Orbital Inflammation With IgG4-Positive Plasma Cells

Manifestation of IgG4 Systemic Disease

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Objective: To describe clinical, radiographic, and morphologic findings in patients with IgG4-positive cells present on orbital biopsy specimens.

Design: Retrospective review (from January 1, 1993, through December 31, 2006) of patients with orbital biopsy specimens that excluded lymphoma; comparison of patients with and without IgG4-positive cells on immunostaining.

Results: Of 21 patients, 11 had increased IgG4-positive cells (defined as >10 cells on biopsy). Symptoms included eyelid or periocular swelling (8 patients) or proptosis (3 patients), with bilateral involvement in 6 patients. Computed tomographic imaging displayed lacrimal gland mass in 10 patients; 6 patients had lesions in other organs. Two patients had increased serum IgG4 levels. In 10 patients without IgG4-positive cells (<10 cells on biopsy), 6 had proptosis, 1 had eyelid swelling, 2 had eyelid mass, and 1 had diplopia, all unilateral. None had systemic symptoms. Patients with IgG4-positive cells had longer symptom duration, and their biopsy specimens showed more background fibrosis, lymphoid hyperplasia, plasma cells, and eosinophils.

Conclusions: The clinical appearance, high incidence of bilateral disease, association with lesions in other organs, and increased IgG4 serum levels in some patients—with an increased number of IgG4-positive cells in the biopsy specimen, which shows more background fibrosis, lymphoid hyperplasia, plasma cells, and eosinophils—indicate that these patients have an orbital manifestation of IgG4-associated systemic disease.


When compared with tumor-forming inflammatory processes occurring in other locations, idiopathic orbital inflammation (IOI) has been found to have several similarities with autoimmune pancreatitis. Both processes mimic neoplasm and are characterized by variable degrees of fibrosis and chronic inflammation.1-3 Both processes tend to respond to and may become dependent on corticosteroid therapy, and unusual clinical manifestations lead to surgical procedures. Autoimmune pancreatitis has been identified as part of the spectrum of IgG4-associated systemic disease.4,5

IgG4-related disease is a recently recognized entity characterized by abundant tissue infiltration by IgG4-positive plasma cells and high serum levels of IgG4.6,7 Although this disease was first recognized as involving the pancreas, several other studies4,8-11 have shown IgG4-positive plasma cell infiltrations in other organs, including retroperitoneal soft tissues, liver, breast, and salivary glands. Recent publications have suggested that IgG4 disease might also affect the lacrimal glands and periorbital tissues.12-17 IgG4-associated disease is now recognized as a systemic process.

This study reports the clinical, radiographic, and pathologic findings in a group of patients in whom orbital biopsy specimens showed features of IOI or lymphoid hyperplasia and increased numbers of IgG4-positive plasma cells and who had clinical manifestations of IgG4-associated disease. These patients were compared with a group of patients whose biopsy specimens did not have increased IgG4-positive plasma cells.

METHODS

Mayo Clinic Institutional Review Board approval was obtained for this study, and only the material from patients who granted permission for research was used. We searched our patient database for records of patients with a diagnosis of IOI, reactive lymphoid hyperplasia, or both and for whom a biopsy was per-
formed to exclude lymphoma from January 1, 1993, through December 31, 2006, at Mayo Clinic, Rochester, Minnesota. For patients in whom the diagnosis of lymphoma had been excluded on the basis of immunophenotyping or molecular genetics studies, archived paraffin-embedded tissues and glass slides, if available, were tested for IgG4 immunostaining.

The biopsy specimens were analyzed by 2 pathologists (J.A.P. and D.R.S.) and evaluated for several histomorphologic features. These features included amount of background fibrosis, lacrimal gland acinar atrophy, presence of obliterator phlebitis, follicular hyperplasia, and cell type in the cellular infiltrate, which included eosinophils, plasma cells, and lymphocytes. Each feature was quantified as absent (0) or present in a small amount (1'), moderate amount (2'), or marked amount (3').

The tissue biopsy specimens had been fixed in 10% buffered formalin and embedded in paraffin. Monoclonal anti-human IgG4 antibody (Zymed Laboratories Inc, San Francisco, California) was applied to 4-µm sections using standard immunohistochemical techniques. Peroxidase activity was visualized by applying diaminobenzidine solution containing 0.05% hydrogen peroxide. Sections were then counterstained with modified Mayer hematoxylin, dehydrated, cleared, and mounted. Appropriate positive and negative controls were run with each batch.

The extent of IgG4-positive plasma cell infiltration was evaluated by 2 pathologists (J.A.P. and A.D.) and scored as negative or positive according to the number of immunohistochemically identified IgG4-positive plasma cells per high-power field (HPF) in each specimen. One HPF covered an area of 0.55 mm². Three HPFs per tissue section were selected, and a mean number of IgG4-positive plasma cells per HPF was calculated using similar criteria to those outlined in other studies.5,6,14 Similar to the study by Sato et al,14 tissue with 0 to 10 positive cells per HPF was scored as negative for IgG4. Tissue with 11 or more positive cells per HPF was scored as positive for IgG4. Since the beginning of this study, 5 patients underwent testing of serum IgG4 levels. Although these results are given in this article, measurement of serum IgG4 was not part of this study for all patients.

Demographic and clinical data, radiologic findings, and treatment and follow-up information for each patient were obtained from the patients' electronic and hospital records. The clinical appearance, follow-up, and morphologic findings in the biopsy specimens were compared between patients who tested positive and negative for IgG4 in the tissue biopsy specimens.

Categorical variables were compared between groups using the Fisher exact test. The Wilcoxon rank sum test was used to compare continuous variables between the groups. \( P < .05 \) was considered statistically significant.

RESULTS

A total of 21 patients were identified from the computerized search. All patients had an orbital biopsy specimen obtained with the purpose of excluding lymphoma. Lymphoma was excluded at the time of diagnostic biopsy by immunophenotyping with immunohistochemistry in 20 patients and with flow cytometry in 1 patient; molecular genetics studies were performed for 7 patients. Of the 19 patients who were followed up (range, 3.0-103.0 months; mean, 55.3 months), none developed lymphoma. Archived orbital biopsy specimens from the patients were tested for IgG4-positive plasma cells by immunostaining. Of these 21 samples, 11 were considered positive for IgG4 (>10 IgG4-positive cells per HPF) and 10 were considered negative for IgG4 (≤10 IgG4-positive cells per HPF).

CLINICORADIOGRAPHIC FINDINGS, TREATMENT, AND FOLLOW-UP

Patients With IgG4-Positive Cells

The group of patients with IgG4-positive cells (>10 IgG4-positive cells per HPF) comprised 5 women and 6 men, with a mean age of 50.4 years (range, 30.0-70.0 years) at the time of biopsy (Table 1). Eyelid or periorbital swelling was the most common disease manifestation (8 patients) and was associated with proptosis in 1 patient. Proposis without swelling was seen in 3 patients, of whom 1 patient each also had diplopia, decreased visual acuity, and pain. The duration of symptoms ranged from 0.8 month to 61.3 months (mean, 21.0 months). For 7 patients, the disease initially was considered localized to the orbit; 2 of these patients had bilateral orbital involvement. The other 4 patients had bilateral orbital involvement in addition to enlarged peripheral lymph nodes; therefore, the disease was considered generalized at first evaluation by the ophthalmologist. Biopsy specimens of these peripheral lymph nodes obtained later showed benign follicular hyperplasia in all 4 patients.

As part of their workup before the biopsy, the patients underwent imaging studies of the orbit. Orbital computed tomography was performed in 6 patients and orbital magnetic resonance imaging in 5 patients; 1 patient underwent both tests. These imaging studies revealed a mass centered in the lacrimal gland region in most patients (10 patients) (Table 1). Three of these patients also had involvement of the extraocular muscles, and 2 had orbital soft tissue involvement with intracranial extension. One patient had involvement of the optic nerve sheath. In 1 patient (patient 16), the disease was centered in the extraocular muscles with involvement of the infraorbital nerves (Figure 1).

Review of the clinical history revealed 4 patients with no significant medical history (Table 1). Five patients had a history of asthma, and 3 patients had a history of recurrent sinusitis. Of importance, 1 patient (patient 15) had a history of idiopathic chronic pancreatitis, which was later characterized as autoimmune pancreatitis, 1 patient (patient 18) had an inflammatory pseudotumor resected from the liver 12 months before the orbital symptoms, and 1 patient (patient 16) had biliary cirrhosis cholangitis. Patients 16 and 18 were 2 of the 3 patients who underwent serum IgG4 testing; both patients were found to have increased levels—563.0 and 167.0 mg/dL, respectively (reference range, 8.0-140.0 mg/dL) (to convert to grams per liter, multiply by 0.01). The other patient tested for serum IgG4 (patient 19) had normal levels (47.7 mg/dL). This patient had a history of parotid gland enlargement thought to be Sjögren syndrome. One patient had had breast cancer and was free of tumor recurrence; 1 patient each had hypertension and hyperlipidemia.

Treatment in the patient group involved rituximab only for 6 patients, corticosteroids only for 4 patients (3
Patients Without Increased IgG4-Positive Cells in Their Orbital Biopsy Specimens

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Mass Location</th>
<th>Side</th>
<th>Ocular Signs and Symptoms</th>
<th>Disease Localized or Generalized</th>
<th>Symptom Duration, mo</th>
<th>Other Lesions</th>
<th>Other Clinical History</th>
<th>Follow-up, mo</th>
<th>Treatment/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/63</td>
<td>LG</td>
<td>R</td>
<td>Eyelid ptosis, diplopia, proptosis</td>
<td>Localized to orbit</td>
<td>5.2</td>
<td>None</td>
<td>MALT lymphoma of the submandibular gland</td>
<td>87.0</td>
<td>Corticosteroids followed by rituximab/NR</td>
</tr>
<tr>
<td>2/F/51</td>
<td>EOM, LG</td>
<td>R</td>
<td>Eyelid swelling</td>
<td>Localized to orbit</td>
<td>5.0</td>
<td>None</td>
<td>Asthma</td>
<td>76.4</td>
<td>Rituximab/recurrence after 22 mo Corticosteroids/NR</td>
</tr>
<tr>
<td>3/M/67</td>
<td>IR, LR, LG</td>
<td>L</td>
<td>Diplopia, swelling, proptosis, proptosis</td>
<td>Localized to orbit</td>
<td>17.0</td>
<td>None</td>
<td>None</td>
<td>26.3</td>
<td>Corticosteroids/NR</td>
</tr>
<tr>
<td>4/F/65</td>
<td>SR, LR, cavernous sinus, pterygoid fossa</td>
<td>L</td>
<td>Diplopia</td>
<td>Localized to orbit</td>
<td>12.6</td>
<td>None</td>
<td>Stage 1 ovarian cancer and essential thrombocytopenia</td>
<td>LTF Radiation treatment/NA</td>
<td></td>
</tr>
<tr>
<td>5/M/51</td>
<td>LG</td>
<td>L</td>
<td>Upper eyelid mass</td>
<td>Localized to orbit</td>
<td>13.3</td>
<td>None</td>
<td>Coronary artery disease</td>
<td>3</td>
<td>Corticosteroids/NR</td>
</tr>
<tr>
<td>6/F/54</td>
<td>LG, EOM</td>
<td>L</td>
<td>Pain, proptosis, diplopia</td>
<td>Localized to orbit</td>
<td>1.9</td>
<td>None</td>
<td>Diabetes mellitus</td>
<td>90.7</td>
<td>Corticosteroids/NR, died of unrelated cause</td>
</tr>
<tr>
<td>7/F/62</td>
<td>LG, SR</td>
<td>L</td>
<td>Proptosis</td>
<td>Localized to orbit</td>
<td>3.0</td>
<td>None</td>
<td>None</td>
<td>103</td>
<td>Radiotherapy and corticosteroids/NR Corticosteroids/NR</td>
</tr>
<tr>
<td>8/F/58</td>
<td>Inferior OST</td>
<td>R</td>
<td>Proptosis, diplopia</td>
<td>Localized to orbit</td>
<td>1.9</td>
<td>None</td>
<td>None</td>
<td>40.3</td>
<td>Corticosteroids/NR</td>
</tr>
<tr>
<td>9/F/71</td>
<td>LG</td>
<td>L</td>
<td>Diplopia, swelling, proptosis, proptosis</td>
<td>Localized to orbit</td>
<td>12.8</td>
<td>None</td>
<td>Hypertension, hyperlipidemia</td>
<td>71.4</td>
<td>Surgical excision/NA Corticosteroids/NA</td>
</tr>
<tr>
<td>10/F/55</td>
<td>LG</td>
<td>R</td>
<td>Swelling, diplopia, mass initially tender</td>
<td>Localized to orbit</td>
<td>14.0</td>
<td>None</td>
<td>Cervical and mediastinal lymphadenopathy</td>
<td>LTF Corticosteroids/NA</td>
<td></td>
</tr>
</tbody>
</table>

Patients With Increased IgG4-Positive Cells (≤10 IgG4-positive cells per HPF) comprised 8 women and 2 men.

Abbreviations: AWD, alive without disease; B, bilateral; EOM, extraocular muscles; IR, inferior rectus muscle; L, left; LG, lacrimal gland; LR, lateral rectus muscle; LTF, lost to follow-up; MALT, mucosa-associated lymphoid tissue; MGUS, monoclonal gammopathy of undetermined significance; MR, medial rectus muscle; NA, not applicable; NR, no recurrence; ON, optic nerve; OST, orbital soft tissue; R, right; SR, superior rectus muscle.

In most patients the disease was in remission after treatment.
men, with a mean age of 58.9 years (range, 51.0-71.0 years) at the time of biopsy. Six patients had proptosis, which was associated with diplopia in 5 patients. One of these patients also reported pain. Two patients had upper eyelid mass, another had eyelid swelling, and the remaining patient had diplopia only. In all patients the disease was restricted to 1 of the orbits, and in all but 1 patient, it was considered localized. The duration of symptoms varied from 1.7 to 14 months, with a mean of 8.7 months. Imaging studies performed in all patients revealed involvement of the lacrimal gland and extraocular muscles in 4 patients, the lacrimal gland only in 4, and the extraocular muscles and/or orbital soft tissues in 2. In 1 of these patients, the disease also involved the cavernous sinus and pterygoid fossa. Serum levels of IgG4 were tested in 2 patients and were within normal limits. Review of the patients’ histories showed that none of these 10 patients had had lesions in other sites. Most patients (6 of 10) were treated with corticosteroids, in association with radiotherapy in 1 and with rituximab in 1. Rituximab only was given to 1 patient and radiotherapy to 1; radiotherapy was the advised treatment for 1 patient who was lost to follow-up. One patient (patient 9) was treated only with partial surgical excision of the mass. Most patients are alive without evidence of disease (6 patients; mean follow-up, 60.2 months). One patient died of unrelated causes, without disease, after 90.7 months of follow-up. In 1 patient, the disease recurred after 22 months of the initial treatment. Two patients were lost to follow-up (Table 1).

**HISTOMORPHOLOGIC FINDINGS IN ORBITAL BIOPSY SPECIMENS OF ALL PATIENTS**

Review of the tissue biopsy specimens in these 21 patients showed a spectrum of morphologic changes that characterizes the diagnosis of IOI or reactive lymphoid hyperplasia (Table 2). Moderate to marked lymphocytic infiltrate...
was present in 11 biopsy specimens, accompanied by marked (3+) lymphoid follicular hyperplasia in 8 patients (Figure 2). Follicular hyperplasia was moderate (2+) in 3 patients, mild (1+) in 6 patients, and absent (0) in 4 patients. Background fibrosis was also observed in 14 patients (mild in 5 patients, moderate in 6, and marked in 3), accompanied by an equivalent degree of acinar atrophy. Plasma cells were present in all biopsy specimens, varying from 1+ (7 patients) to 2+ (9 patients) to 3+ (5 patients). In most biopsy specimens, the plasma cells were present in aggregates surrounding the lymphoid follicles (Figure 3) or interspersed among residual ducts surrounded by fibrosis (Figure 4). Eosinophils were seen in 8 of the 21 patients, 5 patients in small numbers (1+) and 3 patients in moderate numbers (2+) (Figure 5). None of the patients were found to have obliteratorive phlebitis. No foci of necrosis, vasculitis, or granulomas were found.

The analysis of the immunostaining for IgG4 revealed 8 patients with no IgG4-positive cells and 2 patients with 10 or fewer IgG4-positive cells per HPF. These 10 patients were considered to have tested negative for IgG4-positive cells. Eleven patients tested positive for IgG4-positive cells: 11 to 30 cells per HPF in 2 patients and more than 30 cells in 9 patients (Figure 6).

When the histomorphologic features in the biopsy specimens of patients with increased IgG4-positive cells were compared with the biopsy specimens of patients with 0 to 10 IgG4-positive cells per HPF, the former group had a higher incidence of follicular hyperplasia, background fibrosis, numerous plasma cells, and the presence of eosinophils. No morphologic differences were observed between the patients who had numerous (≥31) IgG4-positive cells and those with fewer (11-30) IgG4-positive cells. A comparison between the 2 groups of patients according to their IgG4 status is given in Table 3.

**COMMENT**

In this study, a group of patients with a previous diagnosis of IOI or reactive lymphoid hyperplasia had an increased number of IgG4-positive plasma cells, as seen on...
IgG4-related systemic disease is an inflammatory disorder, likely of autoimmune origin, characterized by increased serum levels of the IgG4 subclass of IgG and increased numbers of IgG4-positive plasma cells in the tissues involved. IgG4-positive plasma cells were first reported in association with autoimmune pancreatitis\(^4,^{18,19}\) and were later reported with inflammatory lesions in other locations.\(^10,^{12,20}\) Morphologically, the lesions in the pancreas and other organs are characterized by a lymphoplasmacytic infiltrate on a background of fibrosis similar to that observed in IOI.\(^1,^{21,22}\) Because of these morphologic similarities, we decided to test for IgG4-positive plasma cells in a group of our patients with IOI and reactive lymphoid hyperplasia.\(^23\)

The findings in our study are similar to those in a few recent publications that have also demonstrated IgG4-positive plasma cells in lacrimal gland biopsy specimens.\(^12,^{14}\) Our patients with increased IgG4-positive cells were also of a wide age range, with no sex predominance. Clinical appearance in most patients included progressive painless eyelid or periorcular swelling; imaging studies showed mass lesions in the region of the lacrimal gland. Bilateral orbital masses were reported in 6 of our 11 patients, in 12 of 21 patients described by Sato et al,\(^14\) in 5 of 6 patients described by Cheuk et al,\(^12\) and in all 4 patients described by Takahira et al.\(^13\) Concomitant involvement of a salivary gland was observed in 2 of our patients but was seen in a higher proportion of patients in the other 3 studies. Similar to the observations of Cheuk et al,\(^13\) 3 of our patients had associated peripheral lymphadenopathy, a finding recently described in patients with IgG4-associated disease.\(^24\) Three of our patients had intrabdominal manifestations of the disease, with involvement of the pancreas, liver, and biliary tract, which had not been observed by the other authors. Two patients had intracranial (cavernous sinus) involvement, 1 of whom had bilateral infiltration of the infratrochlear nerves. Another interesting observation in our group of patients was a history of asthma in 5 patients. Of 3 patients tested for serum levels of IgG4, 2 had increased levels. High serum levels of IgG4 have also been reported by others in patients with lacrimal gland involvement by IgG4-associated disease.\(^12,^{14}\) The morphologic features observed in our patients were similar to those observed by the other authors, with the exception of the presence of eosinophils in 7 of our patients, a finding not reported by others. Obliterative phlebitis, a morphologic finding observed in IgG4-associated disease involving the pancreas,\(^7,8\) and only rarely reported in the lacrimal gland,\(^14\) was not observed in our patients. Table 4 gives a comparison of our findings in the patients with IgG4-positive cells with patients described by other authors.

Recent studies\(^25,^{26}\) have suggested that IgG4-associated disease involving the lacrimal gland can be complicated by lymphoma. In 1 study,\(^25\) 2 cases of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue and 1 case of follicular lymphoma occurred in patients with a previous diagnosis of IgG4-related chronic sclerosing dacryoadenitis. Also, those authors report 3 additional cases of ocular adnexal extranodal marginal zone B-cell lymphoma with numerous monotypic IgG4-positive plasma cells. In 1 patient described by Sato et al,\(^14\) biopsy specimens of their orbital tissue. Except for 1 patient, the clinical appearance included painless eyelid or periorcular tissue swelling, and these patients were thought to have possible orbital lymphoma, which led to a tissue biopsy. When compared with the group of patients who did not have increased IgG4-positive cells, bilateral disease was common in this group (6 of 11), and 4 patients also had disease involving other organs, such as the pancreas, biliary tract, liver, and salivary glands. In addition, the duration of symptoms in these patients was longer, and more of these patients had asthma (5 of 11 patients). Comparison of the morphologic features between the 2 groups showed that the biopsy specimens from the patients with increased IgG4-positive cells had a higher incidence of marked follicular hyperplasia, background fibrosis, numerous plasma cells, and the presence of eosinophils. The distinct clinical appearance, namely, the biopsy findings in association with orbital tissue infiltration by IgG4-positive plasma cells, led us to conclude that the orbital disease in this group of 11 patients was part of a systemic process now recognized as IgG4-related systemic disease.

### Table 3. Patient Comparison by IgG4 Expression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive (n=11)</th>
<th>Negative (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male to female ratio</td>
<td>5:6</td>
<td>8:2</td>
<td>.18</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>50.4</td>
<td>59.7</td>
<td>.17</td>
</tr>
<tr>
<td>Duration of symptoms, mean, mo</td>
<td>21</td>
<td>10</td>
<td>.40</td>
</tr>
<tr>
<td>Unilateral to bilateral disease</td>
<td>5.6</td>
<td>10:0</td>
<td>.01</td>
</tr>
<tr>
<td>Patients with asthma</td>
<td>5</td>
<td>1</td>
<td>.15</td>
</tr>
<tr>
<td>Involvement of other organs</td>
<td>4</td>
<td>0</td>
<td>.09</td>
</tr>
<tr>
<td>Biopsy findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked follicular hyperplasia</td>
<td>6</td>
<td>2</td>
<td>.18</td>
</tr>
<tr>
<td>Background fibrosis</td>
<td>11</td>
<td>3</td>
<td>.001</td>
</tr>
<tr>
<td>Presence of eosinophils</td>
<td>7</td>
<td>1</td>
<td>.02</td>
</tr>
<tr>
<td>Plasma cells (≥2)</td>
<td>11</td>
<td>3</td>
<td>.001</td>
</tr>
</tbody>
</table>

\(^a\)Biopsy specimens showed 11 or more IgG4-positive cells per high-power field.

\(^b\)Biopsy specimens showed 0 to 10 IgG4-positive cells per high-power field.
the lacrimal gland biopsy specimen showed immunoglobulin heavy chain gene rearrangement, suggesting the possibility of B-cell lymphoma. Lymphoma has not developed in any of our patients.

The role of IgG4 in causing a tumor-effect lesion is not yet entirely clear, to our knowledge. IgG4 is the least common of the 4 separate IgG subclasses and accounts for only 3.0% to 6.0% of the total IgG in the serum of healthy persons. IgG4 is characterized by an inability to fix C1q complement and an inability to activate the classic pathway of complement, therefore interfering with immunomediated inflammation.18,19

The presence of increased numbers of IgG4-positive plasma cells in the immunostains, increased numbers of plasma cells and eosinophils, background fibrosis, and prominent lymphoid hyperplasia are features that distinguish these cases from other cases of IOI and reactive lymphoid hyperplasia. Although inflammatory processes of the orbit are relatively common,29,30 IOI represents only 5% to 20% of these cases in different studies.2,3,31 As the name implies, the pathogenesis of IOI has remained elusive, and IOI is often a diagnosis of exclusion, clinically and morphologically. In fact, since its first description by Birch-Hirschfeld in 1930,32 the history of orbital inflammatory pseudotumor, or IOI, has been defined by what it is not.

In conclusion, some in our patient group had increased numbers of IgG4-positive cells in their orbital biopsy specimens and had tissue biopsy specimens showing morphologic features somewhat distinctive from IOI or reactive lymphoid hyperplasia without IgG4-positive cells. They also had a unique clinical appearance with eyelid swelling, bilateral orbital involvement, systemic involvement, and more prolonged disease. An increased IgG4 serum level was observed in some of these patients, as well as an increased association with history of asthma. These observations offer strong evidence that this group of patients represents a distinct group with orbital manifestation of what is now known as IgG4-associated systemic disease. The unique clinical appearance and tissue infiltration by IgG4-positive plasma cells in these patients warrant the separation of orbital manifestation of IgG4 systemic disease from the inflammatory orbital pseudotumor category.

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Additional Contributions: David O. Hodge, MS, from the Division of Biomedical Statistics and Informatics, Mayo Clinic, provided help with the statistical analysis.

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Ophthalmological Numismatics

A brilliant anatomist and surgeon, Antonio Scarpa (1752-1832) received his medical degree at the University of Padua when he was 18 years of age; at age 20 years, he was elected full professor of anatomy and theoretical surgery at the University of Modena. There, with backing from Duke Franz III, he oversaw the construction of the Modena Anatomical Institute. After a decade at Modena, he was summoned by Emperor Joseph II back to the University of Padua to be chair of anatomy, where he was to stay for the remainder of his career. The first to describe “the Scarpa triangle” and the nasopalatine nerve, Scarpa also wrote one of the most important ophthalmological volumes of the 19th century, Saggio di osservazioni ed esperienze sulle principali malattie degli occhi (1801, reprinted and translated many times), in addition to several other highly regarded anatomical and surgical texts, including Tabulae neurologicae (1794), which, like most of his works, was masterfully illustrated by his own drawings.

In 1819, a lifetime portrait medal by Luigi Cossa of 50-mm diameter was struck in bronze to honor Scarpa. The obverse depicts his bust facing left. The reverse has an inscription in 4 lines, LUME/ED ONORE/DELLA/CHIRURGIA, within a wreath of laurel branches.

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