Idiopathic Sclerosing Orbital Inflammation

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Objective: To perform a multicenter review of the clinical features and treatment of 31 patients with idiopathic sclerosing orbital inflammation.

Methods: We included all patients with histologically confirmed idiopathic sclerosing orbital inflammation from 5 regional orbital centers. We reviewed the case notes to determine the clinical presentation, diagnostic features, and response to treatment. The main outcome measures were duration and nature of symptoms, anatomical location of disease, histopathological findings, treatment modalities, treatment efficacy and adverse effects, and final clinical status.

Results: We included 13 male and 18 female patients ranging in age from 7 to 83 years. The average duration of symptoms at presentation was 13.4 months. There was a predilection for the lateral and superior quadrants. Thirteen patients had apical disease, and 4 had extraorbital involvement. Histopathological findings invariably showed sclerosis associated with a sparse mixed cellular infiltrate. Twenty-seven patients were treated with oral prednisolone, response to which was good in 9 patients, partial in 11, and poor in 7. Six patients were treated with a second-line immunosuppressive agent, and 6 received radiotherapy. The response to radiotherapy was generally poor.

Conclusions: Idiopathic sclerosing orbital inflammation is a rare condition that can be difficult to diagnose and manage. Early intervention with immunosuppression in the form of corticosteroids combined with second-line agents can result in control and even regression of the disease.

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Orbital inflammation may be caused by a wide range of specific and nonspecific entities. The inflammation may be classified according to the site or by the nature of the underlying pathology. Idiopathic sclerosing orbital inflammation (ISOI) refers to a rare pathological subgroup of orbital inflammation that is poorly understood and is described in the literature in case reports or small series only. Systemic associations have been described, but clinical features have not been correlated for a large patient cohort. Controversy also exists regarding management. For these reasons, we undertook a multicenter study on our patients with ISOI.

Methods:
The clinical, radiological, and histopathological records of all patients with a diagnosis of ISOI from January 1, 1988, to December 31, 2003, were reviewed. Idiopathic sclerosing orbital inflammation was diagnosed according to clinical and radiological evidence of orbital inflammatory disease in the absence of any known localized or systemic cause, combined with histological evidence on open biopsy of marked fibrosis associated with a sparse, mixed chronic inflammatory infiltrate. In cases where the histological findings raised the possibility of an alternative diagnosis of sclerosing lymphoma, this was excluded by immunohistochemical results demonstrating a polyclonal lymphocyte population. Patients were identified from the following 5 regional centers: Oculoplastic and Orbital Unit, Department of Ophthalmology, Royal Adelaide Hospital; Orbital Plastic and Lacrimal Clinic, Royal Victorian Eye and Ear Hospital, Melbourne, Australia (Dr Selva); Eyelid, Lacrimal, and Orbital Clinic, Department of Ophthalmology, Royal Brisbane Hospital, Brisbane, Australia (Dr McNab); Oculoplastic and Orbital Unit, Department of Ophthalmology, Royal North Shore Hospital, Sydney, Australia (Dr O’Donnell).

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The demographic data and the symptoms and signs at initial examination for each patient are given in Table 1. Thirty-one patients were identified who met the inclusion criteria, consisting of 13 male and 18 female patients, whose ages ranged from 7 to 83 (mean, 44.3) years. Twenty right and 9 left orbits were affected, and 2 patients had bilateral disease. The duration of symptoms before presentation ranged from 1 week to 10 years, with a mean duration of 13.4 months and median of 17 weeks. Only 1 patient had symptoms for less than 4 weeks before presentation. Coexisting autoimmune disease was evident in 1 patient with autoimmune hemolytic anemia, and 1 patient with Raynaud disease. Another had suspected Crohn disease, but this was unconfirmed. Three patients had diabetes mellitus, 3 had asthma, 1 had eczema, and 1 had sinus disease.

The most common symptom at presentation was pain, found in 24 patients. This was described as severe in 2, moderate in 4, mild in 8, and unspecified in 10. Diplopia was the next most frequent symptom, occurring in 13 patients, followed by blurred vision in 9. One patient reported epiphora only.

Proposis was the most common sign, seen in 26 patients (84%). The range of proptosis varied from 1 to 10 mm, with a mean of 3.1 mm. Restriction of extraocular movements was the second most frequent sign, found in 18 patients. Visual acuity was reduced in the affected eye in 12 patients, with a range of 20/30 to no light perception. Four patients had an acuity of worse than 20/80, all of whom had disease at the orbital apex. Color vision was reduced in 10 patients, and a relative afferent pupillary defect was present in 8. Fourteen patients had a ptosis, and 6 had a palpable orbital mass. Two patients had retraction of the lower eyelid, and 2 had optic atrophy at presentation.

The location of disease, as revealed by findings of computed tomography in 30 patients and/or magnetic resonance imaging in 7 patients, is shown in Table 2. Nine patients had involvement of the lacrimal gland, but none of these had pure lacrimal disease. Of those cases with anterior orbital disease, 14 involved the superior and/or lateral area; 1, the superomedial area; and 5, the inferior and/or medial quadrants. Thirteen patients had apical disease, in 4 of whom there was involvement of only the intracanal space and/or muscle cone. The other 9 had a more diffuse pattern of involvement with extension into the extracanal space or anterior orbit. Four patients had extension into the infratemporal fossa, 3 of whom also had involvement of the pterygopalatine fossa. One pa-
The density of the lesions was recorded as the same as muscle in 23 of the 30 patients with computed tomograms. In 2 cases, the density was slightly greater than muscle at the periphery of the lesion and slightly lower centrally, and in another patient the overall density was slightly greater than muscle. In 4 patients the density was not recorded. The lesions were described as heterogeneous in 20, homogenous in 7, and not recorded in 3. Contrast medium was given to 21 patients, 20 of whom showed enhancement, although this was often described as mild or minimal. In 1 patient, there was no enhancement.

The mean and median times from the onset of symptoms to the biopsy were 18.0 and 4.6 months, respectively. In 1 patient, the histological records were unobtainable for this study, although that patient’s histological findings had previously been diagnosed as ISOI. All of the other 30 specimens were characterized by significant sclerosis and a sparse mixed inflammatory cell infiltrate (Table 3 and Figure 1).

The results of blood investigations are shown in Table 4. Four patients had positive findings for antinuclear antibodies, and 2 had unexplained elevated erythrocyte sedimentation rates.

The treatments prescribed and the response to each treatment are summarized in Table 5 and Table 6. Response to treatment was graded as poor (minimal or no benefit), partial (significant but limited improvement), or good (marked improvement). Of the 27 patients treated with oral prednisolone, 9 were judged to have had a good response to treatment; 11, a partial response; and 7, a poor response. Only 1 patient who was receiving high-dose corticosteroids for many years (patient 30) developed severe adverse effects. Six patients were treated with a second-line immunosuppressive agent. Cyclophosphamide was prescribed to 3 patients who had a partial or poor response to prednisolone therapy. The response to cyclophosphamide was partial in 1, poor in 1, and ungraded in 1. Azathioprine sodium was prescribed to 2 patients who had responded well to prednisolone therapy and was used as a corticosteroid-sparing agent. Their response to the combination treatment continued to be good. One patient with a partial response to prednisolone received cyclosporine, but the response was ungraded. Among the 6 patients who received radiotherapy, the response was

<table>
<thead>
<tr>
<th>Table 3. Summary of Histological Findings in Patients With Idiopathic Sclerosing Orbital Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finding</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Sclerosis</td>
</tr>
<tr>
<td>Paucity of infiltrate</td>
</tr>
<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Eosinophils</td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td>Giant cells</td>
</tr>
<tr>
<td>Histiocytes</td>
</tr>
<tr>
<td>Plasma cells</td>
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<table>
<thead>
<tr>
<th>Table 4. Results of Hematological Investigations in Patients With ISOI</th>
</tr>
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<tbody>
<tr>
<td>Investigation</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Complete blood cell count</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ESR 120 mm/h (hemolytic anemia) (n = 1)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CRP 25 mg/L (hemolytic anemia) (n = 1)</td>
</tr>
<tr>
<td></td>
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Abbreviations: ANA, antinuclear antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ISOI, idiopathic sclerosing orbital inflammation; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies.

*Level was 14 U/mL (reference threshold, <3 U/mL).
†Level was 152 IU/mL (reference threshold, <100 IU/mL). Levels of other thyroid markers were within reference ranges.

Figure 1. Photomicrographs show the histological appearance of idiopathic sclerosing orbital inflammation. A, Low magnification shows diffuse inflammation with marked sclerosis (hematoxylin-eosin, original magnification ×100). B, At higher magnification, there is a polymorphous inflammatory infiltrate with prominent eosinophils (hematoxylin-eosin, original magnification ×400).
generally considered poor. Four patients underwent debulking of the inflammatory mass, of whom 2 had complete relief of their symptoms with no recurrence and 1 had a partial relief of pain. There was no effect in the fourth patient.

Table 7 shows the final outcome after comparing the clinical signs at the last assessment with those at presentation for each patient. The average duration of active disease was estimated at 29 months, and the average follow-up was 4½ years.

**COMMENT**

Idiopathic sclerosing orbital inflammation is a rare condition. Its incidence has been estimated at 5% to 7.8% of inflammatory orbital lesions.7,8 When initially seen in patients, it exhibits fewer inflammatory signs and a more chronic onset than does nonspecific orbital inflammation (NSOI). The signs and symptoms in any single patient are dictated mainly by the anatomical location within the orbit, rather than by the specific nature of the disease. Anterior disease shows an inflammatory picture with eyelid swelling and chemosis, but more posterior lesions may show signs of optic nerve compromise. Proptosis and extraocular muscle restriction were the most common signs in this study, in keeping with previous series.7,9 Disease isolated to a single structure was unusual, and the pattern was generally more diffuse. Like Rootman et al,7 we found a predilection for the superior or lateral orbit, but all of our cases involving the lacrimal gland also had disease extending into the orbit. It has been suggested that the lacrimal gland is prone to involvement because it is the only orbital structure that normally contains lymphoid tissue.10 Lymphocytes were the only inflammatory cell type found in all specimens, and it has been suggested that they play a critical role in driving the process that leads to fibrosis.11

Another factor that distinguishes ISOI from NSOI is the tendency in some patients to develop aggressive disease.12-17 We had 4 patients with extension of the inflammatory mass into the infratemporal fossa, 3 of whom also had involvement of the pterygopalatine fossa. Another patient had intracranial disease, another

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**Table 5. Response to Corticosteroid Treatment in Patients With ISOI**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of Symptoms</th>
<th>Oral Prednisolone Treatment</th>
<th>Response</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 d</td>
<td>30 mg 1</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>4 wk</td>
<td>60 mg 3</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>1 mo</td>
<td>60 mg 2</td>
<td>Poor</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>1 mo</td>
<td>80 mg Still tapering</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>1 mo</td>
<td>60 mg 1</td>
<td>Poor</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>6 wk</td>
<td>50 mg 1</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>6 wk</td>
<td>25 mg 3</td>
<td>Partial</td>
<td>Weight gain</td>
</tr>
<tr>
<td>8</td>
<td>2 mo</td>
<td>50 mg 1</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>2 mo</td>
<td>60 mg 1</td>
<td>Poor</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>2 mo</td>
<td>60 mg 2</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>3 mo</td>
<td>None 1</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>4 mo</td>
<td>1 mg/kg 1</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>4 mo</td>
<td>60 mg 4</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>4 mo</td>
<td>60 mg 144</td>
<td>Partial</td>
<td>Cataract</td>
</tr>
<tr>
<td>15</td>
<td>4 mo</td>
<td>60 mg 3</td>
<td>Good</td>
<td>Sleeplessness, euphoria</td>
</tr>
<tr>
<td>16</td>
<td>4 mo</td>
<td>None 2</td>
<td>Poor</td>
<td>None</td>
</tr>
<tr>
<td>17</td>
<td>4 mo</td>
<td>30 mg 3</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>18</td>
<td>4 mo</td>
<td>60 mg 3</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>19</td>
<td>4 mo</td>
<td>50 mg Still receiving maintenance dose (10 mg)</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>20</td>
<td>5 mo</td>
<td>60 mg 2</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>21</td>
<td>5 mo</td>
<td>25 mg 6</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>22</td>
<td>6 mo</td>
<td>None 3</td>
<td>Poor</td>
<td>None</td>
</tr>
<tr>
<td>23</td>
<td>6 mo</td>
<td>50 mg 3</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>24</td>
<td>6 mo</td>
<td>60 mg 48</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>25</td>
<td>6 mo</td>
<td>60 mg 3</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>26</td>
<td>9 mo</td>
<td>50 mg 3</td>
<td>Good</td>
<td>None</td>
</tr>
<tr>
<td>27</td>
<td>20 mo</td>
<td>80 mg 6</td>
<td>Partial</td>
<td>None</td>
</tr>
<tr>
<td>28</td>
<td>2 y</td>
<td>60 mg 1</td>
<td>Poor</td>
<td>None</td>
</tr>
<tr>
<td>29</td>
<td>4 y</td>
<td>50 mg 6</td>
<td>Partial</td>
<td>Weight gain</td>
</tr>
<tr>
<td>30</td>
<td>9 y</td>
<td>50+ mg 120</td>
<td>Poor</td>
<td>Weight gain, psychosis, osteoporosis, raised blood pressure, cardiac failure, cataracts</td>
</tr>
<tr>
<td>31</td>
<td>10 y</td>
<td>None 120</td>
<td>Poor</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse effects; ISOI, idiopathic sclerosing orbital inflammation.
showed bone thinning, and another had anterior spread onto the cheek.

The diagnosis of ISOI has been the subject of some controversy in the literature. In the past, sclerosing changes were thought to represent the end stages of NSOI. Abramovitz et al and others have made the case for ISOI to be a primary fibrosing disorder, with more similarity in pathogenesis to other primary fibrosing diseases such as retroperitoneal fibrosis than to NSOI. This idea was based mainly on the discovery of marked fibrosis early in the course of the disease and by the similarity in cell populations comparing ISOI and retroperitoneal fibrosis. Thus, the diagnosis of ISOI depends largely on the histological picture of marked fibrosis associated with a sparse, mixed chronic inflammatory cell infiltrate. However, it is well recognized that the presentation in ISOI is generally chronic. In the study by Rootman et al, the mean duration of disease before biopsy was 24 months, and the median duration was 7 months. In our study, these mean and median times were 18.0 and 4.6 months, respectively. There might be some doubt about the diagnosis of ISOI when there are long delays between the onset of symptoms and biopsy because the histological picture would be similar to that of chronic NSOI. Although frustrating for researchers, the distinction between the 2 entities ultimately may not be critical to management of the disease because patients with advanced fibrosis and few or no inflammatory signs in both situations are unlikely to respond to treatment. Therefore, the severity of the disease in terms of established fibrosis and the activity reflected in signs and symptoms of inflammation should be considered when planning intervention. However, those with posterior orbital disease may lack inflammatory signs, despite having active disease. It is reasonable, therefore, to consider a trial of treatment in all patients...
with posterior involvement, especially because optic nerve function may be threatened.

The best treatment of ISOI is also controversial. Most studies included few patients, and there have been no randomized or controlled trials. Complicating matters further is the widely ranging duration of symptoms before initiation of treatment. No treatment can be expected to reverse established fibrosis, and it would be unfair to dismiss a treatment as ineffective when there is no response in burned-out disease.

In this study, we found oral prednisolone alone to have a good response in 9 (35%) of the 26 patients (Figure 2 and Figure 3). There was a trend between duration of symptoms and response to prednisolone, with prednisolone having a better effect in those with a shorter duration of disease. The mean duration of symptoms was 14 weeks in those with a good response, 41 weeks in those with a partial response, and 90 weeks in those with a poor response. However, Mombaerts et al\(^{18}\) found no relationship between corticosteroid responsiveness and duration of disease before treatment in 32 patients with orbital pseudotumor, including 7 who had histological evidence of severe fibrosis. Furthermore, they also found no difference in the corticosteroid response rate between sclerosing and nonsclerosing pseudotumors.

Our results suggest a definite role for corticosteroids in ISOI. Fibrosis, even if it is a primary fibrosing condition, must still be preceded by inflammatory cells migrating into tissues and recruiting and activating fibroblasts before collagen is laid down. These events are amenable to intervention by immunosuppression, and corticosteroid therapy should be effective if given in sufficient doses and early enough in the disease process. Other chemotherapeutic agents might be more specific to the mechanism. However, as this is still poorly understood, corticosteroids, which have a broad immunosuppressive effect, should still be considered first-line treatment. There are reports\(^{6,7,18,19}\) of an initial response to corticosteroids followed by recurrence and progression, but there is little information on how the corticosteroid therapy was tapered. Effective immunosuppression needs to be in sufficient dose and maintained for the duration of active disease. Other agents should therefore be considered, particularly for corticosteroid sparing in the control of long-term disease.

Our results suggest that when corticosteroids have been ineffective, other immunosuppressants or radiotherapy has also failed. However, we currently have little knowledge on what is driving the disease and what eventually causes it to become inactive. Until these mechanisms are better understood, it seems reasonable to try other treatments on an empirical basis, with the hope of finding a more specific immunosuppressive agent.

Four patients underwent surgical debulking of the mass, 2 during biopsy and 2 after partial responses to prednisolone therapy. This appeared to cure 2 patients, 1 of whom received no corticosteroid at all, and gave partial relief to a third but had no effect on the fourth. Kennerdell\(^{19}\) also reported good results from surgical ex-
cision. This treatment seems worthy of further investigation and may be the only effective measure in patients with established fibrosis.

Idiopathic sclerosing orbital inflammation remains a poorly understood condition that is difficult to diagnose and treat. Early recognition and biopsy in suspected cases, combined with adequate immunosuppression, appears to offer the best chance of a favorable outcome. Until the pathogenesis is better understood, corticosteroids combined with a corticosteroid-sparing agent such as azathioprine are a reasonable first-line treatment.

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Author Contributions: Dr Hsuan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES