions previously thought to be limited to specific and single organ systems into a cohesive picture of systemic inflammation, linked by similar histopathologic characteristics [15].

6.6 Diagnostic Evaluation

6.6.1 Imaging

Neuroimaging plays a critical role in evaluating presumed NSOI. Although high-resolution orbital computerized tomography (CT) may demonstrate variable enhancement after administration of iodinated contrast material, contrast-enhanced magnetic resonance imaging (MRI) with fat saturation is the imaging study with the highest yield and should be performed when available. Subtle edema of the retrobulbar fat is often one of the earliest changes seen in NSOI. Orbital MRI typically shows a reticular pattern of orbital fat that is isointense to muscle in both T1- and T2-weighted images. In contrast, orbital cellulitis will be hyperintense to muscle in T2 [16]. Kapur has suggested diffusion-weighted

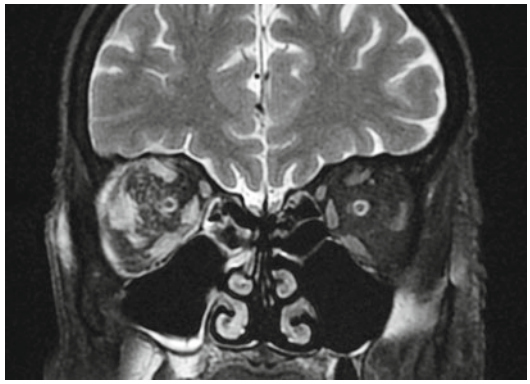

Fig. 6.4 Orbital myositis. MRI, coronal view, shows diffuse retrobulbar fat edema and thickening of all extraocular muscles in right orbit

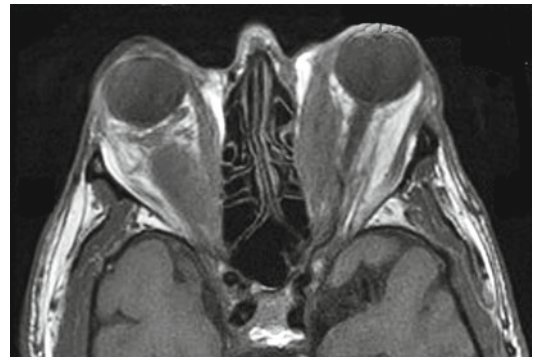

Fig. 6.5 Thyroid-associated orbitopathy. Although tendon spring is expected, in this case, muscle belly enlargement and tendon involvement of the left medial rectus muscle are evident

imaging as a method to distinguish NSOI from cellulitis and lymphoproliferative disease [17] (Fig. 6.4).

Classically, orbital myositis, a specific orbital inflammation and the most common cause of muscle enlargement, demonstrates tendon thickening in addition to extraocular muscle belly enlargement. Inflammation in TAO is generally tendon sparing. However, cases of orbital myositis *without* tendon involvement have been reported [18], and 8 cases of thyroid-associated orbitopathy *with* tendon involvement in a series of 125 patients were reported by Simon [19]. Therefore, extraocular muscle and tendon morphology may be highly suggestive but not pathognomonic in differentiating orbital inflammation as either NSOI or TAO (Fig. 6.5).

6.6.2 Laboratory Testing

Since there is an association between NSOI and other systemic conditions such as rheumatologic disease and IgG4-related disease, the typical laboratory workup for suspected NSOI should include complete blood count (CBC), electrolytes, sedimentation rate (ESR), antinuclear antibody (ANA), anti-ds DNA, antineutrophil cytoplasmic antibody (ANCA), angiotensin-converting enzyme (ACE) level, rapid plasma reagin (RPR), thyroid function tests (TFTs), and serum IgG4.

6.6.3 Biopsy

Orbital biopsy can play a powerful role in the diagnosis of NSOI. Although many authors have advocated empiric steroid treatment while reserving orbital biopsy for atypical, nonsteroid-responsive, or recalcitrant cases of presumed orbital inflammation, such an approach may lead to delay in diagnosis of other causes of inflammation because even malignancy can respond favorably to steroids initially [20]. Biopsy, on the other hand, allows definition of specific disease, identification of systemic implications, and more directed therapeutic treatment plans. Rootman found 50 % of biopsied inflammatory lacrimal gland lesions were associated with systemic disease, including Wegener's granulomatosis, sclerosing inflammation, Sjögren's syndrome, sarcoidal reactions, and autoimmune disease [21]. Except for two classic clinical scenarios, orbital biopsy should be considered whenever medically feasible. These two clinical scenarios are orbital myositis and orbital apex syndrome, as described above. In these cases, characteristic clinical and radiographic findings may strongly support the presumed diagnosis, and the risk of biopsy must be weighed against the risk of a missed diagnosis. However, recurrent orbital myositis or orbital apex syndrome, or those unresponsive to treatment, may warrant orbital biopsy.

6.6.4 Histopathology

Histopathology in the acute phase of NSOI typically reveals a diffuse polymorphous infiltrate composed of mature lymphocytes, plasma cells, macrophages, eosinophils, and polymorphonuclear leukocytes. Vasculitis of small arteries may occasionally be found [1]. In the subacute and chronic phases, an increasing amount of fibrovascular stroma is seen.

6.7 Treatment

6.7.1 Corticosteroids

As the specific pathogenesis of NSOI remains unknown, management is directed toward the common consequences of the inflammatory cascade: tissue inflammation and destruction. High-dose systemic corticosteroids, therefore, are considered the first line of therapy for NSOI, at starting doses of 60–80 mg prednisone per day. The response to steroids is typically rapid, over 1–2 days, although it may not be sustained, and requires a slow taper over weeks to months to avoid recurrence. A slow taper consists of reducing prednisone by 10 mg/day every 1–2 weeks.

However, failure to respond to steroids, dependence on steroids, and steroid intolerance are not uncommon [22, 23]. In addition, the side effects of weight gain, mood swings, insomnia, and gastric distress are common even with short-term therapy.

6.7.2 Steroid-Sparing Agents

Avoiding steroid-associated complications via alternative therapies may be desirable, and a multidisciplinary approach that utilizes the expertise of rheumatologists and/or oncologists is beneficial in organizing such treatment plans. Alternative therapeutic options include antimetabolites, such as azathioprine (Imuran), methotrexate (Rheumatrex), mycophenolate mofetil (CellCept), and leflunomide (Arava); T-cell inhibitors, cyclosporine and tacrolimus; and alkylating agents, cyclophosphamide and chlorambucil.

Recently, several reports have shown promise for biologic agents that have more targeted actions than steroids and are associated with fewer systemic side effects, although some of which are potentially life threatening and require careful monitoring. In particular, Garrity and Miguel found symptomatic and clinical improvement in patients treated with infliximab after failure to respond to conventional treatment or experiencing recurrent orbital inflammation [24, 25].

6.7.3 External Beam Radiation

NSOI is moderately radiosensitive. External beam radiation is often reserved for steroid failure, relapse, or contraindication, in doses ranging from 10 to 30 Gy. In a series of 26 orbits referred for relapse after steroid treatment, steroid resistance, or steroid contraindication, Lanciano reported complete response in 87 % of patients with soft tissue swelling, 82 % with proptosis, 78 % with extraocular muscle dysfunction, and 75 % with pain [26].

Careful patient selection, coordination with an experienced radiation therapist, and treatment planning are essential to maximize efficacy and minimize side effects. Some patients receiving radiation experience increased orbital inflammation, which may be relieved by a short course of oral corticosteroids.

6.7.4 Surgery

Incisional biopsy plays an important role in establishing a correct diagnosis in presumed NSOI, but the treatment afterwards is generally medical. Only occasionally may surgical debulking be an effective alternative to medical and radiation therapy for localized lesions. For the most severe cases of orbital inflammation in which there is irretrievable loss of vision and

uncontrollable pain, the surgical option of exenteration may be considered.

6.8 Prognosis

Although rapid resolution of pain and recovery of vision with steroid treatment is the common clinical course, the risk of recurrence is high. In a series of 24 patients, Maalouf reported a recurrence rate of 55 % [27], and in a series of 21 patients, Mombaerts reported a recurrence rate of 52 % [23]. Yuen reported a treatment failure rate of 37 % in a series of 65 patients [22].

6.9 Future

In the future, the ever-changing, often vague nomenclature used to describe noninfectious, nonmalignant orbital inflammation used presently and in the past will be replaced by designations that describe a key pathological or molecular feature. As this evolution of eliminating the "nonspecific" from this disease proceeds, it will likely bring more insight into the exact pathophysiology of orbital inflammation and provide an opening for the use of targeted biologic immunomodulatory therapy, expanding and improving our current arsenal of treatment beyond steroids.

References

1. Kennerdell JS, Dresner SC. The nonspecific orbital inflammatory syndromes. Surv Ophthalmol. 1984; 29(2):93–103.
2. Birch-Hirschfeld A. Handbuch der Gesamten Augenheilkunde. Berlin: Julius Springer; 1930. p. 251.
3. Rootman J. Why "orbital pseudotumour" is no longer a useful concept. Br J Ophthalmol. 1998;82(4): 339–40.
4. Wladis EJ, Iglesias BV, Gosselin EJ. Characterization of the molecular biologic milieu of idiopathic orbital inflammation. Ophthal Plast Reconstr Surg. 2011; 27(4):251–4.
5. Wladis EJ, Iglesias BV, Adam AP, Nazeer T, Gosselin EJ. Toll-like receptors in idiopathic orbital inflammation. Ophthal Plast Reconstr Surg. 2012; 28(4):273–6.
6. Cockerham KP, Hong SH, Browne EE. Orbital inflammation. Curr Neurol Neurosci Rep. 2003;3(5): 401–9.
7. Mombaerts I, et al. What is orbital pseudotumor? Surv Ophthalmol. 1996;41(1):66–78.
8. Bloom JN, Graviss ER, Byrne BJ. Orbital pseudotumor in the differential diagnosis of pediatric uveitis. J Pediatr Ophthalmol Strabismus. 1992;29(1):59–63.
9. Avni-Zauberman N, Tripathy D, Rosen N, Ben Simon GJ. Relapsing migratory idiopathic orbital inflammation: six new cases and review of the literature. Br J Ophthalmol. 2012;96(2):276–80.
10. McCarthy JM, et al. Idiopathic sclerosing inflammation of the orbit: immunohistologic analysis and comparison with retroperitoneal fibrosis. Mod Pathol. 1993;6(5):581–7.
11. Kovacs EJ, DiPietro LA. Fibrogenic cytokines and connective tissue production. Faseb J. 1994;8(11): 854–61.
12. Raskin EM, et al. Granulomatous idiopathic orbital inflammation. Ophthal Plast Reconstr Surg. 1995; 11(2):131–5.
13. Andrew N, Kearney D, Selva D. IgG4-related orbital disease: a meta-analysis and review. Acta Ophthalmol. 2013;91(8):694–700.
14. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related Sclerosing disease? Am J Surg Pathol. 2007;31(4): 643–5.
15. Stone JH M.D., M.P.H., Yoh Zen M.D., Ph.D., Deshpande V M.D. IgG4-related disease. N Engl J Med. 2012;366:539–51.
16. Uehara F, Ohba N. Diagnostic imaging in patients with orbital cellulitis and inflammatory pseudotumor. Int Ophthalmol Clin. 2002;42(1):133–42.
17. Kapur R, Sepahdari AR, Mafee MF, Putterman AM, Aakalu V, Wendel LJ, Setabutr P. MR imaging of orbital inflammatory syndrome, orbital cellulitis, and orbital lymphoid lesions: the role of diffusion-weighted imaging. AJNR Am J Neuroradiol. 2009; 30(1):64–70.
18. Patrinely JR, et al. Computed tomographic features of nonthyroid extraocular muscle enlargement. Ophthalmology. 1989;96(7):1038–47.
19. Ben Simon GJ, Syed HM, Douglas R, McCann JD, Goldberg RA. Extraocular muscle enlargement with tendon involvement in thyroid-associated orbitopathy. Am J Ophthalmol. 2004;137(6):1145–7.
20. Papalkar D, et al. A rapidly fatal case of T-cell lymphoma presenting as idiopathic orbital inflammation. Orbit. 2005;24(2):131–3.
21. Rootman J, editor. Orbital disease: present status and future challenge. Boca Raton: Taylor & Francis Group, LLC; 2005. p. 1–13.
22. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: distribution, clinical features, and treatment outcome. Arch Ophthalmol. 2003;121(4):491–9.
23. Mombaerts I, et al. Are systemic corticosteroids useful in the management of orbital pseudotumors? Ophthalmology. 1996;103(3):521–8.

24. Garrity JA, Coleman AW, Matteson EL, et al. Treatment of recalcitrant idiopathic orbital inflammation (chronic orbital myositis) with infliximab. Am J Ophthalmol. 2004;138:925–30.
25. Miguel T, Abad S, Badelon I, Vignal C, et al. Successful treatment of idiopathic orbital inflammation with infliximab: an alternative to conventional steroid-sparing agents. Ophthal Plast Reconstr Surg. 2008;24(5):415–7.
26. Lanciano R, Fowble B, Sergott RC, Atlas S, Savino PJ, Bosley TM, Rubenstein J. The results of radiotherapy for orbital pseudotumor. Int J Radiat Oncol Biol Phys. 1990;18(2):407–11.
27. Maalouf T, et al. What has become of our idiopathic inflammatory pseudo-tumors of the orbit? Orbit. 1999;18(3):157–66.