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Non-specific orbital inflammation: Current understanding and unmet needs

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ABSTRACT

Non-specific orbital inflammation (NSOI) is a noninfectious inflammatory condition of the orbit. Although it is generally considered the most common diagnosis derived from an orbital biopsy, it is a diagnosis of exclusion, meaning that the diagnosis requires exclusion of a systemic process or another identifiable etiology of orbital inflammation. The clinical diagnosis of NSOI is ill-defined, but it is typically characterized by acute orbital signs and symptoms, including pain, proptosis, periorbital edema, chemosis, diplopia, and less commonly visual disturbance. NSOI poses a diagnostic and therapeutic challenge: The clinical presentations and histological findings are heterogeneous, and there are no specific diagnostic criteria or treatment guidelines. The etiology and pathogenesis of NSOI are poorly understood. Here we recapitulate our current clinical understanding of NSOI, with an emphasis on the most recent findings on clinical characteristics, imaging findings, and treatment outcomes. Furthermore, gene expression profiling of NSOI and its implications are presented and discussed.

1. Introduction

Non-specific orbital inflammation (NSOI) was first described in 1905 by Birch-Hirschfield, who termed the condition 'orbital pseudotumor'(Birch-Hirschfeld, 1905). He described four patients with exophthalmos and a clinical impression of a benign or malignant orbital tumor, but surgical exploration revealed only inflamed tissue. The terminology has persisted for more than 100 years. However, the term 'pseudotumor' has been criticized by orbital researchers since the end of the last century (Grove and Weber, 2013; Mombaerts et al., 1996a; Rootman, 1998; Shields and Shields, 2013). The term describes what it is not rather than what it is (Mombaerts et al., 1996a). Furthermore, the diagnosis was used as an umbrella terminology to designate a variety of conditions. Specific diagnoses such as lymphoproliferative disorders and vasculitis were being recognized and excluded from this entity. The diagnosis was becoming less frequent with an improvement in diagnostic techniques. So, multiple alternative names have been suggested to label this entity more accurately to reflect etiologic, clinical, and histopathological characteristics. Emerging terms include 'non-specific orbital inflammation', 'idiopathic orbital inflammation', 'idiopathic non-granulomatous orbital inflammation' (Shields and Shields, 2013), 'idiopathic orbital inflammatory disease'(Gunalp et al., 1996), and 'idiopathic orbital inflammation syndrome'(Swamy et al., 2007). These terms commonly suggest this condition comes from an inflammatory process of unknown etiology. Although these designations are increasingly replacing 'orbital pseudotumor', 'orbital pseudotumor' is still commonly used in the clinical setting.

NSOI is challenging to define in one sentence, but it is currently understood to be inflammatory conditions of the orbit without identifiable local or systemic causes (Jacobs and Galetta, 2002; Swamy et al.,

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2007). It comprises a heterogeneous group of disorders and is a diagnosis of exclusion. The classical clinical presentation is the acute or subacute onset of proptosis, periorbital swelling and erythema, pain, diplopia, visual disturbance, and response to treatment with oral corticosteroids (Harris, 2006). However, there are numerous individual variations. The diagnosis is still challenging because the etiology is unknown and relies on the clinician's experience and intuition. There are no laboratory tests that can be used to diagnose NSOI and no consensus criteria or guidelines for diagnosis. Although it is a diagnosis of exclusion, what is excluded varies greatly among clinicians.

Our purpose is to improve the insight into NSOI and to achieve an updated clinical understanding. This review provides a comprehensive overview of knowledge regarding NSOI. We present our recent data about clinical features and treatment outcomes. We will briefly summarize our gene expression data in terms of possible molecular diagnosis (Rosenbaum et al., 2015c, 2015d). We will also discuss the role of imaging studies in the diagnosis of NSOI.

2. Classification

NSOI has highly variable histological and clinical features. From such heterogeneity, a need arose to make subcategories. Several classification systems based on onset of symptom, histopathology, and anatomical location have previously been proposed (Bijlsma et al., 2012b; Blodi and Gass, 1968; Fujii et al., 1985; Gunalp et al., 1996; Mombaerts et al., 1996a; Nugent et al., 1981; Rootman and Nugent, 1982; Swamy et al., 2007; Yan et al., 2006; Yuen and Rubin, 2003).

2.1. Onset of symptoms

A classification based on the onset of symptoms has been employed (Gunalp et al., 1996; Nugent et al., 1981; Rootman and Nugent, 1982; Sekhar et al., 1993). Acute onset NSOI was classified when the onset was within days to weeks, and chronic NSOI was defined as onset within weeks to months. Some researchers used 3 sub-classifications: acute, subacute, and chronic onset of symptoms (Young et al., 2017).

2.2. Location

The most commonly used classification is based on the orbital structures involved. NSOI can affect any orbital structure. It may involve a specific orbital tissue in a localized form, or multiple structures, or the entire orbit diffusely. The sub-classifications include lacrimal (lacrimal gland, LG), myositic (extraocular muscle, EOM), anterior (sclera, uvea, Tenon's capsule), posterior (orbital apex), and diffuse (Rootman and Nugent, 1982). Some subsequent authors have referred to the anterior subset as periscleritic (Gunalp et al., 1996; Yan et al., 2004) and the posterior subset as apical (Yuen and Rubin, 2003). Clinical features and imaging study findings are quite different according to the subtype. Tolosa-Hunt syndrome, which is characterized by unilateral headache around the brow and eye associated with cranial nerve palsies and evidence of granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit (Headache Classification Committee of the International Headache Society (IHS), 2013), is considered as a very close or overlapped disease entity of apical NSOI. Optic perineuritis is a form of NSOI in which the target tissue is the optic nerve sheath (Hickman, 2016; Zhang et al., 2014). Optic perineuritis may be included in the apical subset of NSOI, but sometimes it is separately classified because of the unique clinical characteristics such as optic disc swelling, visual field defects, relatively preserved visual acuity, and optic nerve sheath enhancement on imaging (Hickman, 2016; Purvin et al., 2001).

2.3. Histopathology

Another classification system is based on the pathological characteristics of the lesion. The histological findings vary, and the subtypes suggested include classic, granulomatous, vasculitic, eosinophilic, and sclerosing (Fig. 1) (Mombaerts et al., 1996a). The classical form, which is also called lymphoid, is characterized by a mixed cellular infiltrate consisting of plasma cells, lymphocytes, macrophages, polymorphonuclear leukocytes, and eosinophils with various degrees of reactive fibrosis and edema. In lacrimal NSOI, various degrees of gland destruction and atrophy of acini and ducts are usually seen (Luemsamran et al., 2017). The granulomatous form is characterized by infiltration of histiocytes and multinucleated giant cells. It must be carefully diagnosed after excluding sarcoidosis, granulomatous polyangiitis (GPA), and mycobacterial or fungal infection (Harris, 2006). Vasculitis of small vessels is seen in the vasculitic form. The eosinophilic form displays prominent tissue eosinophilia without vasculitis. The sclerosing form is notable for unique clinicopathological and prognostic characteristics (Hsuan et al., 2006; Pemberton and Fay, 2012; Rootman et al., 1994). Significant sclerosis and a sparse mixed inflammatory cell replacing normal anatomical structures are the distinctive features.

2.4. Limitations

The classification systems mentioned above have their own merits and demerits. The classification based on the onset of symptoms is simple, easy to apply, and does not require additional laboratory tests. However, the onset of symptoms is relatively subjective depending on the patients' statement, and it is difficult to determine the optimal cut-off between acute and chronic NSOI. Classification by location is commonly used but depends on the ability of imaging modalities. Orbital magnetic resonance imaging (MRI) has superior soft tissue resolution compared to computed tomography (CT) and it is possibly more sensitive in detecting fat infiltration. The role of imaging studies in the diagnosis of NSOI will be further described and discussed in section 6.3. Histopathological classification can be affected by the accuracy of surgical biopsy. Biopsy is not always performed to diagnose NSOI, especially when the lesion is located in the orbital apex, and histopathological classification cannot be applied to these cases. Bijlsma et al. (2012b) validated NSOI classification systems based on onset, location, and histopathology, and reported that a two-dimensional combined classification system using location and histopathology showed good reliability, feasibility, and face validity.

3. Etiology & pathogenesis

3.1. Etiologies

The etiology of NSOI remains unknown. It has been suggested that NSOI is caused by an immune or autoimmune process, infection, or drugs (Harris, 2006; Mombaerts et al., 1996a). NSOI is considered of non-infectious origin, but it has been postulated that NSOI may be caused by subclinical infection or an immune process secondary to infection (Bijlsma et al., 2013; Harris, 2006). NSOI after upper respiratory tract infection, influenza vaccination, and paranasal sinusitis have led to the hypothesis that preceding infection might provoke NSOI (Dylewski et al., 2001; Manusow et al., 2015; Purcell and Taulbee, 1981). Interestingly, a few studies have suggested Epstein-Barr virus (EBV) as a possible pathogen causing NSOI. EBV is one of the human herpesvirus types that can invade lymphocytes and epithelial cells. EBV has been implicated in various neoplastic diseases, including nasopharyngeal cancer, stomach cancer, and lymphomas (Fukayama et al., 2019; Li and Chng, 2019; Morris, 2019). Jin et al. (2013) detected EBV DNA in 16 NSOI tissue samples and reported 94% positivity. Ren et al. (2017) also reported a higher positive expression rate of EBV-encoded small RNAs in NSOI tissue samples compared to thyroid eye disease (TED) samples using *in situ* hybridization. These results reinforce the support a potential triggering role of EBV infection in the pathogenesis of NSOI.

NSOI can occur in association with other rheumatologic diseases,

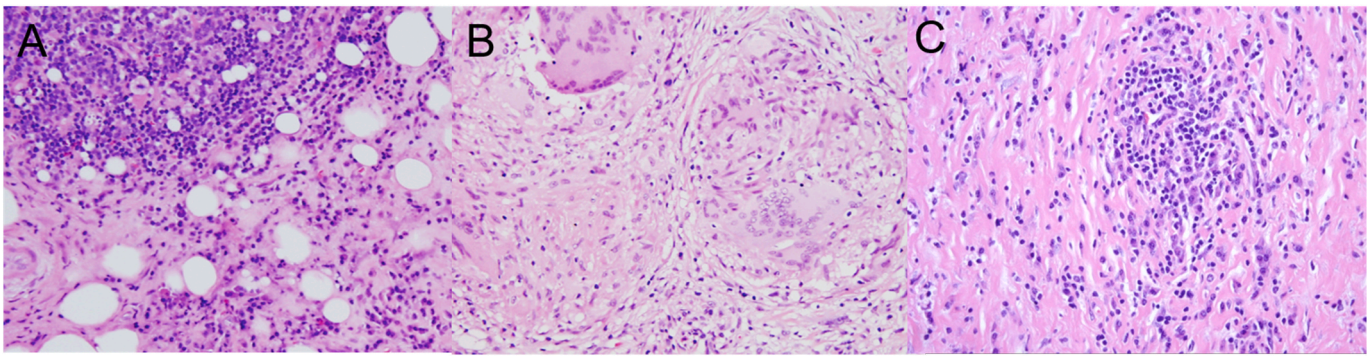

Fig. 1. Histopathological subtypes of non-specific orbital inflammation (NSOI).
(A) classical NSOI which shows chronic inflammatory infiltrate with mature lymphocytes mixed with plasma cells, neutrophil, eosinophil, histiocytes, and macrophages, (B) granulomatous NSOI characterized by histiocytic infiltration, multinucleated giant cells, and noncaseating granulomas, (C) sclerosing NSOI showing prominent fibrosis and less cellular infiltrates.

which implies that NSOI comes from an immune-mediated process. Garrity et al. (2004) reported on the efficacy of infliximab (a monoclonal antibody to the cytokine tumor necrosis factor) in 7 patients with recalcitrant NSOI. In their study, 6 of 7 patients had various comorbid conditions such as Crohn's disease, psoriasis, hypothyroidism, discoid lupus, or Behçet disease. Several case reports about NSOI associated with Crohn's disease also have been reported. Most reports were cases with orbital myositis (Culver et al., 2008; Durno et al., 1997; Ishihara et al., 2020; Maalouf et al., 2001), but dacryoadenitis (Hwang et al., 2001) and perineuritis (McClelland et al., 2012) were also reported. Mombaerts et al. (Mombaerts and Koornneef, 1997) commented that orbital myositis was associated with an autoimmune disease in 10% of patients. In a Netherlands case-control study, a weak trend for the association between NSOI and autoimmune disease was also reported (Bijlsma et al., 2011b). The authors suggested genetic predisposition or a dysregulated immune system could explain the co-occurrence of NSOI with autoimmune diseases. In this comorbidity, the orbital inflammation is regarded as a secondary immunologically mediated condition, rather than a part of multifocal disorder (Harris, 2006). In a report of NSOI associated with Crohn's disease, histopathological examination showed inflammatory infiltrates with non-specific T-cells in orbital tissue, but granulomatous inflammation in ileal tissue. Such a discordance suggested the orbital inflammation would be an immune reaction and not a distant focus of Crohn's disease (Maalouf et al., 2001).

NSOI occurs in approximately 0.1–0.4% of patients taking an aminobisphosphonate (Keren et al., 2019). Bisphosphonates inhibit osteoclast-mediated bone resorption and are used for treating osteoporosis, Paget disease, osteolytic bony metastasis, multiple myeloma, and more (Maraka and Kennel, 2015; Reyes et al., 2016). There are two main groups of bisphosphonate: non-aminobisphosphonates and aminobisphosphonates. Aminobisphosphonates, which contain a nitrogen group, are a newer and more potent generation. There have been several case reports of orbital inflammation associated with aminobisphosphonate treatment, and improved awareness of the association has resulted in increased reporting (Chehade et al., 2019; Cunningham et al., 2016; Herrera et al., 2019; Keren et al., 2019; Peterson and Bedrossian, 2012; Vora et al., 2014). A suggested mechanism is the structural homologies that aminobisphosphonates share with a ligand for γδ T-cells, resulting in activation of this subset of T cells. This activation leads to the release of cytokines and inflammatory mediators (Kunzmann et al., 1999).

3.2. Hypothesized pathogenesis

Although the associations with subclinical infections and systemic diseases have been reported and an immune-mediated process has been suggested, very little is known about the specific pathogenic mechanism of NSOI. Harris (2006) previously outlined the pathogenetic construct of NSOI based on the cellular composition of the inflammatory infiltrate and general immunological mechanisms. The classical NSOI histopathology shows a benign, nonspecific inflammatory pattern with a cellular infiltrate of lymphocytes, plasma cells, and histiocytes. Autoantigens, exogenous antigens such as viral products, or other triggering factors are processed by antigen-presenting macrophages or dendritic cells. Macrophages present antigens to Th-cells initiating a cellular immune response cascade. A humoral response mediated by B-cells is also initiated. Wladis and coworkers (Wladis et al., 2011) conducted quantitative assays for cytokines in biopsy specimens of NSOI patients and reported that multiple cytokines are upregulated in a significant fashion. IL-12, TNF-α, and IFN-γ were most highly expressed in NSOI, suggesting Th1is a dominant pathogenetic pathway.

A study based on serum micro-RNA (miRNA) suggested differentially expressed miRNA-cluster was associated with immune pathway activation (Laban et al., 2020a). The serum miRNA expression levels were compared among NSOI, non-Hodgkin orbital lymphoma, and control groups. An increased expression of a cluster of 8 miRNAs was identified in patient groups compared to the control group. The cluster consisted of miR-29a-3p, miR-193a-5p, miR-223-3p, miR223-5p, miR-148a-3p, miR-365a-3p, miR-143-3p, and U6 snRNA. Pathway enrichment analysis revealed this miRNA-cluster was enriched for mitogen-activated protein kinase signaling, p53 signaling, and interleukin signaling pathways, which are well-known pathways related to inflammation and cancer.

The pathogenic role of dendritic cells in NSOI is also noteworthy. Flow cytometry of peripheral blood of patients with NSOI revealed plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) type-2 were decreased (Laban et al., 2020b). Orbital microenvironment was also investigated by deconvolutional transcriptome analysis and revealed decreased pDCs and cDCs in biopsy specimens of NSOI patients. Dendritic cells are versatile antigen-presenting cells and modulate immune responses by cross-talking with other immune cells from local microenvironment (Worbs et al., 2017). Altered distribution or functional disturbance of DCs are known to be a common feature of several autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus (Ganguly et al., 2013; Qian and Cao, 2018).

Our laboratory has collected formalin-fixed, paraffin-embedded orbital biopsies from international centers and characterized the patterns of gene expression from these tissues using microarray (Rosenbaum et al., 2015c, 2015d, 2015e, 2016, 2017). Additional characterization using the technique of RNA-Seq is in progress. Principal coordinate analysis (PCoA) is a technique to appreciate how similar or different two complex data points might be. We have used PCoA to show quite clearly that NSOI is a heterogeneous collection of diseases

(Rosenbaum et al., 2015c, 2017), a conclusion also supported by the variable histology. We also characterized gene expression from other causes of orbital inflammation such as TED (Rosenbaum et al., 2015e), sarcoidosis (Rosenbaum et al., 2015b), or GPA (Rosenbaum et al., 2015c). A surprising finding was that roughly half of the tissues showed a pattern of gene expression indistinguishable from GPA (Rosenbaum et al., 2015c). Among those tested, these subjects were negative for antineutrophil cytoplasmic antibody (ANCA) (Rosenbaum et al., 2015c), but this test is known to have limited sensitivity when this disease does not involve lung or kidney. The pattern of gene expression has led us to conclude that many patients with NSOI suffer from a limited form of GPA. In additional support of this conclusion is the excellent response in many patients with GPA to either methotrexate (Smith and Rosenbaum, 2001) or rituximab (Suhler et al., 2014). These observations are discussed further in section 6.5.

3.3. Sclerosing NSOI and IgG4-related ophthalmic disease

Sclerosing NSOI is a histological variant of NSOI characterized by dense fibrous tissue with a sparse inflammatory cell infiltrate consisting of lymphocytes, eosinophils, histiocytes, and plasma cells (Rootman et al., 1994). Sclerosing NSOI is characterized by an insidious, chronic, progressive sclerosing process. It is also notorious for poor response to corticosteroid treatment and frequent cicatricial sequelae including visual loss (Brannan, 2007; Chen et al., 2010; Hsuan et al., 2006). Although sclerosing NSOI has been thought to be a subtype of NSOI, it is now considered as a distinct variant that has unique clinicopathological characteristics (Brannan, 2007). Sclerosing NSOI is still a poorly understood condition, but the association with sclerosing NSOI and other fibro-sclerosing systemic diseases has been noted. We have analyzed gene expression in tissue from patients with orbital fibrosis and noted that transcripts characteristic of pulmonary fibrosis such as fibronectin, lumican, thrombospondin, and collagen types I and VIII are common to both orbital and pulmonary fibrosis (Rosenbaum et al., 2015a). McCarthy et al. reported histopathological and immunohistochemical similarities between sclerosing NSOI and retroperitoneal fibrosis (McCarthy et al., 1993). Riedel's thyroiditis, sclerosing cholangitis, mediastinal fibrosis, and mesenteritis were reported to be associated with sclerosing NSOI as well (Aylward et al., 1995; Berry-Brincat and Rose, 2012; Pemberton and Fay, 2012). Since approximately 2005, all of these sclerosing conditions have been partly explained as components of IgG4-related disease (IgG4-RD). IgG4-RD is a collection of inflammatory diseases with unknown cause. It can be diagnosed by an infiltrate of IgG4-positive lymphoplasmacytic cells, mass-like lesion formation in various organs, and elevated serum IgG4 (Goto et al., 2015). IgG4-related ophthalmic disease (IgG4-ROD) is an ocular manifestation of IgG4-RD. Common clinical involvement patterns are LG enlargement, enlarged orbital nerves with EOM involvement, and orbital fat infiltration (McNab and McKelvie, 2015; Park et al., 2018).

Because of the histopathological similarity and common clinical features, the possibility has been raised that a substantial number of cases of NSOI, especially sclerosing NSOI, are in fact IgG4-ROD (Fig. 2). Retrospective review of the biopsy specimens of non-granulomatous NSOI, accompanied by immunohistochemical staining of IgG and IgG4 revealed 5–20% of cases classifiable as IgG4-ROD (Andrew et al., 2015). Regarding sclerosing NSOI, Sa et al. (2015) reported 11 (46%) of 24 sclerosing NSOI patients were redefined as IgG4-ROD. A prospective cohort study from France also reported higher IgG4 immunostaining positivity in sclerosing NSOI (48%) than in classical NSOI (21%) (Abad et al., 2019). A Taiwanese group recently reported high IgG4 immunopositivity in non-sclerosing NSOI (53.3%) as well as sclerosing NSOI (48.4%) (Tsai et al., 2019). Our group studied IgG4 staining in 42 orbital biopsies from patients with NSOI as well as 66 control orbital tissues associated with other diagnoses (Wong et al., 2014). Using the criteria of at least 30 IgG4 staining plasma cells per high powered field and a ratio of IgG4 to IgG staining of at least 0.4 (Cheuk et al., 2008; Lindfield et al., 2012), only 2 of 20 orbital adipose tissues stained positively and only one of 22 lacrimal tissues stained positively. Moreover, tissue from subjects with other diagnoses such as GPA could also stain positively for IgG4. Direct comparisons among these studies are impossible because of diverse criteria for IgG4-positivity: The criteria for a minimum IgG4-positive plasma cell infiltrate used was between 10 and 100 cells

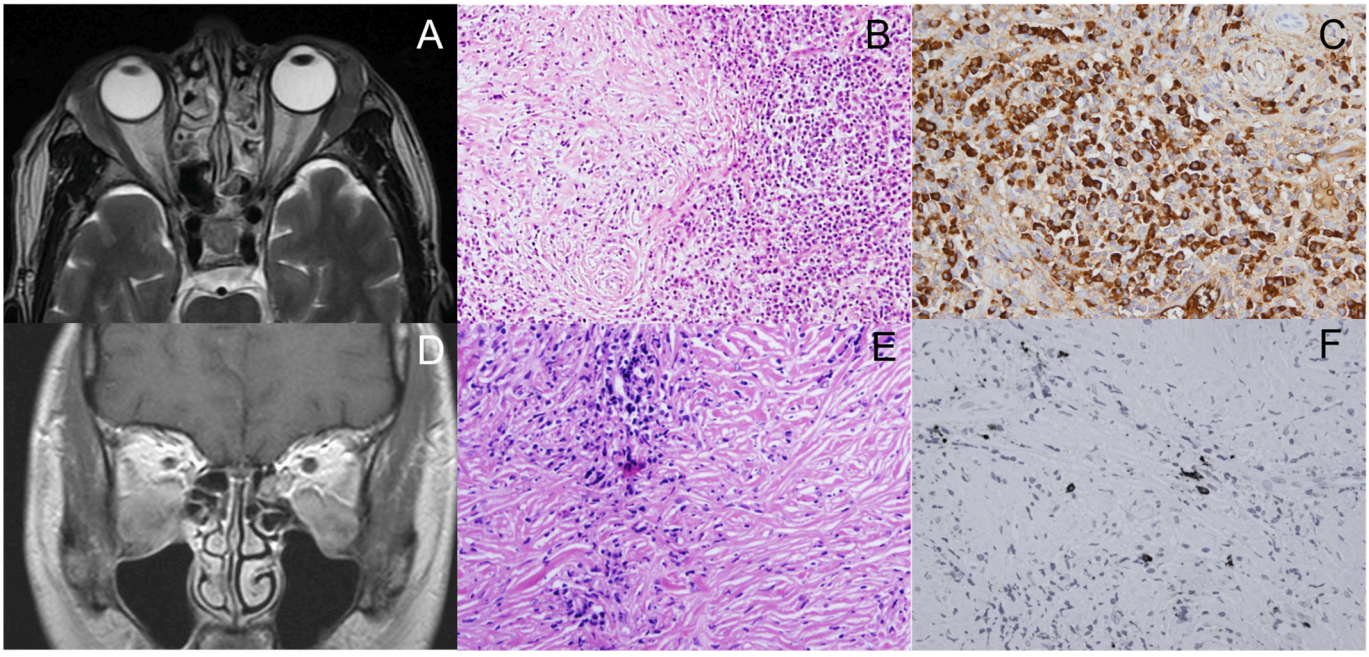

Fig. 2. IgG4-related ophthalmic disease and sclerosing non-specific orbital inflammation (NSOI).
Case 1. (A) Enlargement of both lacrimal glands with hypointense signal intensity on axial T2-weighted magnetic resonance image (MRI), similar to brain. (B) Incisional biopsy reveals lymphoplasmacytic infiltration with fibrosis of lacrimal gland. (C) IgG4 immunostaining positivity (more than 100 IgG4 (+) cells/high powered filed) implies IgG4-related ophthalmic disease. Case 2. (D) Orbital coronal T1 enhanced MRI showing bilateral inferior orbital masses. (E) Histopathology shows dense fibrosis with lymphocytic infiltration. (F) Negative IgG4 immunostaining suggests sclerosing NSOI.

per high power field. A ratio criteria for IgG4-positive cells to IgG-positive cells was 40% in most articles (Deshpande et al., 2012; Goto et al., 2015; Umehara et al., 2012). Nevertheless, these studies have suggested a modest link or overlap between NSOI and IgG4-ROD. IgG4-RD might be more common in some geographic areas such as Southeast Asia; this difference could contribute to the variable prevalence reported in these series.

4. Clinical characteristics

4.1. Establishment of clinical database from international consortium

Although NSOI is the third most commonly diagnosed orbital disease after TED and lymphoproliferative disease, accounting for 4.7–8% of all orbital diseases (Shields et al., 2004; Yuen and Rubin, 2003), there have been few articles which have clinically characterized NSOI. We assembled an international consortium of orbital surgeons and orbital researchers for comprehensive research on orbital inflammatory diseases. The diagnosis of NSOI was made based on the clinical information and pathological review at the center where biopsy was obtained. The patients had undergone tissue biopsy between January 2006 and December 2018 and were diagnosed with NSOI. All biopsies were processed as formalin-fixed, paraffin-embedded samples and sent to Oregon Health & Science University (OHSU) and Emory University for further pathological review. Slides from each specimen were stained with hematoxylin and eosin and were independently re-evaluated by two ocular pathologists (David J Wilson & Hans E Grossniklaus) without any knowledge of the prior diagnosis. Additional stains were requested when necessary. A few cases with an inconclusive diagnosis were excluded. Besides collecting a library of tissue samples, we also have collected detailed clinical data and established a structured database. Clinical data were managed with REDCap (Research Electronic Data Capture) tools hosted at OHSU. The study protocol was approved by the institutional review board at OHSU and at each of the contributing centers. This retrospective cohort encompasses 173 patients with NSOI from 12 centers across 3 continents. The diagnosis of NSOI was pathologically supported after a surgical biopsy in all patients. Of the 173 patients in this cohort, 32 patients were excluded (incomplete data, n = 23, or inconclusive diagnosis, n = 9). Hence, 141 patients were included in the analysis (Table 1).

Table 1
Number of subjects with non-specific orbital inflammation from each center participating in the international consortium for the research on orbital inflammatory diseases.

Center	Country	Number of subjects (n = 141)
Oregon Health & Science University	United States, OR	41
University of Miami	United States, FL	27
Medical College of Wisconsin	United States, WI	27
Ophthalmic Surgeons and Consultants of Ohio	United States, OH	12
King Khaled Eye Specialist Hospital	Saudi Arabia	8
University of British Columbia	Canada	6
Wake Forest University	United States, NC	6
University of Adelaide	Australia	4
Columbia University	United States, NY	3
University of California San Diego	United States, CA	3
Emory University	United States, GA	2
Silkiss Eye Surgery, Oakland	United States, CA	2

4.2. Demographics

The mean age at initial presentation was 49.4 years (range 6–96 years) and the peak incidence was in the 6th decade of life (Fig. 3). Of all patients, 68.1% were female and the male to female ratio was 45:96. A higher incidence in the adolescent years was remarkable in females. As for race and ethnicity, 53.9% were Caucasian, 16.3%, African American, 12.1% Hispanic, and 4.3% Asian. Unilateral disease occurred in 78% of cases with an even distribution between right and left orbits (Table 2).

4.3. Clinical presentations

History and presenting symptoms of the study population are outlined in Fig. 4. The predominant presenting symptom was proptosis (54.6%), followed by diplopia (41.8%) and pain requiring medication (34.8%). The evidence of optic nerve dysfunction was evident in the clinical course in 9.2% of the patients. The distribution of the symptoms was quite different according to the major location of inflammation. The patients who had available imaging data were divided into anterior (68 patients), myositic (19 patients), and posterior (26 patients) NSOI. In anterior NSOI, chemosis (43%) was the most common symptom, followed by proptosis (39%), and pain (34%). Diplopia (89%) was the predominant symptom in myositic NSOI, followed by proptosis (78%) and pain (32%). In posterior NSOI, proptosis (69%), diplopia (57%), and pain (42%) were common symptoms. Evidence of optic nerve dysfunction was common in posterior NSOI (35%), and less common in myositic (10%) and anterior NSOI (3%). Acute (<1 week), subacute (1–4 weeks), and chronic (>4weeks) onset of symptoms occurred in 25 (17.7%), 60 (42.5%), and 46 (32.6%) respectively. The mean duration of clinical symptoms prior to biopsy was 5 months, ranging from 1 to 144 months.

4.4. Orbital sites involved on imaging studies

Detailed information on radiologic image findings was available in 113 patients. We counted all orbital structures involved on imaging (Swamy et al., 2007). The most frequent localization of inflammation included the LG (60.2%), retrobulbar orbital fat (37.2%), and EOM (20.3%). The anterior extraconal fat was involved in 8.8%, orbital apex involvement was noted in 5.3%, and scleral infiltration was found in 2.7%. Extra-orbital extension was noted in 4.4% (Table 3). Looking into cases with EOM involvement (n = 23), most have a single affected muscle (n = 15). Two muscles were affected in 4 cases, and three muscles in 4 cases. The total number of muscles affected by NSOI in our series was 35. The most frequently involved rectus muscle was superior rectus (n = 13), followed by inferior rectus (n = 9), lateral rectus (n = 8), and medial rectus (n = 5). The number and patterns of EOMs were listed in Table 4.

4.5. Comparisons with other large studies

We reviewed detailed data of prior articles which had a relatively large number of cases, and compared their data to ours (Table 5) (Blodi and Gass, 1968; Gunalp et al., 1996; Yan et al., 2004; Yuen and Rubin, 2003). One of the largest case series was published more than 50 years ago before the establishment of current concepts of NSOI (Blodi and Gass, 1968). Their histopathological diagnosis and classification may not be reliable, and their study population possibly included some cases with reactive lymphoid hyperplasia (Mombaerts et al., 1996a). Another large case series that included 209 cases of NSOI was reported from China (Yan et al., 2004). The purpose of that study was to differentiate NSOI from lymphoid tumor using clinical and pathological points of view. They briefly described the clinical features of NSOI in their results. Our data from the international consortium are comparable in size with these two studies and strengthened by pathologically supported

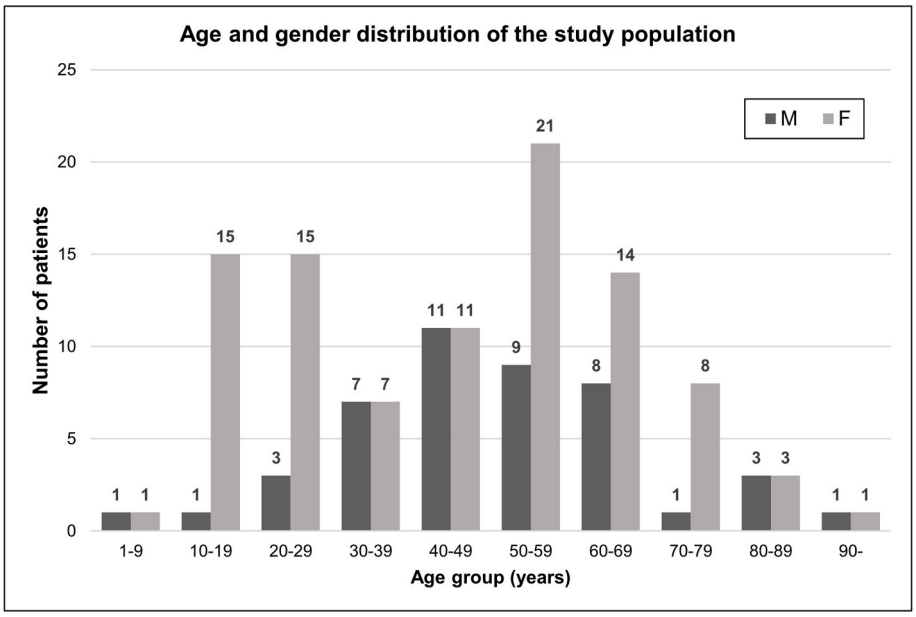

Fig. 3. Age and gender distribution of the patients with non-specific orbital inflammation (n = 141).

Table 2
Demographics of the patients with non-specific orbital inflammation (n = 141).

Variables		Value
Age, median (range), years		49.4 (5.9–96.1)
Gender, n (%)	Male	45 (31.9)
	Female	96 (68.1)
Race, n (%)	Asian	6 (4.3)
	Black	23 (16.3)
	Hispanic	17 (12.2)
	White	76 (53.9)
	Others	3 (2.1)
	Unknown	16 (11.3)
Laterality, n (%)	Right	55 (39.0)
	Left	55 (39.0)
	Both	31 (22.0)

diagnosis, elaborate data, and treatment outcomes.

Our data suggest NSOI occurs typically in middle-aged women. The peak incidence in middle age has been repeatedly reported in the

Table 3
Orbital site involved with non-specific orbital inflammation on imaging studies (n = 113).

Orbital site	Number of patients (%)
Lacrimal gland	68 (60.2)
Extraocular muscle	23 (20.3)
Retrobulbar orbital fat	42 (37.2)
Anterior extraconal fat	4 (8.8)
Sclera	3 (2.7)
Orbital apex	6 (5.3)
Other[a]	5 (4.4)

[a] Sinus in 3, Nasolacrimal duct in 2.

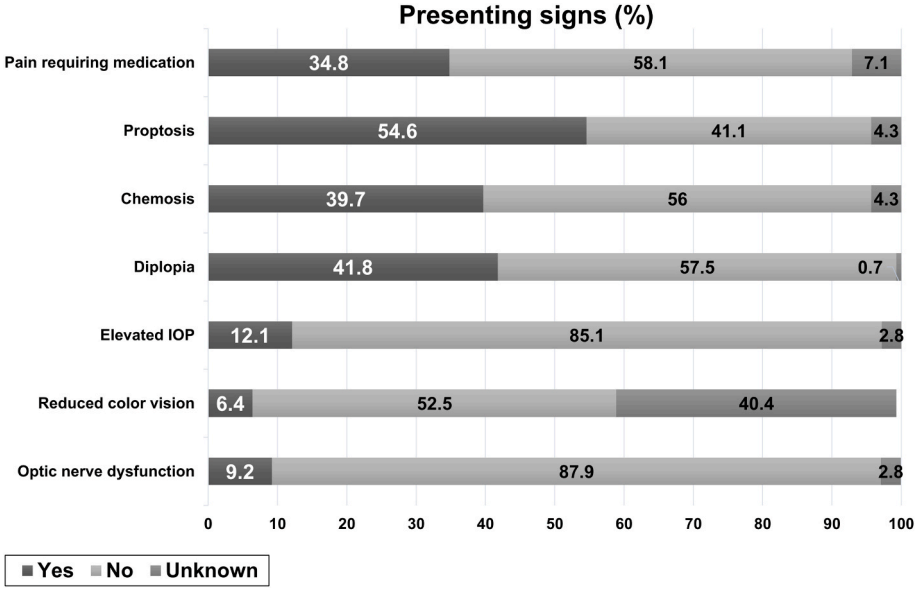

Fig. 4. Presenting signs (%) (n = 141).

Table 4
Number and patterns of extraocular muscles involvement in non-specific orbital inflammation (n = 23).

Number of involved muscles	Pattern	Number of patients
1	SR	7
	LR	3
	MR	3
	IR	2
2	IR + LR	2
	SR + LR	1
	SR + IR	1
3	SR + IR + LR	2
	SR + IR + MR	2

SR = superior rectus muscle, LR = lateral rectus muscle, IR = inferior rectus muscle, MR = medial rectus muscle.

literature (Blodi and Gass, 1968; Gunalp et al., 1996; Swamy et al., 2007; Yan et al., 2004; Yuen and Rubin, 2003). The percentage of pediatric patients (less than 20 years old) was reported as 16.4% by Blodi and Gass, and it was 12.8% in our data. Gender predilection is still controversial. Equal gender distribution has been reported in some studies (Blodi and Gass, 1968; Gunalp et al., 1996; Swamy et al., 2007; Yan et al., 2004). However, Yuen and Rubin (2003) reported 1.8:1 female predominance regardless of the subtypes. Similarly, about 2:1 female predominance was observed in our study population. Bilateral disease accounted for 22%, comparable to other previous studies that reported 18–26% with bilateral involvement (Yan et al., 2004; Yuen and Rubin, 2003). Older publications tended to report a lower proportion of bilateral cases, less than 10%. That may reflect the absence of sensitive imaging modalities that can detect asymmetric bilateral cases. Racial distribution showed NSOI was most in White, followed by Black, Hispanic, and Asian. However, these data should be interpreted carefully. Although our consortium included 12 centers from 3 continents, centers outside of North America are under-represented.

In many studies, the classical clinical presentation was described as “acute onset of pain, edema, erythema, chemosis, and less commonly visual loss” (Espinoza, 2010; Jacobs and Galetta, 2002). However, clinical presentations are quite different according to the affected anatomical structures and there can be many variations (Harris, 2006). Although acute or subacute onset is regarded as a diagnostic feature (Mombaerts et al., 2017), the results of this study suggested the onset of disease can also vary widely, from acute onset with rapid progression to slow and insidious course. In our study population, proptosis was the most common (54.6%) presenting sign consistent with other large studies (Blodi and Gass, 1968; Gunalp et al., 1996; Swamy et al., 2007). Pain has been known as one of the typical signs of NSOI and was reported as one of the highly-ranked consensus diagnostic criteria items (Mombaerts et al., 2017). However, it was less frequent (34.8%) in our study. The frequency of pain reported ranged from 24% to 69%, indicating that pain is not an ‘essential’ sign for diagnosing NSOI (Blodi and Gass, 1968; Swamy et al., 2007; Yan et al., 2004; Yuen and Rubin, 2003). Visual disturbance by optic nerve dysfunction was present in 9%, comparable to other studies reporting 4–21% (Blodi and Gass, 1968; Gunalp et al., 1996; Swamy et al., 2007; Yan et al., 2004).

Imaging studies are widely used to evaluate the extent of inflammation. Imaging features can be analyzed by affected orbital structures or described as subtypes. We analyzed orbital structures involved, and LG was the most commonly affected anatomical structure, followed by orbital fat and EOM. Swamy et al. (2007) analyzed imaging data in a similar way, but the most commonly involved structure was orbital fat, followed by LG and EOM. This discrepancy is still present when imaging features were analyzed by subtypes. Günalp et al. (Gunalp et al., 1996) reported the most frequent type of lesion was diffuse orbital inflammation, while Yuen et al. (Yuen and Rubin, 2003) reported that dacryoadenitis was the most common type. The largest case series published by Yan et al. did not analyze imaging findings separately. They proposed classifying NSOI based on their own criteria reflecting clinical, radiological, and surgical findings. The most common type was a focal mass which was not specified with regard to the anatomical location, so it was impossible to be compared with other studies.

A strength of our characterization of the clinical aspects of NSOI is the relatively large size of the study and the international sources for data. Weaknesses include potential inconsistencies in the disease characterization. For example, an ANCA or a chest CT scan was not obtained for all subjects. Although we reviewed histopathology of a biopsy of all

Table 5
Comparison of the demographics and clinical presentations between previous studies about non-specific orbital inflammation and this study.

	Blodi and Gass (1968)	Gunalp et al. (1996)	Yan et al. (2004)	Yuen and Rubin (2003)	This study (2020)
Number of patients	140	132	209	65	141
Biopsy performed, n (%)	140 (100)	96 (72.7)	178 (85.2)	19 (29)	141(100)
Age, years	Frequent in middle age	46.5, mean	44.4, mean	45, mean	49, median
Gender (male:female)	69:61	62:70	118:91	22:43	45:96
Bilateral disease, n (%)	8 (5.7)	10 (7.6)	38 (18.2)	17 (26.2)	31 (22.0)
Presenting symptoms, n/total (%)					
Pain	27/113 (24)	–	50 (24)	45/65 (69)	49/141 (35)
Proptosis	65/114 (57)	108/132 (82)	135 (66)	21/65 (32)	77/141 (55)
Chemosis	–	26/132 (20)	30 (14)	19/65 (29)	56/141 (40)
Diplopia	21/50 (42)	30/132 (23)	39 (19)	20/65 (31)	59/141 (42)
Optic nerve dysfunction or atrophy	19/113 (17)	5/132 (4)	15 (7)	–	13/141 (9)
Swelling/edema	48/113 (42)	–	114 (55)	49/65 (75)	–
Ptosis	21/111 (19)	29/132 (22)	26 (12)		–
Imaging study available, n (%)	–	84 (63)	Not shown	63 (97)	113 (80)
Classification criteria	–	Subtypes	Subtypes (based on clinical, radiological, surgical findings)	Subtypes	Orbital structures involved
Characteristics, n (%)		Diffuse 40 Myositis 21 Dacryoadenitis 14 Encapsulated mass 5 Tolosa-Hunt 2 Perineuritis 1 Periscleritis 1	Focal mass (43) Lacrimal (32) Diffuse (10) Myositis (8) Acute (2) Perineuritis (2) Periscleritis (2) Eyelid (1)	Dacryoadenitis 21 Myositis 19 Concurrent dacryoadenitis and myositis 5 Orbital apex 6 Others 14	Lacrimal gland 68 (60) Extraocular muscle 23 (20) Orbital fat 46 (41) Sclera 3 (3) Optic nerve 6 (5) Others 5 (4)

cases, there is a possibility that other specific orbital inflammatory diseases can be included in the study population. In some cases, reporting of data may have been incomplete. To be included in our series, a biopsy was required and that could have some skewing effect on case selection. Myositic NSOI was found in 17% of our cases based on imaging, but we collected very few orbital muscle biopsies as many surgeons were cautious about damage to the muscle from the procedure. Finally, some centers contributed more cases than others and geographic factors could affect many aspects of the disease. Despite these limitations, our series has a number of strengths as noted above.

5. Differential diagnosis

Differential diagnoses of NSOI include specific orbital inflammatory conditions associated with systemic or local diseases, orbital tumors accompanied with inflammatory signs, and orbital cellulitis. TED, GPA, sarcoidosis, IgG4-ROD are relatively common orbital inflammatory conditions associated with systemic diseases, and should be excluded to make a diagnosis of NSOI. Various additional immunologic diseases including Erdheim-Chester disease, Churg-Strauss syndrome, systemic lupus erythematosus, Sjögren's syndrome and inflammatory bowel disease can be accompanied by orbital inflammation. Ruptured dermoid cyst, lymphangioma and dacryops are representative orbital benign diseases that sometimes can mimic NSOI (Gordon, 2003). Orbital lymphoproliferative disease, such as reactive lymphoid hyperplasia, atypical lymphoid hyperplasia and lymphoma, is an important differential diagnosis of NSOI because it is sometimes clinically, radiologically, and pathologically difficult to distinguish from orbital inflammation, but the treatment and prognosis are quite different (Yan et al., 2004). Orbital cellulitis is also a major differential diagnosis of NSOI. It can be usually differentiated from NSOI by history of sinusitis, dental surgery, or systemic infection, but atypical infection caused by tuberculosis, parasites or fungi may produce profound inflammation and can resemble NSOI (Gordon, 2006).

6. Diagnostic testing

6.1. Ophthalmologic evaluations

Although major technical advances have been made in the field of medicine, in-depth history taking and physical examinations are still mandatory in the diagnosis of orbital inflammation. Ophthalmologic examination includes eyelid assessment (ptosis, retraction, lid lag, swelling, erythema), orbital assessment (proptosis, palpable mass, tenderness), evaluation of EOM limitation, globe (injection, chemosis, intraocular inflammation, retinal abnormality), and optic nerve function (relative afferent pupillary defect, color vision, visual field, visual acuity) (Lutt et al., 2008).

All these examinations aim to reveal the character of inflammation, the anatomic location of inflammation, the degree of inflammation, and the functional complications. Information from the exams provide some clues for diagnosis and guidance of strategy for further work-up. For example, TED usually shows bilateral involvement; eyelid signs like eyelid retraction and lid lag are the hallmarks of the disease. Ocular involvement is common in GPA and includes episcleritis, scleritis, keratitis, and uveitis (Ismailova et al., 2018). There are also several ocular findings suggestive of sarcoidosis, such as keratic precipitates, conjunctival nodules, iris nodules, or posterior uveitis (Yang et al., 2017). Eyelid dermatitis is a common skin manifestation of Sjögren's syndrome and dry eye with severe ocular surface damage is well known mucosal complication of Sjögren's syndrome (Foulks et al., 2015; Generali et al., 2017; Odani and Chiorini, 2019).

As for ocular motility, myositic NSOI frequently shows the limitation in the same direction as the action of the affected muscle although the degree of limitation is variable (Kang et al., 2020), pain on eye movement is also characteristic. Restrictive myopathy showing limitation in the opposite direction of the action of the affected muscle is usually accompanied with EOM enlargement in TED. Ocular motility is relatively normal and pain is rare in IgG4-ROD related myositis (McNab, 2020).

6.2. Laboratory tests

Baseline laboratory investigations include a complete blood count, basic metabolic panel, and inflammatory markers, such as sedimentation rate or C-reactive protein. Some authors reported that NSOI can be an antecedent to systemic inflammatory disease, suggesting the importance of systemic work-up (Tsukikawa et al., 2019).

Thyroid function tests including thyroid stimulating hormone and anti-thyroid antibodies are necessary to diagnose TED. Most TED patients are hyperthyroid, whereas 10–15% of the patients are euthyroid at the time of diagnosis (Bahn, 2010). Anti-thyroid antibodies are helpful to make a diagnosis in these patients and thyroid stimulating antibody was reported to be a sensitive marker to make a diagnosis of euthyroid TED (Kazuo et al., 1997; Suzuki et al., 2018). ANCA positivity has a high predictive value for GPA. (Suwanchote et al., 2018). Chest radiography or chest CT are used for the investigation of suspected sarcoidosis (Lutt et al., 2008). Serum IgG4 level $\geq$135 mg/dl is one of the diagnostic criteria for IgG4-RD, but it is not specific or sensitive for the diagnosis of IgG4-ROD (Umehara et al., 2012; Wallace et al., 2014). If Sjögren's syndrome is suspected, an antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, total serum IgG, and antibody to Ro are useful screening tests (Kassan and Moutsopoulos, 2004). A diagnosis of Sjögren's syndrome would be very unusual if all the above are normal. However, minor abnormalities in these screening tests are common and not diagnostic of Sjögren's or another immune-mediated disease. The American College of Rheumatology and the European League Against Rheumatism have proposed classification criteria for Sjögren's syndrome (Shiboski et al., 2017). These rely heavily on the results of a minor salivary gland biopsy, the detection of anti-Ro antibody, and objective evidence for a dry mouth.

These antibody tests may be selectively chosen after a careful history taking and comprehensive physical examination. However, unfortunately, serologic tests have a limited role in the diagnosis of NSOI. There is no diagnostic or surrogate marker for NSOI: these tests are not used to diagnose NSOI but to exclude other possible diseases. In addition, most blood tests have limited sensitivity. The results can be false-negative when the disease has mild activity or the lesion is localized to the orbit (Mombaerts et al., 2016).

6.3. The role of imaging studies

6.3.1. Imaging characteristics

Orbital imaging studies including CT and MRI are essential for evaluation of orbital inflammation. CT is often the first-line imaging modality because of its availability, rapid temporal resolution, and good inherent contrast of the orbital fat, muscle, bony structures, and air in the adjacent paranasal sinuses (Ding et al., 2011). MRI is superior to CT in evaluating the optic nerve, optic nerve sheath, and extra-orbital extension, and the sensitivity can be maximized by multiple coronal views, fat suppression, and contrast enhancement with Gadolinium-DTPA (Hardman et al., 1995). In theory, MRI might be superior in establishing a diagnosis and detecting activity of inflammation, but we are unaware of a study directly comparing orbital MRI to CT to test this hypothesis.

The imaging findings are quite variable and depend on the anatomic location and histopathological characteristics (Fig. 5). LG involvement can be seen in various kind of diseases, including TED, NSOI, Sjögren's syndrome, sarcoidosis, GPA, lymphoma, and IgG4-ROD. Lacrimal NSOI is shown as diffuse enlargement with homogenous enhancement. Preservation of gland shape and involvement of both the orbital and palpebral lobes is characteristic (Ferreira et al., 2018). Lesion extension

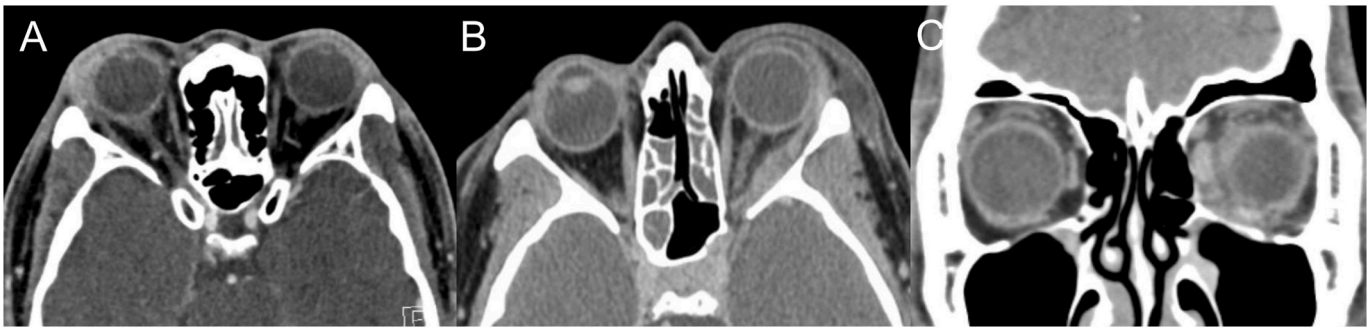

Fig. 5. Anatomical localization of non-specific orbital inflammation.
(A) lacrimal gland (right eye), (B) extraocular muscle (left lateral rectus), (C) orbital fat (left inferomedial extraconal space).

beyond the LG can be seen in GPA and lymphoma (Luemsamran et al., 2017). On CT and MRI, myositic NSOI usually shows unilateral, asymmetric enlargement of muscles with strong enhancement. Surrounding infiltration making ragged and fluffy margins are more characteristic of NSOI. The tendon thickening together with the muscle belly thickening is a differentiating point from TED (Ferreira et al., 2018; Gordon, 2006; Jacobs and Galetta, 2002; Montagnese et al., 2016). Orbital fat usually exhibits diffuse or ill-defined infiltration but can present as a more localized mass (Ferreira et al., 2018). Although bilateral LG is the most common location of IgG4-ROD, enlargement of trigeminal nerve branches is the characteristic imaging finding strongly suggestive IgG4-ROD (Elkhamary et al., 2020; Park et al., 2018). Bony or mucosal sinus involvement are rare in NSOI, and other diseases such as GPA, IgG4-ROD, or malignancy should be primarily considered (Mombaerts et al., 2017). Continuous extension from ethmoidal air cells and subperiosteal abscess formation can be seen in orbital cellulitis (Jacobs and Galetta, 2002; Lutt et al., 2008). The MRI signal intensity of inflammatory lesions is hypo- or isointense on T1-weighted image (T1-WI). The signal intensity of T2-WI depends on tissue composition like edema (hyperintense) and fibrosis (hypointense) (Fig. 6).

Imaging studies can provide important information and offer clues to the diagnosis of orbital inflammation. These are commonly used in the clinic, but the actual diagnostic value of radiologic orbital imaging has not been well elucidated. It is unknown how accurately a radiologist can assess the cause of orbital inflammation on an orbital imaging study and how accurately the disease activity can be determined.

6.3.2. Diagnostic value of imaging studies in diagnosing NSOI

In order to investigate the accuracy of orbital imaging in diagnosing orbital inflammation, we collected orbital imaging scans of various orbital inflammatory diseases in a university center (OHSU). We asked two neuro-radiologists to review the images, make a diagnosis, and assess the activity of inflammation in the absence of clinical information. Clinical diagnosis served as a reference standard. The diagnosis of NSOI was made on the basis of clinical signs and symptoms suggestive of orbital inflammation and no evidence of systemic disease association, supported by pathological evidence. The image library included 22 scans (CT 10 scans, MRI 12 scans) from 14 patients with NSOI (Lee et al., manuscript submitted). Our study showed the accuracy of radiologic diagnosis for NSOI was 77.3%. Lacrimal NSOI was misdiagnosed as sarcoidosis in a bilateral case, and as TED or normal in mild cases. One diffuse NSOI was mistaken for IgG4-ROD when the inflammation extensively affected the orbit. Regarding the inflammation activity, orbital MRI showed high sensitivity (83.3%) but low specificity (16.7%) for detecting active NSOI using the clinician's assessment as the gold standard. We could not reach a conclusion about the utility of orbital CT to detect activity because the study included no CTs obtained during a clinically inactive period. This reflects when clinicians order imaging. The results of our study imply that it is sometimes difficult to make a precise diagnosis of NSOI based on only imaging without any clinical information. These results also suggest NSOI in particular is a diagnosis of exclusion not only for clinicians, but radiologists as well. Although some features are somewhat specific on imaging, these must still be correlated with the clinical findings to establish a diagnosis of NSOI. Further studies are in progress to determine the utility of imaging in differential diagnosis of orbital inflammation.

6.3.3. New MRI protocols

Conventional MRI has limitations to separate orbital inflammation from infection or lymphoma. Although characteristics from T1-WI and T2-WI can be useful for differentiation, signal intensities in these sequences can overlap (Kapur et al., 2009). Morphological features also have limitations in making a differential diagnosis.

With the advances in MRI techniques, new protocols have been proposed to improve the diagnostic performance of MRI in diagnosing orbital inflammation. Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps has been increasingly investigated to characterize orbital lesions focusing on discrimination of NSOI and

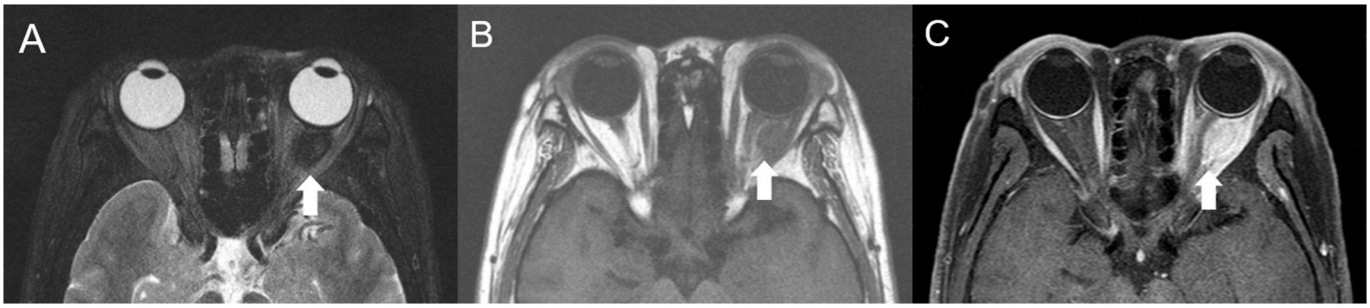

Fig. 6. Magnetic resonance images of pathologically proven non-specific orbital inflammation.
An intraconal mass of the left orbit (arrow) shows hypointense signal on T2-weighted axial MRI image (A), and isointense signal on axial T1-weighted MRI image (B). Contrast enhancement image (C) reveals heterogeneous, moderate enhancement on enhanced axial T1-weighted fat saturated MRI.

orbital lymphoma. DWI is a specific MRI sequence that uses the diffusion of moving water protons to generate a contrast among different kinds of tissues (Fatima et al., 2014). High signal intensity on DWI is associated with lower intensity on ADC maps. Orbital lymphoma shows lower ADC value because of the high cellularity that reduces the available diffusion space for water, whereas NSOI has higher ADC due to tissue edema (Sepahdari et al., 2010). However, a considerable overlap in ADC value among NSOI and orbital lymphoma has been repeatedly reported and restricts its clinical use (Fatima et al., 2014; Hiwatashi et al., 2018; Sepahdari et al., 2010). Heterogeneous cellular composition of NSOI is the major explanation for the low ADC value (Fatima et al., 2014; Ren et al., 2018).

Dynamic contrast enhanced MRI (DCE-MRI) also was suggested to differentiate inflammation from neoplastic lesions. DCE-MRI utilizes fast T1-WI following a bolus injection of gadolinium contrast agent. It provides imaging of the microcirculation and gives hemodynamic information (Asaumi et al., 2003; Hu et al., 2017). Several pharmacokinetic curves and measurements have been investigated to discover a reliable parameter for differentiation. Hu et al. (2017) reported k_{ep} (reflux rate constant from extracellular extravascular space to blood plasma) and v_e (volume fraction of the extracellular extravascular space) showed good diagnostic performance to discriminate malignant orbital lymphoma and benign inflammatory and lymphoproliferative lesions. A study using analysis of histogram parameters of DCE-MRI also suggested k_{ep} was the independent predictor for malignant orbital lymphoma (Xu et al., 2019).

These MRI protocols have their own merits and demerits, but they can complement one another. The diagnostic accuracy can be enhanced by combining two or more modalities. Ren et al. (2018) suggested the combined model of conventional MRI and ADC map achieved higher diagnostic accuracy than using either alone in terms of differentiating orbital lymphoma and NSOI. It is likely that the usefulness of these new protocols will become more apparent in the future in terms of the differential diagnosis of NSOI.

6.3.4. Positron emission tomography-computed tomography (PET-CT)

PET-CT has been widely used for the diagnosis, staging, and patient monitoring in the oncology field. PET-CT provides data combining functional information from PET and structural information from CT (Kalemaki et al., 2020). Fluoro-deoxy-D-glucose (FDG) PET-CT detects FDG uptake that is caused by increased glucose metabolism, which is often seen in malignancies. However, elevated FDG uptake can also be detected in inflammatory diseases. There are publications that reported the role of FDG-PET in the detection of IgG4-ROD and the assessment of TED activity (Dong et al., 2019; Tokue et al., 2015; Uslu-Beşli et al., 2017). Besides FDG, other radiopharmaceutical tracers are available for PET-CT. Recently, Laban et al. (2019) investigated the use of Zirconium-89-labelled (^{89}Zr) rituximab PET-CT for refractory orbital inflammation. The study cohort included 8 patients with NSOI, and the authors reported lacrimal or diffuse NSOI showed strong uptake while myositic and apical NSOI had low to moderate uptake. They also commented that the uptake pattern was inhomogeneous with focal density suggesting ^{89}Zr-rituximab PET-CT can be used to target the biopsy. Although PET-CT is not yet commonly used in NSOI, further research is required to define its role of PET-CT in the diagnosis and treatment of NSOI.

6.4. Biopsy first? Steroid therapy first?

There have been long debates about the timing of biopsy. When the diagnosis is indefinite even after thorough clinical examinations, laboratory tests, and imaging studies, some clinicians recommend a therapeutic trial of corticosteroid, and others recommend biopsy. Some researchers commented that biopsy is not always necessary and steroid responsiveness can confirm the diagnosis of NSOI (Jacobs and Galetta, 2002). On the other hand, other researchers insist that biopsy is essential to exclude other diseases and make a definitive diagnosis.

The advantage of biopsy is to obtain an orbital tissue specimen which may have valuable histologic information for diagnosis. Immunohistochemistry, immunophenotyping, and gene rearrangements can be added when IgG4-ROD or lymphoproliferative disease are suspected (Mombaerts et al., 2016). The disadvantage of the biopsy is the risk of orbital surgery itself. Significant and permanent morbidities like vision loss, limitation of EOM, or ptosis can occur after orbitotomy and biopsy. The risk increases when the lesion involves the orbital apex or EOMs (Dagi Glass and Freitag, 2016). In addition, orbitotomy in an inflamed orbit may be technically more difficult than on a normal orbit because of a high orbital pressure and distorted anatomical structures.

Mombaerts et al. (2019) recently provided some important clinical recommendations to obtain an optimal tissue sample from a biopsy. A tissue sample should be biopsied from accurate location and multiple specimens should be retrieved if the lesion had heterogeneity on imaging. The sufficient size of the specimen is also important for preparing possible special staining, immunohistochemistry, or molecular tests in addition to routine hematoxylin-eosin staining. In the process of biopsy, the surgeon should be careful not to damage tissue during dissection and sampling.

A trial of corticosteroid is based on the belief that the diagnosis can be roughly made by the thorough ancillary testings. It is also less invasive than orbital biopsy. It can be simultaneously diagnostic and therapeutic: some clinicians consider rapid and significant steroid responsiveness a clue to the diagnosis of NSOI (Bijlsma et al., 2012a). However, the possibility of erroneous diagnosis can be made when based on the response to the steroid trial. Corticosteroid is a strong, nonspecific anti-inflammatory drug, so specific orbital inflammatory diseases like TED, sarcoidosis, GPA, and even lymphoma can respond to the corticosteroid treatment.

In 2016, a survey of an international panel of experts in the Orbital Society was performed in order to establish a consensus on candidate diagnostic items. The panelists agreed that tissue biopsy is recommended for non-myositic NSOI, while corticosteroid can be tried first for myositic NSOI (Mombaerts et al., 2017). We agree with the opinion that the diagnostic approach framework is different according to the locational subtypes. LG and orbital fat are relatively easier to approach surgically and tissue biopsy should be actively pursued. If the lesion involves the orbital apex or EOM, biopsy should be considered with caution and empirical corticosteroid treatment may be appropriate if the lesion is unlikely to represent an infection or malignancy. However, even in these cases, biopsy and tissue confirmation should be reconsidered if the response is questionable or the clinical course is atypical. In addition, corticosteroids and any immunosuppressant should ideally be stopped 2 weeks prior to biopsy because these drugs may obscure the pathologic characteristics of the specimen (Mombaerts et al., 2019).

6.5. Molecular diagnosis and NSOI

Molecular diagnosis using transcriptomic analysis has been widely used in malignant diseases. Especially in lymphomas, histology alone cannot always distinguish among diagnoses; gene expression profiling can contribute to the precise diagnosis (Schmitz et al., 2018). Orbital inflammation has some parallels with lymphoma: 1) there are several sub-diagnoses to be differentiated, 2) the pathologist often cannot make a precise diagnosis only by histopathologic evaluation, 3) systemic work-up and therapeutic strategy are different among these diagnoses (Rosenbaum et al., 2015d). For these reasons, we have performed a series of studies on the characterization of orbital inflammation on the basis of gene expression profiling using microarray. Our group assembled an international consortium of orbital surgeons and ocular pathologists to collect and analyze orbital tissues. After a pathological and clinical review, a consensus diagnosis was made for each orbital biopsy specimen. The diagnoses included NSOI, sarcoidosis, GPA, TED, and healthy controls. RNA microarray experiment was performed using a GeneChip Human Genome U133 Plus 2.0 array (Affymetrix, Santa Clara,

CA), which contains over 54,000 probe sets for 47,000 human transcripts and variants. To illustrate the dissimilarity across the disease entities in terms of gene expression profile, we used PCoA. In a PCoA plot, the relative gene expression similarity of two tissue samples is represented by the distance between two points (Fig. 7). PCoA plots were made using all probe sets that showed a significant difference between at least one disease group and the normal control group (FDR $p < 0.05$ and 1.5-fold difference). In studies on orbital adipose tissue, heatmaps also showed that GPA and sarcoidosis groups had relatively consistent gene expression patterns that differed considerably from tissue from controls without disease. The gene expression pattern in TED was consistent but relatively similar to the control group. NSOI gene expression usually differed markedly from controls but it also displayed anticipated heterogeneity as discussed below. (Fig. 8). It should be noted, however, that the tissues from subjects with TED were collected late in the course of the disease when orbital decompression was deemed necessary. It is possible that more inflammatory markers would have been detected earlier in the disease course.

The transcriptome analyses provided novel findings that could help to characterize NSOI molecularly (Rosenbaum et al., 2015c). The gene expression profiles of NSOI were more heterogeneous than other groups, consistent with clinical features. Both PCoA plots and heatmaps revealed that a subset of the NSOI profiles is very similar to GPA, suggesting some patients previously diagnosed as NSOI may actually have a limited form of GPA. Furthermore, random forest classification analysis using 20 top-ranked differentially expressed transcripts among TED or GPA versus normal showed that 52% of NSOI samples were consistent with a diagnosis of GPA (Rosenbaum et al., 2015d).

These results implied that gene expression profiling could subdivide NSOI into at least two groups based on the similarity to GPA. Our own molecular profiling studies suggested that nearly half of all patients with NSOI might have a limited form of GPA (Rosenbaum et al., 2015c). As is often true for patients with a limited form of GPA, the ANCA test is usually negative in this group. We strongly suspect that these patients respond to immunosuppression as with methotrexate or rituximab, but prospective data are sorely needed to test this concept more rigorously (Rosenbaum et al., 2016). In the future, a molecular diagnosis might be added to evaluate NSOI patients to identify those with the GPA phenotype so that treatment can be tailored accordingly. That would require validation and availability through a laboratory with Clinical Laboratory Improvement Amendments certification before clinical use.

7. Therapeutic management

Some mild cases of NSOI can resolve spontaneously without treatment and simple observation or non-steroidal anti-inflammatory drugs may be acceptable (Harris, 2006; Mendenhall and Lessner, 2010). However, early and sufficient treatment is generally required to reduce inflammation effectively, prevent recurrence and protect orbital tissue from scarring (Montagnese et al., 2016). Therapeutic options include corticosteroid, immunomodulating agents, biological agents, radiation therapy, and surgical debulking (Carruth and Wladis, 2012; Espinoza, 2010; Gordon, 2006; Harris, 2006; Mendenhall and Lessner, 2010; Montagnese et al., 2016). The majority of patients with NSOI respond well to corticosteroid treatment. Accumulating evidence has suggested the benefits of immunomodulating agents and biological agents. Some investigators reported the usefulness of radiation treatment or surgical debulking to reduce inflammation. It is hard to compare the efficacy of each treatment modality because of the wide variations of patients, arbitrary dosage protocol, and inconsistent definition of treatment success or failure. There are no well-designed, randomized controlled clinical trials for treatment of NSOI, and most publications are small, retrospective case studies.

7.1. Corticosteroid

Oral corticosteroid is still the mainstay of treatment (Carruth and Wladis, 2012; Espinoza, 2010; Jacobs and Galetta, 2002; Mendenhall and Lessner, 2010; Young et al., 2017). The initial dose is frequently 1 mg/kg of prednisolone or prednisone per day. Rapid response within 24–48 h and dramatic improvement of signs and symptoms are typical (Jacobs and Galetta, 2002). Following initial high dose, systemic steroid administration should be tapered off gradually to prevent recurrence and avoid secondary adrenal insufficiency. There is no established protocol or schedule for steroid tapering, but usually tapering occurs over weeks to months. Despite the argument that a trial with corticosteroid can be diagnostic, the efficacy of corticosteroid is fair but not ideal. Mombaerts et al. (1996b) analyzed the effects of systemic steroid in 27 patients with NSOI and reported a 78% response rate, 37% cure rate, and 52% recurrence rate. Yuen and Rubin (2003) reviewed the

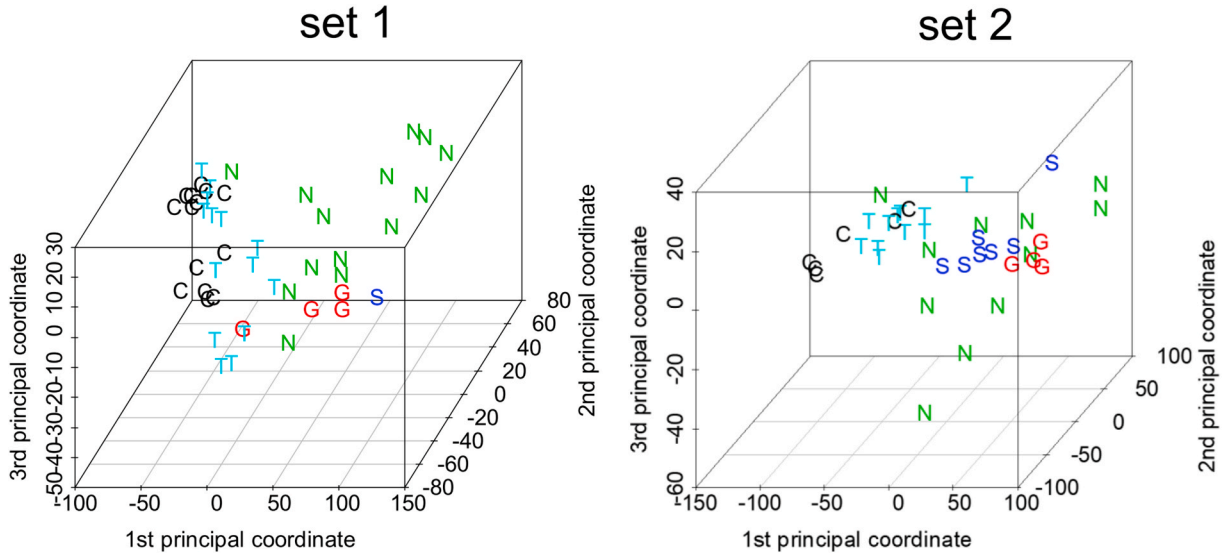

Fig. 7. Principal coordinate analysis plots based on gene expression profiles of orbital fat samples of orbital inflammatory diseases.
The distance between points on the plot indicates the relative difference between gene expression profiles of two samples. In both sets, the NSOI samples were relatively more scattered than the other groups in the plots. C: Control, G: Granulomatosis with polyangiitis, N: Non-specific orbital inflammation, S: Sarcoidosis, T: Thyroid eye disease.

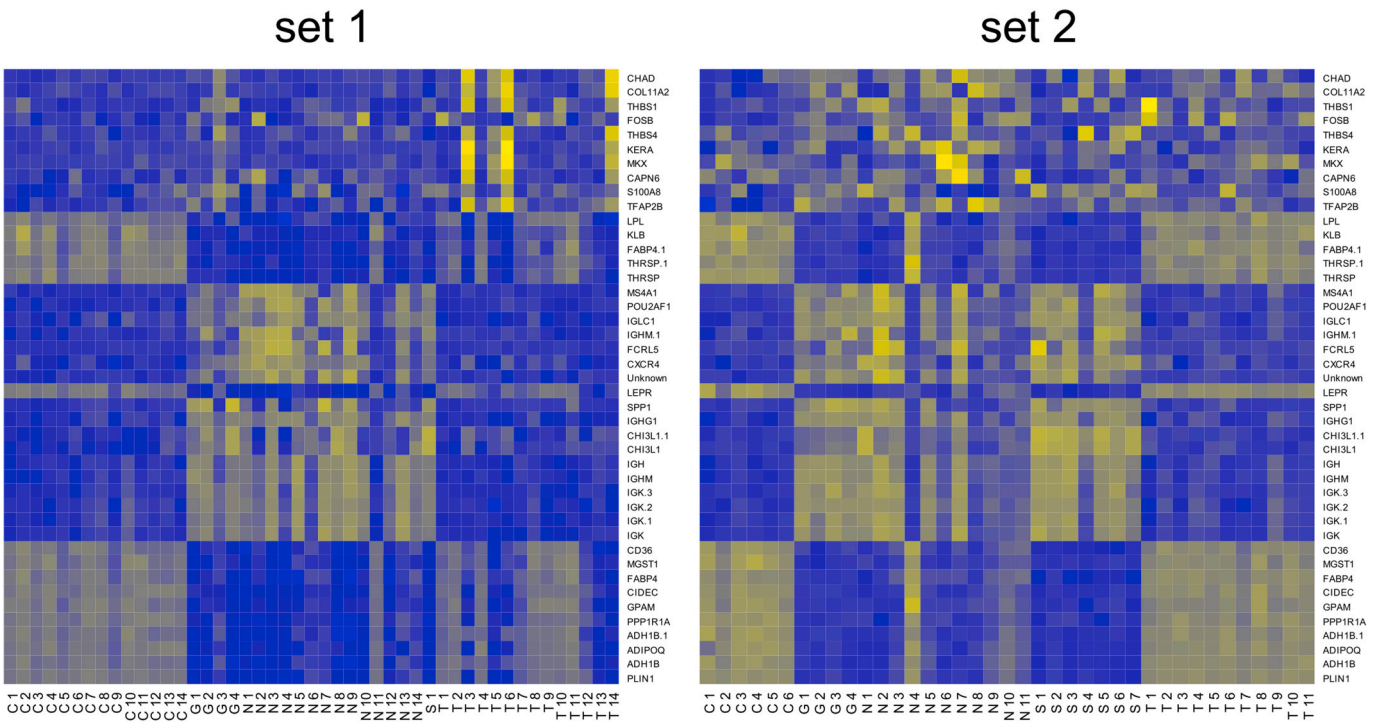

Fig. 8. Heatmaps showing relative gene expression levels from orbital fat samples based on the top 10 genes that differentially expressed in each disease group compared to control.

There were 43 unique genes due to overlapping. Yellow indicates high expression and blue indicates low expression. C: Control, G: Granulomatosis with polyangiitis, N: Non-specific orbital inflammation, S: Sarcoidosis, T: Thyroid eye disease.

treatment outcomes of 65 NSOI patients collected over 10 years. Most of the patients had been treated with a steroid-centered regimen, and the treatment success rate was 63% with a mean of 20 months follow-up. The effects of two administrative routes of corticosteroid (intravenous methylprednisolone followed by oral prednisolone versus oral prednisolone) were compared and showed no difference in terms of shortening of treatment duration, lowering cumulative dose, and decreasing symptoms (Bijlsma et al., 2011a). There is no clear evidence that intravenous corticosteroid administration is more effective than oral steroid, and oral corticosteroid may be the primary choice except for severe cases with optic nerve dysfunction. Long-term use of corticosteroid has numerous adverse effects including diabetes, hypertension, osteoporosis, gastrointestinal disorders, weight gain, and adrenal insufficiency (Miloslavsky et al., 2017). Close monitoring for possible side effects is mandatory, and a switch to another modality must be considered in cases with chronic or recurrent disease (Gordon, 2006). Some researchers investigated the effects of intra-orbital corticosteroid injection as a primary or adjuvant treatment modality for NSOI (El Nasser, 2013; Leibovitch et al., 2007; Reggie et al., 2018). Intra-orbital triamcinolone is especially beneficial when injected during biopsy or debulking surgery (Reggie et al., 2018).

7.2. Immunosuppressive agents

Methotrexate (MTX) is the most commonly used steroid-sparing immunomodulating agent for the management of orbital inflammation (Hayden et al., 2007; Rivera-Grana et al., 2015; Rubinov et al., 2018; Shah et al., 1992; Smith and Rosenbaum, 2001; Young et al., 2017). A study of 14 patients with orbital inflammation showed a beneficial effect of MTX in 64% of the patients at a dose of 15–20 mg per week. MTX was indicated when the patients were unable to taper or tolerate systemic corticosteroid. Two patients discontinued treatment because of adverse events (Smith and Rosenbaum, 2001). Fatigue, gastrointestinal disturbance, hair loss, and elevated liver enzymes are common side effects. Supplementing dietary folate and regular monitoring of liver enzyme are needed to minimize these adverse effects. Mycophenolate mofetil (MMF) is a relatively new immunomodulating drug, which has been commonly used to prevent organ transplant rejection. There are a few case series describing MMF treatment in orbital inflammation (Hatton et al., 2005; Patel et al., 2011; Thorne et al., 2005). Hatton et al. reported the treatment outcomes of MMF as a steroid sparing or steroid avoiding agent in 5 patients with NSOI (Hatton et al., 2005). In one patient, MMF was used because of the poorly controlled diabetes mellitus, and the remaining 4 patients had recurrent orbital inflammation after tapering or corticosteroid. The average dose used was 2.2 g/d. With a median follow-up period of 8.5 months, 4 cases achieved complete response, whereas MMF was discontinued in 1 patient because of nausea. Common side effects are gastrointestinal disturbance, nausea, rash, myalgia, headache, and rarely myelosuppression. Cyclosporine A (CsA) interferes with the production of interleukin-2, resulting in a decrease of T-cell activity. Kidney dysfunction, immunosuppression, and hypertension are the main side effects and renal function must be monitored during administration. Gingival hyperplasia, hair growth, and myalgia are frequently encountered. There have been only sporadic case reports noting favorable treatment outcomes of low-dose CsA reducing orbital inflammation (Diaz-Llopis and Menezo, 1989; Sanchez-Roman et al., 1993; Zacharopoulos et al., 2009). CsA was indicated when the patient showed poor response to steroid with side effects (Zacharopoulos et al., 2009), or when the patient had the third relapse following the combination treatment of steroids and azathioprine (Sanchez-Roman et al., 1993). There was one case report observing that topical 0.05% CsA was apparently effective in treating recurrent idiopathic myositis and scleritis (Gumus et al., 2009). Azathioprine is an analog of mercaptopurine that inhibits enzymes in purine metabolism, as purine bases are incorporated into DNA and RNA (Chiu and Rubin, 2004). There have been only a few case reports of therapeutic use of azathioprine in NSOI (Rootman et al., 1994).

7.3. Biological agents

More recently, monoclonal antibodies targeting inflammatory cytokines, mediators, or their receptors have been highlighted as novel immunomodulating agents. These biologic drugs act in a specific manner and are thought to be superior to conventional immunosuppressive drugs regarding their efficacy and safety for specific indications. Rituximab is a chimeric monoclonal antibody that recognizes the B-cell surface antigen CD20. However, rituximab is also effective in diseases generally considered to be T-cell mediated, suggesting that the mechanism of action is through T-cell B-cell interaction. Rituximab has been used for various noninfectious orbital inflammatory diseases including TED, IgG4-ROD, and GPA (Baslund et al., 2012; Chen et al., 2014; Dammacco, 2018; Ginter and Migliori, 2016; Ibrahim et al., 2012; Joshi et al., 2015; Khanna et al., 2010; Precausta et al., 2017; Starr et al., 2019; Vannucchi et al., 2010; Vrcek et al., 2018). Suhler et al. (2014) reported the efficacy of rituximab in 10 patients with refractory orbital inflammation, half of whom had NSOI. All patients were included when they showed intolerance, failure to respond to, or inability to taper treatment below prednisolone 10 mg/day along with 1 systemic immunosuppressive agent. With a total dose of 1000–2000 mg, the orbital disease grading scale was improved in 3 NSOI patients. There are also a few case reports demonstrating the effectiveness of rituximab in the treatment of NSOI (Abell et al., 2015; Ibrahim et al., 2012; Kurz et al., 2009; Schafranski, 2009; Shao et al., 2013). Infliximab is a chimeric monoclonal antibody that inhibits tumor necrosis factor (TNF) alpha. It can bind both soluble and membrane bound TNF, and can neutralize biological activity of TNF. Infliximab has been successfully used in the treatment of various kinds of uveitis, including Behçet's disease, spondylitis associated uveitis, and Vogt-Koyanagi-Harada disease (Ashkenazy et al., 2019; Hatemi et al., 2019; Khalifa et al., 2010; Sfikakis et al., 2019; Sharma et al., 2019; Zmuda et al., 2013). There is rising evidence that infliximab is promising as a steroid-sparing therapy for recalcitrant NSOI (Kapadia and Rubin, 2006). Several case reports describing the treatment of NSOI with infliximab have been reported (Miquel et al., 2008; Osborne et al., 2009; Sahlin et al., 2009; Wilson et al., 2004). In 2004, Garrity and coworkers reported treatment outcomes of infliximab in 7 patients with chronic orbital myositis (Garrity et al., 2004). All patients were treated with infliximab alone or combined with methotrexate after the failure of conventional therapy, and showed a favorable response in terms of pain, diplopia, and the cessation of steroid. Adalimumab (humanized anti-TNF monoclonal antibody), tocilizumab (monoclonal antibody against interleukin-6 receptor), and daclizumab (monoclonal antibody against intereukin-2) were also reported to be effective in some case reports (Garcia-Pous et al., 2007; Silpa-Archa et al., 2016; Verma et al., 2013). However, etanercept, which is a TNF receptor p75-Fc fusion protein, has been reported to be paradoxically associated with inflammatory eye diseases, like scleritis, uveitis, and orbital myositis (Couderc et al., 2014; Gaujoux-Viala et al., 2012; Taban et al., 2006).

7.4. Radiation therapy

Radiation therapy has been traditionally considered an effective alternative in recalcitrant or recurrent NSOI or in patients with contraindications to corticosteroids (Lanciano et al., 1990; Lee et al., 2012; Matthiesen et al., 2011; Mokhtech et al., 2018; Prabhu et al., 2013; Sergott et al., 1981). Low-dose radiation averaging 15–20 Gy delivered in 10 fractions over 2–3 weeks is used. Common complications included blepharitis, dry eye, and cataract. These effects are usually mild and well-tolerated. Treatment success rate varied from 62 to 90% (Orcutt et al., 1983; Sergott et al., 1981). Recently, Mokhtech et al. (2018) retrospectively analyzed long-term treatment outcomes of radiotherapy in 20 patients (24 orbits) with NSOI. Pathology-supported diagnosis was made in 16 (80%) patients, and corticosteroid was attempted in 17 patients as a first-line treatment. Symptomatic improvement was noted in 75%, and the local control rates were 63% and 53% at 5 and 10 years.

7.5. Risk factors for recurrences

There is no consensus treatment guideline or protocol for NSOI and it is hard to calculate the precise recurrence rate. In the literature, the recurrence has been reported as 38–52% of patients (Mombaerts et al., 1996b; Swamy et al., 2007; Yuen and Rubin, 2003). In terms of risk factors for recurrence, some researchers suggested specific location or histopathological characteristics were a risk factor for recurrence. Diffuse or myositis subtype was suggested to be associated with recurrence (McNicholas et al., 1991; Young et al., 2017). Lee et al. (2016) reported that the recurrence rate was higher in patients with enlarged infraorbital nerve. It is still controversial whether histologic subtype is a risk factor for recurrence. Swamy et al. (2007) reported that there was no correlation between the histological subtype and the relapse rate. Young et al. (2017) also published similar recurrence rates based on histological subtypes. Recently, Braich et al. (2018) compared demographic and clinical factors between NSOI patients with single recurrence and multiple recurrences, and suggested several risk factors for multiple recurrence. Identified factors included: younger age, bilaterality, optic disc edema, poor initial response to steroid, sclerosing variant, rapid steroid taper, and short period to the first recurrence.

Contralateral recurrence and migratory relapse were also reported in the literature (Avni-Zauberman et al., 2012; Browne et al., 2009; Mannor et al., 1997; Maurer and Zierz, 1999; Mombaerts and Koornneef, 1997) and clinicians should be careful to monitor patients with NSOI after resolution of inflammation. Mombaerts and Koornneef (1997) investigated the treatment outcomes and recurrence in 16 patients with orbital myositis, and reported 9 of them had one or more recurrences. Interestingly, inflammation recurred at the contralateral orbit in 6 patients, and showed alternating pattern of relapse from muscle to another muscle, and from one orbit to the other orbit. Avni-Zauberman et al. (2012) reported 8 migratory recurrence episodes in 6 patients with orbital inflammation including recurrence at a different EOM of the contralateral orbit, recurrence at a different EOM of the same orbit, and migratory recurrence at a different site. Multiple flitting recurrence involving bilateral lacrimal glands and EOMs was also reported in a pediatric patient (Browne et al., 2009).

We analyzed treatment modalities used, recurrence rate after the first treatment, and risk factors of recurrence using our clinical database from the international consortium (72 patients who were followed up at least 6 months) (Table 6). Initial treatment included oral corticosteroid (n = 44, 61%), observation (n = 9, 12.5%), oral corticosteroid with methotrexate (n = 6, 8.3%), intravenous corticosteroid followed by oral corticosteroid (3, 4.2%), nonsteroidal anti-inflammatory drugs (n = 4, 5.5%), oral corticosteroid with intra-orbital steroid injection (n = 3, 4.2%), methotrexate with intra-orbital steroid injection (n = 1, 1.4%), methotrexate (n = 1, 1.4%), intra-orbital steroid injection (n = 1, 1.4%). With a median follow-up period of 16 months, 24 patients (33.3%) had a recurrence and needed to change treatment modality. Comparing demographic and clinical variables, EOM involvement on imaging was the

Table 6
Primary treatment modalities used for patients with non-specific orbital inflammation (follow-up ≥ 6 months, n = 72).

Treatment modalities	Number of patients (%)
No medication	9 (12.5)
Oral steroid	44 (61.1)
Oral steroid + methotrexate	6 (8.3)
Intravenous steroid + oral steroid	3 (4.2)
Oral nonsteroidal anti-inflammatory drugs	4 (5.5)
Oral steroid + intraorbital steroid injection	3 (4.2)
Methotrexate + intraorbital steroid injection	1 (1.4)
Methotrexate	1 (1.4)
Intraorbital steroid injection	1 (1.4)

only significant, identifiable risk factor associated with recurrence (Table 7).

7.6. Therapeutic approach used by the authors

Our own approach to treatment is always guided by patient preference, the patient's personal history such as liver disease that might preclude the use of methotrexate or diabetes which might complicate the use of prednisone, and the disease severity. In general, we initiate oral corticosteroids at a mutually agreeable dose with an aim to eliminate or minimize the dosage within two to three months of the start of treatment. We usually prescribe calcium and vitamin D to reduce bone loss and we monitor the glucose, weight, mood, and blood pressure while on steroid therapy. Since recurrences are common, we start a steroid sparing drug concomitantly with the prednisone or shortly after prednisone is begun. Methotrexate, preferably at 20 mg/week subcutaneously, along with 1 mg/day of folic acid is our usual choice based on cost, convenience with weekly dosing, and published experience. We caution patients about immunosuppression, oral sores, fatigue, liver damage, infection, rare pneumonitis, hair loss, and cytopenia. We routinely discuss the need for vaccinations and the rationale to hold methotrexate during an active infection. We also alert the patient that frequent lab work will be required. Many ophthalmologists will partner with another specialist such as a rheumatologist who has experience with immunosuppression. We discuss reducing or tapering immunosuppressive therapy if a patient has been asymptomatic for about a year. If a patient does not tolerate methotrexate or has a contraindication, azathioprine at 1.5 mg/kg orally is a good alternative. Some experts measure thiopurine methyltransferase before starting azathioprine as a low enzyme level might correlate with increased risk. Azathioprine should not be given with allopurinol. And it sometimes causes a flu-like reaction which is frequently mistakenly attributed to infection rather than an adverse effect of the medication. Rituximab is our biologic of choice for patients who fail an anti-metabolite based on our published experience (Suhler et al., 2014) and because many patients with NSOI might have a limited form of GPA (Rosenbaum et al., 2015c; Stone et al., 2010). We are not strong supporters of local corticosteroid injection because triamcinolone can cause fat atrophy (Park and Chang, 2017). We also rarely recommend radiation because it causes ocular dryness and we often find the benefits are temporary. Despite the efficacy of teprotumumab in treating thyroid eye disease (Douglas et al., 2020; Patel et al., 2019; Smith et al., 2017), we are not aware of data to supports its use to treat NSOI. We recognize that randomized controlled data on treatment are lacking and many approaches can be justified.

Table 7
Comparison of clinical variables in patients with or without recurrence following treatment of non-specific orbital inflammation (follow-up $\geq$ 6 months, n = 72).

Variable	No recurrence (n = 48)	Recurrence (n = 24)	p-value
Follow-up duration, mean ± SD, *months*	22.0 ± 23.6	33.4 ± 29.1	0.08
Age, mean ± SD, *years*	47.14 ± 23.1	40.82 ± 16.3	0.24
Male, n (%)	12	11	0.07
Bilateral disease, n (%)	8	7	0.21
Onset type, acute:subacute: insidious	5:22:15	7:8:8	0.15
Presenting symptom, Yes:No			
Pain requiring medicine	17:27	11:11	0.38
Proptosis	30:17	13:8	0.89
Chemosis	16:29	9:13	0.67
Elevated intraocular pressure	8:37	4:20	1.00
Diplopia	23:24	17:7	0.07
Reduced color vision	3:28	4:11	0.19
Optic nerve dysfunction	3:42	5:18	0.10
Orbital structure involved	***n* = *41***	***n* = *22***	
Lacrimal gland, Yes:No	23:18	12:10	0.92
Extraocular muscle, Yes:No	7:34	9:13	0.03
Orbital fat, Yes:No	16:25	11:11	0.40
Orbital apex, Yes:No	2:39	3:19	0.33

8. Summary and future directions

NSOI is a collection of diseases which can be distinguished by characteristics which include anatomic location, imaging, response to therapy, and molecular heterogeneity. As molecular diagnostic precision advances and becomes standardized, undoubtedly the term NSOI will be subdivided and replaced by more accurate descriptors that will convey greater information about pathogenesis and prognosis.

Predicting the future is fraught with incorrect assumptions, but we feel confident in hypothesizing five shifts that could occur over the next decade. First, the understanding of pathogenesis will improve rapidly. Molecular diagnosis is a major first step and will advance with wider adaptation and validation. RNA can be interrogated at the level of its regulation as by methylation or by micro RNAs. We have undertaken a pathway analysis based on the interactions of proteins coded by RNA (Verma R et al. manuscript submitted). This study indicates that the activation of the IGF-1 pathway is not restricted to thyroid eye disease. An extrapolation from this is that a subset of patients with NSOI might benefit from teprotumumab, a treatment approach that would not subject patients to immunosuppression. It is also now possible to investigate mRNAs at the level of a single cell. Such an approach is radically changing the understanding as to how fibroblasts and adipocytes contribute to rheumatoid arthritis (Mizoguchi et al., 2018). It will undoubtedly be extrapolated to orbital inflammation. Second, imaging technology continues to improve. "Big data" derived from large databases may help us improve the accuracy of imaging and allow the radiologist to determine disease activity more accurately than a clinician. Modified MRI protocols could contribute to this. In addition, ultrasound has potential advantages over CT and MRI because it could be delivered at point of care and it can determine blood flow. Third, fibrosis is currently a huge nemesis that defies medical therapy. But treatments are emerging for fibrosing diseases in other organs (Li et al., 2019). It is likely that orbital fibrosis will yield to some of these approaches as well. Fourth, tears are a relatively untapped resource in investigating orbital disease. Tear studies have been reported for thyroid eye disease (Aass et al., 2016; Hagan et al., 2016). The LG can be perturbed directly in NSOI or indirectly by adjacent inflammation as by local cytokine production. Tears will provide biochemical information for diagnosis, disease activity, and prognosis while being far easier to access than a biopsy. And fifth, therapy will advance. Above we note teprotumumab's potential as well as treatment directed at preventing fibrosis. Greater understanding of pathogenesis will point to novel therapies with a "precision" approach much as is occurring in the field of oncology. This review is intended to provide clinicians and researchers an overview of a vexing and often misunderstood clinical challenge. We hope that it will serve as a platform to actualize what is possible in the years ahead.

CRediT authorship contribution statement

Min Joung Lee: Conceptualization, Writing - original draft, Project administration. **Stephen R. Planck:** Data curation, Funding acquisition, Writing - review & editing. **Dongseok Choi:** Formal analysis, Data curation, Writing - review & editing. **Christina A. Harrington:** Data curation, Writing - review & editing. **David J. Wilson:** Visualization, Investigation, Writing - review & editing. **Roger A. Dailey:** Investigation, Writing - review & editing. **John D. Ng:** Investigation, Writing - review & editing. **Eric A. Steele:** Investigation, Writing - review & editing. **Bronwyn E. Hamilton:** Investigation, Visualization, Writing - review & editing. **Sang In Khwarg:** Visualization, Writing - review & editing. **James T. Rosenbaum:** Conceptualization, Project administration, Funding acquisition, Writing - review & editing.

Declaration of competing interest

Dr. Rosenbaum is a consultant to Janssen, Abbvie, Roche, UpToDate, Novartis, Gilead, UCB, Santen, Horizon, Corvus, Celldex, Lilly, and Eyevensys, and has received research funding from Alcon Research Institute and Pfizer. Dr. Dailey is a consultant to Horizon and Bio-logic Aqua Research Inc. and Dr. Ng is a consultants to Bio-logic Aqua Research Inc. The other authors report no conflicts of interest.

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