Non-Specific Orbital Inflammation and Sclerosing Variant

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Our article includes a total of 260 cases of biopsy proven NSOI from over 10 countries, including reports, case series, as well as studies which subjected tissue to pathological RNA extraction and microarray assays and analysis, to further assess the pathophysiology of the disease.5,10 Emphasis has been put on therapeutic agents, particularly on corticosteroids, to further advance the discussion regarding propensity towards remission and relapse of the disease. The role and the timing of orbital biopsy is also discussed.1

2. Results
2.1 Demographic characteristics

A total of 260 cases of NSOI were included in this review. There was a slight predisposition for the disease in males (54.2%). The average age of onset was 51.5 years of age. In a review by Ting et al., out of 166 cases identified, 53.1% were female and the mean age was 53.7 years of age.

Moreover, the data presented in this review spanned multiple continents around the world, including but not limited to countries such as the US, Brazil, Spain, Italy, Romania, Morocco, Israel, and Japan. In addition, multiple races were included in the sample, including Caucasian, African-American, Asian, and Latino. The youngest patient in the sample was only eight-years old, while the oldest patient was eighty years old.

2.2 Signs and Symptoms

Swelling was the most common sign in our article and was present in 67% of the sampled patients. This was followed by proptosis (63%), orbital pain (54%), diplopia (25%) and redness (25%). Swamy et al. reported similar findings: swelling (79%), proptosis (63%), orbital pain (58%), and diplopia (38%).17 Additionally, Yuen et al. performed a 10-year retrospective review of 65 patients with NSOI who where treated at a single institution, and found the following: swelling (75%), orbital pain (69%), redness (48%), and proptosis (32%).18 Although swelling was also the most common finding in this arti-

Abstract

This systematic review of biopsy proven cases of non-specific orbital inflammation and sclerosing variant from 2010-2016 attempts to elucidate new findings regarding the demographic profile of the diseases. Discussion of histopathology is emphasized, as to describe the most common presenting features of non-specific orbital inflammation as well as to discuss its molecular profile. This review also discusses the therapeutic approach and discusses the “steroids vs. biopsy first” controversy regarding non-specific orbital inflammation. The incidence of IgG4 and its relationship to non-specific orbital inflammation is also discussed.

Keywords: Non-Specific Orbital Inflammation; Idiopathic Orbital Inflammation; Orbital Pseudotumor; Idiopathic Sclerosing Orbital Inflammation; Sclerosing Variant of Non-Specific Orbital Inflammation.
The incidence was slightly lower than in the other studies. In addition, the signs and symptoms of NSOI found in this article were consistent with those reported by Lutt et al. and Mombaerts et al. 19-23

It is important to bear in mind that visual acuity was reported in only a minority of cases. Of the biopsy proven NSOI cases that disclosed the visual acuity, a slight majority presented with a visual acuity better than 20/40 (33.3%), while a portion of patients also presented with vision worse than 20/40 (25%). 24,25

There were 2 reports of NSOI which presented with an accompanying severe panuveitis. 26-28

2.3 Systemic Associations

Of the 260 patients in this review, 38% were found to have NSOI associated with various autoimmune diseases, as well as atopy. 29-31 In a series of 58 patients at the Orbital Center of Amsterdam, Mombaerts et al. found that 10% were diagnosed with NSOI and an underlying autoimmune condition. Additionally, in a study of 25 patients by Yuen and Ruben, 84% had an underlying systemic autoimmune disease, including but not limited to Behcet’s disease, rheumatoid arthritis, juvenile idiopathic arthritis, and Crohn’s disease without any of the conditions being more prevalent than the others. 32-36 Moreover, in a study of eight patients, Attabay et al. found that 62.5% of patients possessed antibodies reactive with 55- and/or 64-kilodalton (kd) eye muscle membrane proteins. 37-39 This finding as well as the rapid response to corticosteroids support the hypothesis that NSOI might be a predominantly autoimmune disorder. 40-43

2.4 Histopathological Findings

2.4.1 Biopsy location

We found that the diagnostic biopsy involved the orbital tissues in 58% of cases, and the lacrimal gland in 17%. Approximately 25% of the patients underwent biopsy of “other” tissue sites, that were not disclosed in the articles reviewed.

With respect to the location of the inflammation, 16% of patients in the review reported an extra-conal location, while an intra-conal location accounted for 8% of patients. Approximately 21% of inflammatory processes was located anteriorly, compared to 21% of the inflammation located posteriorly within the orbit. The rest of the cases reviewed failed to specify the precise location of the inflammation. 44-49

2.4.2 Histopathological analysis

This review revealed that the majority of cases exhibited a mixed B-cell and T-cell response (26.7% Table 1-62.5% Table 2). The majority of biopsies presented with accompanying fibrosis as the most common type of inflammatory change (46.6%). Lee et al. found that fibrocytes in NSOI expressed substantial levels of CD40. Ligation of CD40 increased IL-6 expression. 50 Granulomatous inflammation was also present in an important amount of cases (40%). A minor set of specimens demonstrated a vasculitic component (8.3%). Rosenbaum et al. reported that NSOI may actually be a limited form of granulomatosis with polyangiitis, since they share a similar RNA gene expression profile. 61-64

We found a high prevalence of IgG4 disease in our review (16.7%-33.3%) with a similar number of cases between orbital and lacrimal biopsies. The Newcastle Eye Centre Study described a much lower incidence of IgG4 in their article (2.8%), but discussed that increased awareness of this pathological entity might increase its diagnosis in the near future. Interestingly, the Japanese study group of IgG4-related ophthalmic disease estimated geographical prevalence to be much higher (21.6%). 65,66 All cases in our data set followed the comprehensive diagnostic criteria for IgG4-related disease, modified after Umehara et al. (Figure 1), for biopsy. 67,68 An overwhelming amount of cases in our sample of IgG4-RD NSOI presented with accompanying fibrosis (90%), which may signal an overlap with the sclerosing variant of NSOI. 69-70

2.5 Treatment

Our review set revealed substantial corticosteroid use (87.7%), as the initial treatment of NSOI. Similarly, Swamy et al. report the use of steroids in an overwhelming number of patients in their study (79%). Approximately half of patient were given steroids as the sole treatment modality (54.25%). A considerable number of patients were placed on combined therapy, with corticosteroid and immunosuppressive therapy (45.8%). Swamy et al. reported that one third of the patients in their study required two or more medications to achieve remission of symptoms (30%). A common combination therapy in our review was the addition of Rituximab to supplement corticosteroid therapy (12.5%). Suhler et al. reported a case series of 10 patients, in which 70% achieved remission and symptom relief with the aforementioned combination therapy. Methotrexate was also used in combination with corticosteroid therapy with moderate frequency (12.5%). Smith et al. presented an article in which Methotrexate is a well tolerated alternative to corticosteroid therapy in cases of NSOI. 81-84

Surgery (i.e orbitotomy, surgical debulking) was reserved for the minority of cases in our review (8.3%). Radiation therapy in combination to steroid therapy was used in a minority of patients in with rapidly advancing disease (4%). 85 Matthiessen et al. reported 25% of their patients achieved an initial complete response to radiotherapy (defined as complete resolution of symptoms and complete tapering of corticosteroid use without symptomatic recurrence). One case described the use of periorbital injection of triamcinolone given that the patient had a history of tuberculosis for which he underwent lobectomy. Comparatively, Nasser reported a pool of 45 patients which received a combination of betamethasone sodium phosphate and betamethasone dipropionate.
Enghelberg M et al. Orbital inflammation.

2.5.1 Outcomes

An overwhelming amount of patients in this review were given corticosteroids (87.5%) at the time of the index presentation, or in close proximity in time to the orbital biopsy. Some (12.5%) had worsening of their symptoms after initial corticosteroid therapy was initiated. Over half of patients in the review required combination therapy given they were unable to completely taper corticosteroids (54.25%) without relapse of symptoms. In their article, Mombaerts et al. showed that 78% of patients responded initially to corticosteroid therapy, but 52% of these patients experienced recurrences after an initial response or taper. Of the cases that suffered a definitive relapse in our review, few were treated with steroids alone (8.25%) and even fewer (4%) had a relapse on combined immunosuppressive therapy plus corticosteroid therapy.

3. Discussion

Our comprehensive review of published literature suggests that the successful response of NSOI, regardless of its etiology, to corticosteroid therapy is reasonable to validate the approach of Dagi Glass et al: Corticosteroid first. The trend in the population that was reviewed seems to signal that regardless of what is revealed by histopathological analysis, the great majority of the cases respond favorably to corticosteroid therapy. Biopsy rarely guides therapy in NSOI. For this reason a trial of corticosteroid therapy is a sound approach, presuming an infectious etiology or neoplasm has otherwise been ruled out. Performing a biopsy in typical cases of NSOI poses potential risks and complications of a procedure which in the vast majority of cases does not lead to a change in the therapeutic regimen. Biopsy seldom reveals pathology which is not amenable to a corticosteroid trial. Biopsy should be reserved for cases in which initial steroid therapy fails and the patient’s disease has an atypical and recalcitrant course. Furthermore, clinical practice supports the use of steroids as a starting point prior to biopsy.

After proper ophthalmological evaluation, the work-up of NSOI should begin with an MRI of the brain and orbits with and without contrast. Serological analysis should include RPR, FTA-ABS, as well as a tuberculin skin test, and a chest x-ray. Serological analysis of other common infectious agents in the patient’s locale should be incorporated into the work-up. Any infectious process must be properly ruled-out prior to starting a trial of steroids. Concomitantly, patients should also undergo serological analysis in search of an underlying autoimmune condition; the work-up should include ANA, ANCA levels, ESR, ACE levels, serum lysozyme, complement levels, as well as IgG4 serum levels.

It is important to note the advancements in molecular biology and receptor analysis of NSOI. Wladis et al. demonstrated the increase in six cytokines which were significantly elevated in NSOI, interleukin-2, -8, -10, -12, gamma interferon, and tumor necrosis factor.

IgG4 Disease Diagnosis Criteria, modified after Umehara et al.

<table>
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<th>1</th>
<th>+</th>
<th>2</th>
<th>+</th>
<th>3</th>
<th>=</th>
<th>Diagnosis of IgG4-RD</th>
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<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG4 &gt; 135mg/dl</td>
<td>Histopathology *: IgG4/IgG Ratio &gt;0.4 and &gt;10 IgG4+ cells per HPF</td>
<td>[\text{Definite}]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG4 &gt; 135mg/dl</td>
<td>Histopathology: Not available or not diagnostic</td>
<td>[\text{Probable}]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG4 &gt; 135mg/dl</td>
<td>Histopathology: Not available or not diagnostic</td>
<td>[\text{Possible}]</td>
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<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG4 &gt; 135mg/dl</td>
<td>Histopathology: Not available or not diagnostic</td>
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There have not been studies demonstrating the superiority of any combination of monoclonal antibody therapy, and/or immunosuppressive agents in NSOI. Achieving final remission and unburdening chronic steroid therapy by initiation of a steroid sparing agent has been widely accepted, with excellent results even in recalcitrant cases. Although this acute inflammatory process responds very well to corticosteroids, rapid discontinuation of steroid therapy leads to unnecessary relapse, which could be interpreted as an aggressive disease course by some clinicians. For this reason we propose an extended tapering regimen once corticosteroid therapy is initialized. Biopsy should be performed when in need of differentiating NSOI from lymphoma, IgG4-RD from its Sclerosing Variant or other pathology in which treatment might vary.

The wider recognition and increased testing for IgG4-related disease has increased in more recent studies. In our review it was noted that IgG4-RD from its Sclerosing Variant or other pathology in which treatment might vary.

The incidence of probable IgG4-RD disease using both the Umehara et al. and Deshpande et al. criteria was found to be between 16.7%-33.3%. Presenting with accompanying fibrosis in 90% of cases. Geographical variations do exist for the incidence of IgG4 orbital disease. Lastly, clinicians may reserve the need for biopsy in an atypical disease course, orbital inflammation that does not respond to a trial of corticosteroid, or if malignancy is suspected.

5. Method of literature review

The authors conducted a MEDLINE search using the Pubmed database (National Library of Medicine) from September 2010 through June 18, 2016, as to continue the review published in 2010 by Pemberton et al. The search was limited to articles in English or articles with English abstracts. Only articles with biopsy proven cases were included in the study. Various combinations of keywords were used, including Idiopathic Orbital Inflammation, Idiopathic Orbital Pseudotumor, Orbital Inflammation and Non-Specific Orbital Inflammation.

Sclerosing Variant

1. Introduction

Idiopathic Sclerosing Orbital Inflammation (ISOI) is also known as the sclerosing variant of Nonspecific orbital inflammation. Classically, it has been described as an insidious, persistent, and rapidly progressive sclerosing process that is often refractory to the mainstays of treatment most commonly utilized in NSOI.

To date, there have been two main landmark studies examining the literature pertaining to ISOI. Rootman et al. were the first to systematically review the literature. Rootman at al’s review of 16 cases, concluded that ISOI was a unique pathological entity representing 7.8% of all inflammatory lesions of the orbit. It was concluded that the disease entity was refractory to radiotherapy and corticosteroid therapy, and it was unable to be determined whether a specific treatment regimen provided superior outcomes. The cases reviewed by Rootman et al were dating prior to 1994.

Subsequently, Pemberton et al conducted a systemic review of the literature of biopsy proven ISOI between 1994 and September 2010. 71 eyes from 61 total cases were examined. 75 Results of the study were similar to those of Rootman et al, with main presenting symptoms of proptosis (73%) and pain (49%) with the most common treatments being systemic corticosteroids alone (34%) or corticosteroids plus other treatment (51%), but minimal...
knowledge was gained in terms of the characteristics and management of the disease. Since that time there have been 15 published articles containing 19 cases of ISIO. The aim of this review is to update the seminal articles by Pemberton et al and Rootman et al. 10

2. Results

2.1 Demographic Characteristics

The demographic data for 19 patients is presented in Table 3, 42.4% (8/19) were male and 57.6% (11/19) were female, which is different from the slight male predominance in Pemberton et al’s data (54.1%) and the larger male predominance in Rootman et al’s study (68.8%). The mean age of presentation was in the fifth decade, approximately age 53 (Std. Dev. 22.39), compared to Pemberton et al’s figure of 48 years of age and Rootman et al’s figure of 42 years of age.

2.2 Signs and Symptoms

Most patients in this review had an average of 2 symptoms (31.6%). Patients reporting 1 and 3 symptoms were equal (15.8%). The most common signs and symptoms from our data set were pain, proptosis, swelling, red eye, and diplopia (52.6%, 52.6%, 52.6%, 36.8%, 26.3%) respectively. This is similar to the data reported by Pemberton et al. The most common signs and symptoms reported by Pemberton et al were proptosis, restricted ocular motility, pain, and diplopia (73%, 55%, 49%, 34%). Visual acuity was better than 20/40 in 26.3% of cases, worse than 20/40 in 42.1% of cases, and not disclosed in 31.6% of cases. 97

The Pemberton et al data set showed 44% of patients with 20/20 vision, 22% with 20/25 – 20/60 vision, 11% with 20/200-20/400 vision and 4% with vision that was count fingers or worse. 99

2.3 Systemic Associations

An underlying autoimmune condition was present in 42.1% of the cases (Table 3) in this review. Neoplasms were encountered in 15.8% of cases. No systemic associations were present in 42.1% of cases. Pemberton et al did not report on systemic associations.

2.4 Histopathological analysis

The most common histopathological entity found was the presence of mixed B-cell and T-cell infiltration (47.4%) followed by significant IgG4-immunostaining (42.1%) and isolated T-Cell infiltration was noted in a minority of cases (10.5%). 90 Pemberton et al only reported 1 case of the studied 61 cases to be positive for IgG4; however, only 5 cases reported pertinent immunohistochemistry data. Interestingly, evidence of vasculitis which is a common histopathological feature of IgG4-RD was present in 10.5% of cases in this review. 97

2.5 Treatment

Steroids remain the mainstay of treatment and were used in 78.9% of cases in this review. Immuno-modulators were used in 52.6% of cases. Dual combination therapy was used in 42.1% of cases. Steroids were used in 42.1% of cases as well. Only 5.3% of cases utilized a combination of three agents for treatments.

Rituximab was used in 21.1% of cases (4 of 19) and resulted in full remission in 75% of cases (3 of 4). This is in contrast to Pemberton et al, who reported on the use of rituximab in only 1 of 61 cases, which resulted in only partial resolution of symptoms in that patient. 100-103

3. Discussion

Comparison of this review with Pemberton et al and Rootman et al may be found in Table 3. Mean age of presentation for the present article was slightly higher at age 53, compared to Pemberton et al’s figure of 48 and Rootman et al’s figure of 42. Signs and symptoms were largely similar between the three studies, with pain and diplopia as the top two signs and symptoms. 1,5 Two significant differences were noted when comparing the data in this review with Pemberton et al’s and Rootman et al’s studies were the prevalence of IgG4+ immunohistochemistry studies and the reported and beneficial use of certain immuno-modulators in ISIO. 91, 101-104

The histopathological analysis of 42.1% of cases in this review were positive for IgG4, perhaps suggesting a large association with IgG4 sclerosing disease or other autoimmune disease processes. Furthermore, vasculitis was present in 10.5% of examined cases, an association not previously reported in either Pemberton et al or Rootman et al. Systemic associations of importance were present in 57.9% of cases. Autoimmune comorbidity was present in 42.1% of cases and neoplastic process was comorbid in 15.8% of cases.

The mainstay of therapy utilized in this review remains high dose corticosteroids, but novel immunotherapies were utilized with varying success. No specific therapy proved to provide statistically superior outcomes; however, of note, rituximab was used in 21.05% of cases (4 of 19) and resulted in full remission in 75% of these cases (3 of 4). 43, 105

Although the demographics, signs, and symptoms of ISIO proved to be similar in our systematic review when compared to Pemberton et al and Rootman et al, our data suggests that ISIO may have a largely autoimmune etiology, as suggested by the high prevalence of IgG4 positivity. The data presented demonstrates that immunomodulators like rituximab, methotrexate, and azathioprine are being used with increasing frequency and seemingly showing better efficacy when compared to the traditional steroid therapy alone. Further study is warranted to elucidate which immunomodulators provide greatest efficacy in treating ISIO.

4. Methods

The authors conducted a MEDLINE search using the PubMed database (National Library of Medicine) from September 2010 through June 18, 2016. The search was limited to articles in English or articles with English abstracts. Various combinations of keywords were used, including Idiopathic Sclerosing Orbital Inflammation, Idiopathic Sclerosing Orbital Pseudotumor, and Sclerosing Orbital Inflammation.

From September 2010 to June 2016, there have been 15 published articles with 19 patients and 19 only biopsy proven ISIO patients, excluding small individual case reviews. Articles were reviewed, data extracted and subsequently ablated in excel format. Parameters of examination included demographics, signs, symptoms, history, systemic findings, visual acuity, pathological findings and specimen site, radiological findings, treatments, and outcomes.