IgG4-Related Ophthalmic Disease. Part II: Clinical Aspects

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Purpose: To review the current state of knowledge of IgG4-related ophthalmic disease (IgG4-ROD).

Methods: A review of the literature and personal experience of the authors.

Results: IgG4-related disease is a recently recognized fibroinflammatory disorder that may affect 1 or more organs. It is characterized by lymphoplasmacytic infiltrates with large numbers of IgG4 positive plasma cells, storiform fibrosis, obliterative phlebitis, and eosinophil infiltration as well as peripheral eosinophilia, and in some cases, elevated serum levels of IgG4. These features are not always seen, and the diagnosis should be made by integrating clinical, imaging, and histopathological data, with reference to recently defined diagnostic criteria. IgG4-ROD forms a significant proportion of what has previously been labeled "idiopathic orbital inflammation" or reactive lymphoid hyperplasia. Orbital disease may occur alone, at the same time as disease elsewhere, or metachronously with systemic disease. Although almost any ocular adnexal tissue may be affected, there are several commoner recognizable patterns of IgG4-ROD: (1) sclerosing dacryoadenitis; 2) enlargement of orbital nerves (most commonly the infraorbital nerve) associated with orbital myositis and lacrimal gland disease, often in combination with paranasal sinus disease, eosinophilia, and systemic involvement; and 3) sclerosing orbital inflammation. Patients with IgG4-ROD should be investigated and monitored for other organ involvement. Some patients with IgG4-related disease may develop lymphoma, usually marginal zone lymphoma of mucosa-associated lymphoid tissue type. Treatment of IgG4-ROD includes the use of corticosteroids and other immunosuppressants. Rituximab has been shown to be very effective. Longer term studies on the natural course and treatment of IgG4-ROD are needed.

Conclusions: Patients presenting with orbital inflammatory lesions should have biopsies obtained whenever possible. The examining pathologist should routinely look for features of IgG4-ROD, and if found, the patient should be investigated for other organ involvement. Early treatment may prevent destructive changes in affected tissues.

(*Ophthal Plast Reconstr Surg* 2015;31:167–178)

IgG4-related disease (IgG4-RD) is a recently recognized entity characterized by tumefactive lesions with dense lymphoplasmacytic infiltration, rich in IgG4-positive plasma cells, fibrosis, usually of a storiform pattern, and in some organs, an obliterative phlebitis. Serum IgG4 levels may be elevated or normal. Large numbers of tissue eosinophils may also be seen, as well as elevated numbers of circulating eosinophils. The orbit is a frequently involved site (IgG4-related ophthalmic disease [IgG4-ROD]), and a significant proportion of patients with orbital disease will have disease elsewhere at presentation, or develop it subsequently.

The disease is not "new," but IgG4 was first implicated and recognized by Japanese researchers in 2001, in a group of patients with autoimmune pancreatitis (AIP) with elevated serum IgG4 levels.[1] It was soon recognized that extrapancreatic fibroinflammatory lesions, rich in IgG4+ plasma cells, were common in patients with AIP.[2] Since then, the condition has been described in almost all organs, the commonest being the biliary tree, retroperitoneum, salivary glands, orbit, lymph nodes, kidneys, lungs, meninges, aorta, breast, prostate, thyroid, pericardium, and skin.

The first part of this review (published earlier) summarizes the nomenclature, epidemiology, pathology and pathogenesis, as well as published diagnostic criteria. This second part of the review covers clinical aspects of IgG4-ROD.

OCULAR ADNEXAL IGG4-RD

The pattern of ocular adnexal involvement in pathologically diagnosed IgG4-ROD has been described in a Japanese study detailing 65 cases from 7 institutions.[3] Of the 65 cases, 31 (57.7%) had lacrimal gland lesions alone, and 34 (52.3%) had lesions in other areas, and of these, only 8 (12.3%) did not have any lacrimal gland involvement. Next most common was trigeminal nerve involvement in 25 (38.5%), then extraocular muscle (EOM) involvement in 16 (24.6%), diffuse orbital fat disease in 15 (12.3%), a circumscribed orbital mass lesion in 11 (16.9%), eyelid lesions in 8 (12.3%), and 1 case of nasolacrimal duct disease. Six patients (9.2%) presented with optic nerve compromise and 8 (12.3%) with restriction of ocular motility. Importantly, no patient reported sensory disturbance or pain in the distribution of the affected branches of the trigeminal nerve. All but 2 patients had an elevated serum IgG4 level.

A report from the United States on 21 patients with IgG4-ROD again found the lacrimal gland the most commonly involved site (13/21, 61.9%).[4] Four patients had EOM disease, 6 had orbital soft tissue involvement, and 2 had trigeminal nerve disease. In this group overall, 7 patients (37%) had a normal serum IgG4 level.[4] The relative frequency of involvement of different anatomical sites within the orbit from these 2 large series is summarized in Table.

Commoner patterns of involvement in IgG4-ROD are:

1. Dacryoadenitis (which may be unilateral or bilateral and may be associated with salivary gland enlargement [previously often labeled Mickulicz disease])

Accepted for publication October 23, 2014.

The authors have no financial or conflict of interest to disclose.

Presented in part at the Oculofacial Subspecialty Day of the American Academy of Ophthalmology meeting on November 2013 in New Orleans, LA.

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DOI: 10.1097/IOP.0000000000000364

Frequency of involvement of anatomical sites within the orbit in 2 large series of pathologically verified IgG4-ROD cases

	Bilateral disease	Lacrimal gland	Trigeminal nerve	EOM	Orbital fat	Eyelid	NLD
Sogabe et al.[3](n = 65)	76% (93% of LG)	88%	39%	25%	40%	12%	1.5%
Wallace et a.l[4](n = 21)	71%	62%	9.5%	19%	28.6%	0%	9.5%

EOM, extraocular muscle; NLD, nasolacrimal duct; LG, lacrimal gland.

2. Enlarged orbital nerves (usually the infraorbital) with EOM and lacrimal gland involvement
3. Orbital fat involvement (usually in combination with lacrimal gland and other tissue involvement)
4. Sclerosing orbital inflammation without lacrimal gland involvement (less common).

IgG4-Related Dacryoadenitis. As noted above, lacrimal gland involvement is the commonest manifestation of IgG4-ROD.[3,5–10] It was also one of the earliest reported extrapancreatic sites of IgG4-RD.

An early report described 6 patients with chronic sclerosing dacryoadenitis, 5 of which were bilateral, and 3 of which had salivary gland disease as well.[5] An evolution from predominantly lymphoid hyperplasia to markedly atrophic lacrimal gland with fibrosis was noted in 1 patient who had sequential biopsies. A further case with sequential biopsies has shown progressive fibrosis over time.[11] (This contrasts with the case illustrated in Figures 1 and 2, who had a short history with dense fibrosis on biopsy.) No cases showed obliterative phlebitis. This may be because lacrimal gland biopsies are generally small and the venules in the lacrimal gland are also relatively small.

Soon after, a series of 4 cases of bilateral sclerosing dacryoadenitis, all associated with salivary gland disease, was reported.[12] Three of 4 responded well to oral corticosteroids and the fourth, a diabetic, had the lacrimal glands excised. Other

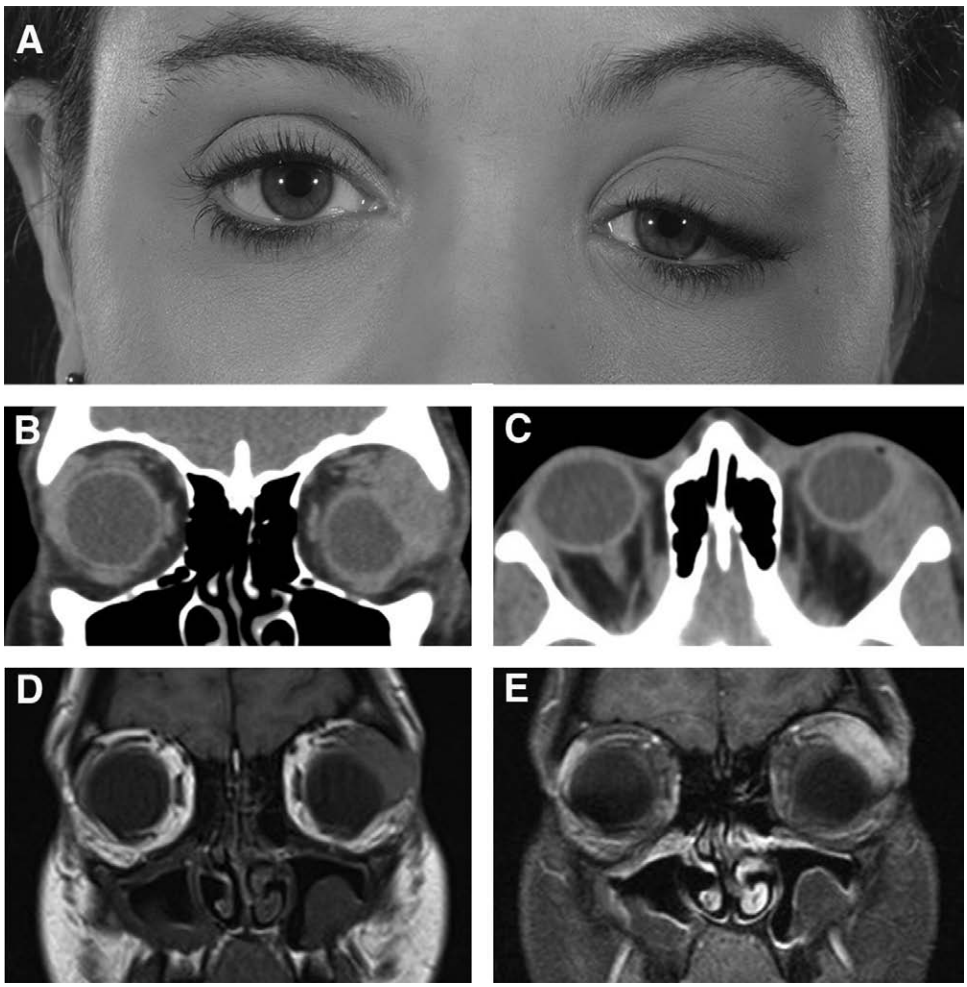

FIG. 1. Case 1. Unilateral sclerosing dacryoadenitis. **A,** A 27-year-old female, otherwise well, presented with 4 weeks increasing left upper eyelid swelling with mild ache, and a hard tender mass in the left lacrimal gland. **B** and **C,** CT scans show a grossly enlarged lacrimal gland with flattening of the globe. **D** and **E,** MRI shows a discrete lacrimal gland lesion, which enhances with gadolinium. CT chest, abdomen, and pelvis were normal. She responded well to a course of oral steroids but was lost to follow up after 6 months.

case reports of sclerosing dacryoadenitis associated with salivary gland disease have appeared.[13,14] An illustrative case is shown in Figure 3.

A larger series of 12 patients with IgG4-related dacryoadenitis found half had bilateral disease.[15] Nine of 14 had other features of IgG4-RD, including sialadenitis in 5, AIP in 4, retroperitoneal fibrosis in 2, and lymphadenopathy in 8. Serum IgG4 levels were significantly higher in those patients with other manifestations of IgG4-RD compared with those with dacryoadenitis alone. Six of the 12 had a history of allergy with an elevated IgE level. Oral corticosteroids were effective in 7 patients, but dacryoadenitis relapsed in 2 patients, both of whom had very high serum IgG4 levels and associated AIP. An example of a patient with bilateral lacrimal gland and orbital soft tissue disease associated with sclerosing cholangitis and rhinosinusitis is illustrated in Figure 4.

Interestingly, there may be reduced tear and saliva production in patients with AIP in the absence of lacrimal or salivary gland enlargement, and this improves after corticosteroid treatment.[16]

Although bilateral dacryoadenitis has been much more commonly reported than unilateral disease, a number of cases of unilateral dacryoadenitis, more often in patients without evidence of disease elsewhere, have been noted. An example is illustrated in Figures 1 and 2.

The consensus statement published by Deshpande et al.[17] sets minimum numbers of IgG4+ plasma cells for various organs, and for lacrimal gland, this was set at >100 per hpf. Andrew et

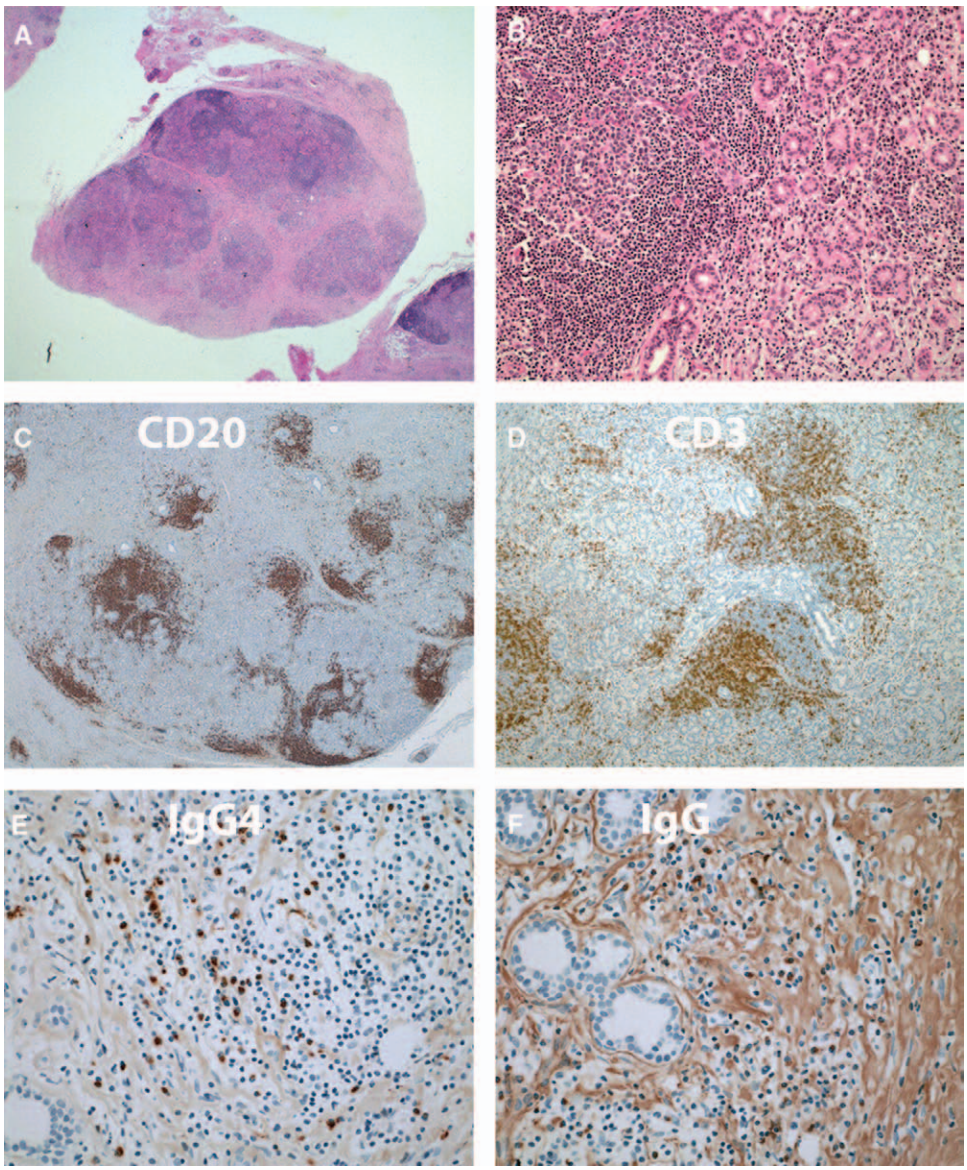

FIG. 2. Case 1. Histopathology. **A,** Biopsy showed a hard, pale mass in the lacrimal gland, which on H and E section on low power showed masses of lymphoplasmacytic infiltrate separated by bands of fibrosis. **B,** On higher power, the lymphoplasmacytic infiltrate also separated portions of relatively normal glandular structures with some reactive follicle formation. **C,** Immunohistochemical staining for CD20+ lymphocytes showed many within areas of lymphoplasmacytic infiltrate and follicle formation. **D,** Immunostaining for CD3, a T-cell marker, shows numerous T-cells. **E,** Immunostaining for IgG4 shows large numbers of IgG4+ plasma cells up to 96 per high power field. **F,** Immunostaining for IgG shows smaller numbers of IgG+ plasma cells (but more diffuse background staining, of no significance) and a ratio of IgG4+/IgG+ plasma cells of 137%. Serum IgG4 levels were normal.

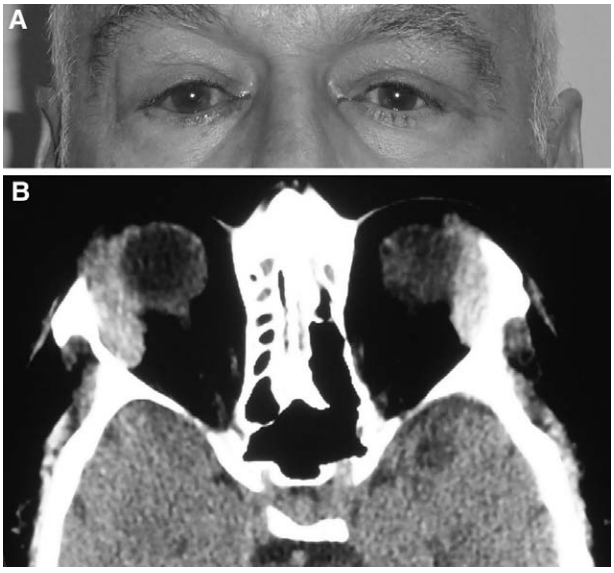

FIG. 3. Case 2. Previously called "Mickulicz disease," bilateral lacrimal and salivary gland disease. **A,** A 58-year-old man presented in late 2012. A year before, an enlarged left submandibular gland was removed and diagnosed as Mickulicz disease. An enlarged right submandibular gland was removed 3 months before presentation. There was a long history of rhinosinusitis, endoscopic sinus surgery a year earlier, and a 3-year history of asthma. For 9 months, he had noted swelling in both upper eyelids and mild ptosis. The lacrimal glands were palpably enlarged and firm, and both parotid glands were enlarged. **B,** An axial CT scan showed bilateral, symmetrically enlarged lacrimal glands. Serum IgG4 levels were markedly elevated at 5.42 g/l ($N < 0.86$ g/l), and he had a mild eosinophilia and ESR of 29. Biopsy of 1 lacrimal gland showed firm, pale tissue, with atrophic gland, dense fibrosis, and reactive lymphoid follicles, 90 IgG4+ plasma cells/hpf, and an IgG4+/IgG+ plasma cell ratio of 150%. Review of the salivary glands showed similar pathology. He was started on 40 mg of prednisolone with a good clinical response, but recurrence of symptoms when reduced below 7.5 mg. Azathioprine was introduced with low dose prednisolone, with a good and well maintained response.

al.[18] used this figure to look at all previously published cases of so-called IgG4-ROD involving the lacrimal gland. Many cases did not specify the number of IgG4+ cells/hpf, but used terms such as "numerous" or "abundant." A third (24/72) had numbers between 10 and 100 per hpf, and 23/72 (32%) had >100 per hpf. All had a ratio of IgG4+/IgG+ plasma cells of >40%. This serves to emphasize the importance of investigators publishing detailed data in reported cases and also emphasizes the need to correlate the pathology, clinical features, and imaging to reach a diagnosis. Many of the cases with numbers of IgG4+ plasma cells between 10 and 100 per hpf had clinical features of other organ involvement such as lacrimal gland disease and lymphadenopathy.

Enlarged Orbital Nerves. One feature of IgG4-ROD that is highly suggestive of the diagnosis is enlargement of 1 or more of the branches of the trigeminal nerve, most commonly the infraorbital nerve (ION). This change is usually seen in combination with disease of the lacrimal glands, EOMs, and adjacent paranasal sinuses, and many of the patients will have a peripheral eosinophilia, a history of rhinosinusitis, and often evidence of other organ involvement.

Probably the earliest report of enlarged IONs in combination with EOM disease was that of Siqueira et al.[19] in 2002.

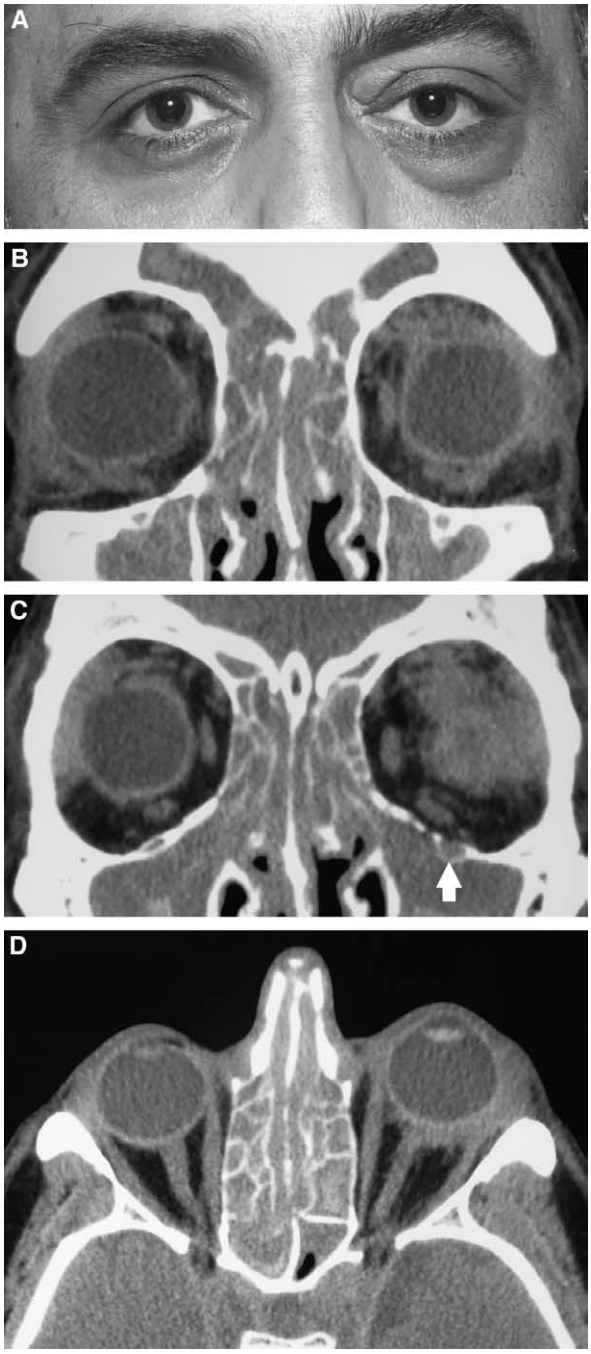

FIG. 4. Case 3. Bilateral, asymmetric lacrimal gland and orbital fat disease, rhinosinusitis, on background of sclerosing cholangitis. **A,** A 41-year-old man presented mid 2009 with 5 months swelling in the left lacrimal gland and chronic rhinosinusitis. He had recently developed grossly deranged liver function tests and was found to have autoimmune sclerosing cholangitis, and grossly elevated serum IgG4 levels of 19.8 g/l ($N < 0.86$ g/l). **B, C,** and **D,** Coronal and axial CT scans show pansinusitis and poorly defined enlarged lacrimal glands with an infiltrative process spilling over into the orbital fat. In (**C**), there is possible enlargement of the infraorbital nerve (*arrow*). Biopsy of the left lacrimal gland showed chronic sclerosing dacryoadenitis with large numbers of IgG4+ plasma cells and a ratio of IgG4+/IgG+ plasma cells of 41%. He was treated with oral steroids, with improvement in his orbital and nasal symptoms and normalization of liver function tests, but relapse on tapering of the oral steroids, treated with Azathioprine and low dose steroids.

These authors described a patient with bilateral ION enlargement with "orbital myositis" and a mixed inflammatory cell infiltrate. It predated knowledge of IgG4-ROD, and immunohistochemistry for IgG4+ plasma cells was not performed.

Very few entities cause enlargement of the ION and its canal, and almost none other than IgG4-ROD will lead to bilateral ION enlargement. Ohshima et al.[20] looked at 71 cases of orbital lymphoproliferative disorders and examined the ION in coronal section in all cases. When the ION was larger than the optic nerve, they defined this as ION enlargement. Among their 71 cases, 16 were of IgG4-ROD. A total of 9 cases were found with ION enlargement, and 8 of these had IgG4-ROD and the ninth had IgG4+ mucosa-associated lymphoid tissue lymphoma. None of the non-IgG4-ROD had ION enlargement.

A further study from Japan looked at 68 patients diagnosed with "IgG4-related Mickulicz disease" and measured the ION diameter in all cases and then compared them to a control group.[21] ION enlargement (defined as greater than 2 standard deviations above the mean of the control group) was found in 20 of 68 patients with IgG4-ROD and no patients in the control group. They also found a significant correlation between ION enlargement and elevated serum IgG4 levels.

A group of 11 patients with AIP has been examined for ION enlargement.[22] The mean thickness of the ION in patients with AIP was 3.8 ± 2.0 mm compared with 2.6 ± 0.5 mm in a control group ($p < 0.05$). In 5 of the 11 AIP patients, the nerve was larger than 5 mm in diameter. Corticosteroid therapy was shown to reduce the thickness of the nerves in 3 treated patients.

The ION may be very large, with bony expansion of the infraorbital canal, and extension into the inferior orbital fissure, and through the foramen rotundum, intracranially. The frontal nerve may also be involved, but less commonly.[23] Clinically, patients with enlarged nerves do not usually have any symptoms other than mass effect. Rare instances of sensory loss have been reported.[24,25]

Nerves other than the ION or frontal nerve may be affected in IgG4-RD. Inoue et al.[26] examined 106 patients with IgG4-RD and found 21 peripheral nerve lesions in 7 patients, most commonly in the orbit, with 9 orbital nerve lesions, and also 4 perioptic nerve lesions. There were also 7 paravertebral nerve lesions and 1 greater auricular nerve lesion.

Histopathologically, affected nerves are found to have masses of lymphocytes, plasma cells, and eosinophils, with large numbers of IgG4+ plasma cells. The nerve fascicles are intact and the disease appears to involve the epineurium principally.[27] Fibrosis is not usually a feature of nerve involvement.

We have seen a number of patients with orbital inflammation and IONs.[28] Of 14 patients (10 male), aged 29 to 76 years (median 49), 12 had bilateral orbital inflammatory disease (86%). The ION enlargement was unilateral in 8 and bilateral in 6, and 4 also had frontal nerve enlargement. One patient also later developed unilateral perioptic nerve disease. No patient had sensory loss. All 14 had enlarged EOMs, 9 (64%) had lacrimal gland enlargement, and all 14 had a history of rhinosinusitis, with 5 having had sinus surgery. (Fig. 5) Regional lymphadenopathy was present in 7 (50%). Eight of 14 had peripheral eosinophilia. When IgG4 serum levels were tested, they were elevated in 6 of 7 cases, and 7 of 13 fulfilled the current criteria for the number and ratio of IgG4+ plasma cells. When nerve biopsies were obtained, they always showed "reactive lymphoid hyperplasia" usually with large numbers of IgG4+ plasma cells.

In this series, a number of patients had been observed over very long periods, usually with the diagnosis of IgG4-ROD

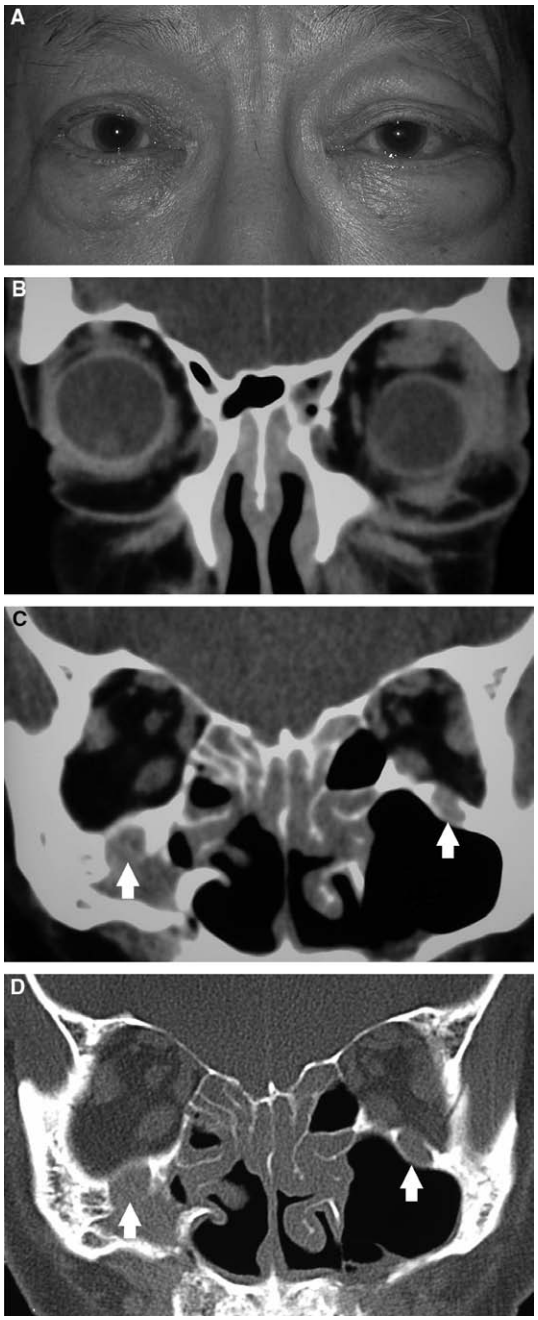

FIG. 5. Case 4. Lacrimal gland swelling, cervical lymphadenopathy, asthma, chronic rhinosinusitis, enlarged infraorbital nerves, developed diffuse large B-cell lymphoma and died from lymphoma. **A,** A 51-year-old man first presented in 1991 with a year of left lacrimal gland swelling, cervical lymphadenopathy, asthma and chronic sinusitis, and an urticarial rash. He had been labeled as Sjögren disease but had negative serology. Biopsy of the left lacrimal gland was diagnosed as reactive lymphoid hyperplasia. He responded well to oral steroids and chlorambucil. **B, C,** and **D,** CT scans showed lacrimal gland disease with some mild enlargement of some EOMs, rhinosinusitis and changes from previous sinus surgery, and grossly enlarged infraorbital nerves and canals on each side (*arrows*). He returned in 2008 with increasing bilateral proptosis. He was rebiopsied and found to have large numbers of IgG4+ plasma cells. He was treated with oral prednisolone and methotrexate with a good response. Two years later, he developed diffuse large B-cell lymphoma, initially arising in lymph nodes, and died from his disease 18 months later.

being made much later. Some patients evolved from a pattern of bilateral enlarged lacrimal glands, usually with symmetrical salivary gland enlargement (previously called Mickulicz disease) to later enlargement of EOMs and enlarged IONs. An illustrative case is shown in Figure 6.

EOM Enlargement. As noted above, EOM enlargement is common in IgG4-ROD, especially in those patients with enlarged orbital nerves. (see Fig. 6) There may be a single muscle involved, or more commonly multiple muscles. Wallace et al.[4] found 4 of 27 (14.8%) patients with IgG4-ROD had EOM enlargement, and all these had other orbital structures involved. Sogabe et al.[3] found 16 of 65 (24.6%) patients with IgG4-ROD had EOM enlargement. Only 1 of these 16 patients had a single muscle enlarged. The order of frequency of EOM enlargement was inferior rectus, followed by superior rectus–levator complex, lateral rectus, medial rectus, inferior oblique, and superior oblique, a pattern similar, but not identical to, Graves orbitopathy. The nature of the strabismus seen in patients with IgG4-ROD differs from that seen in Graves orbitopathy, with IgG4-ROD patients having a lesser degree of restrictive strabismus despite often very large muscles.

The EOM enlargement commonly seen in association with enlarged orbital nerves in patients with IgG4-ROD has rarely been examined histopathologically. The case reported by Siqueira et al.,[19] which predated knowledge of IgG4-ROD, and did not have immunohistochemistry performed for IgG4+ plasma cells, but had many features of IgG4-ROD, did have a biopsy of the inferior oblique muscle, and this showed a mixed and dense inflammatory cell infiltrate of polyclonal B- and T-cells with some fibrosis.

Sclerosing Orbital Inflammation. A proportion of patients with sclerosing orbital inflammation affecting tissues other than the lacrimal gland will have IgG4-ROD. Winn and Rootman[29] reported 13 cases of sclerosing orbital inflammation and found 2 with multifocal fibrosclerosis, which is considered part of the IgG4-RD spectrum. Both of these patients had bilateral orbital disease. These authors reviewed 68 case reports of sclerosing orbital inflammation, none from large series, and found 34 (50%) had features of multifocal fibrosclerosis. Of the cases with multifocal fibrosclerosis, 69% had bilateral orbital disease, whereas only 3.6% (2 cases) without systemic disease had bilateral orbital disease. It would seem therefore that a large proportion of patients with bilateral sclerosing orbital inflammation will have what has been called multifocal fibrosclerosis and what is now known to be IgG4-RD.

Eosinophilic angiocentric fibrosis has now also been shown to be part of the IgG4-RD spectrum.[30] Eosinophilic angiocentric fibrosis has typically affected the nasal cavity and adjacent paranasal sinuses, but cases of eosinophilic angiocentric fibrosis affecting the adjacent lacrimal drainage apparatus and the orbit have been reported.[31–33] An illustrative case is shown in Figure 7.

Other Orbital and Ocular Adnexal IgG4-RD Manifestations. IgG4-related disease of the lacrimal drainage apparatus has been reported in a small number of cases. Unilateral and bilateral lacrimal sac disease have been described.[34,35] Ginat et al.[36] described the imaging features in 9 patients with IgG4-ROD and 2 of these had lacrimal sac disease. Wallace et al. found 2 patients with lacrimal drainage apparatus disease among 27 with IgG-ROD. Both had multiorgan disease.[4] A case of lacrimal sac diverticulitis due to IgG4-RD has also been reported.[37]

Scleral and conjunctival IgG4-RD has also rarely been reported.[4,38–40] Two of 4 cases had a mild nongranulomatous anterior uveitis and 1 had conjunctival involvement, which has not previously been reported in IgG4-RD.[38]

An intriguing group of publications has reported raised numbers of IgG4+ plasma cells in patients with xanthogranulomatous disease of the orbit and ocular adnexa.[4,41–44] Verdijk et al.[44] reexamined 16 cases of ocular adnexal xanthogranulomatous disease seen over a 25-year period, and 8 of 16 (50%) showed >50 IgG4+ plasma cells/hpf and a ratio of IgG4+/IgG+ plasma cells >40%. Two of these 8 patients had signs of systemic disease, with lymphadenopathy and salivary gland enlargement. None of the 8 patients with features of IgG4-RD had Erdheim–Chester disease (ECD), and the 2 patients of the 16 in this series with ECD had normal levels of IgG4 and no increase in IgG4+ plasma cells on biopsy.

Erdheim–Chester disease, one of the subtypes of ocular adnexal xanthogranulomatous disease, is known to develop lesions in the retroperitoneum and many other tissues often affected by IgG4-RD, and also develops bone lesions that is not a feature of IgG4-RD. In addition, ECD has been recognized to be associated with the BRAF V600E mutation, a protooncogene, and successful therapy with vemurafenib, a BRAF enzyme inhibitor.[45] This suggests that in ECD at least, the pathogenesis is quite different to IgG4-RD.

Mudhar et al.[41] reported xanthogranulomatous ocular adnexal disease in a patient with a prominent population of IgG4+ plasma cells (80% IgG4+). Singh et al.[43] described 2 patients with necrobiotic xanthogranuloma with features of systemic IgG4-RD in 1 (AIP, sclerosing cholangitis), and markedly elevated numbers of IgG4+ plasma cells (119 per hpf, and a ratio of 55% IgG4+/IgG+ plasma cells), as well as a markedly elevated serum IgG4. Their second patient had "dramatically elevated numbers of IgG4+ plasma cells." A case of adult-onset asthma and periocular xanthogranulomas has also been reported in association with lymphoplasmacytic sclerosing pancreatitis.[42] We have also seen a patient with IgG4-related AIP of longstanding who also had bilateral orbital disease, which on biopsy showed definite features of necrobiotic xanthogranuloma, who has responded well to low dose oral steroids.

What the exact relationship between IgG4-RD and ocular adnexal xanthogranulomatous disease is remains to be elucidated. One further feature common to both is the dramatic response to Rituximab.[46–48] It should be noted that a number of other pathologic entities have large numbers of IgG4+ plasma cells found on biopsy, and ocular adnexal xanthogranulomatous disease is probably just another of these. It certainly has very distinct pathologic findings not found in IgG4-RD.

Mehta et al. have reported a case of a fibroinflammatory disease of the face, eyelids, and periorbita, as well as bone erosion of the sphenoid, with 55 IgG4+ plasma cells/hpf in tissue samples. These authors did not give an IgG4+/IgG+ plasma cell ratio and there were no systemic features of IgG4-RD and the diagnosis of IgG4-RD is uncertain.[49] It should be noted that bone erosion is otherwise not usually seen in IgG4-ROD, although bone remodeling as seen with enlargement of the ION and the infraorbital canal is commonly seen. Bone erosion is a more common feature of GPA (Granulomatosis with polyangiitis, or Wegener granulomatosis).[50]

STAGING OF IGG4-RD

If a patient presents to an ophthalmologist and is diagnosed with IgG4-ROD on the basis of clinical examination,

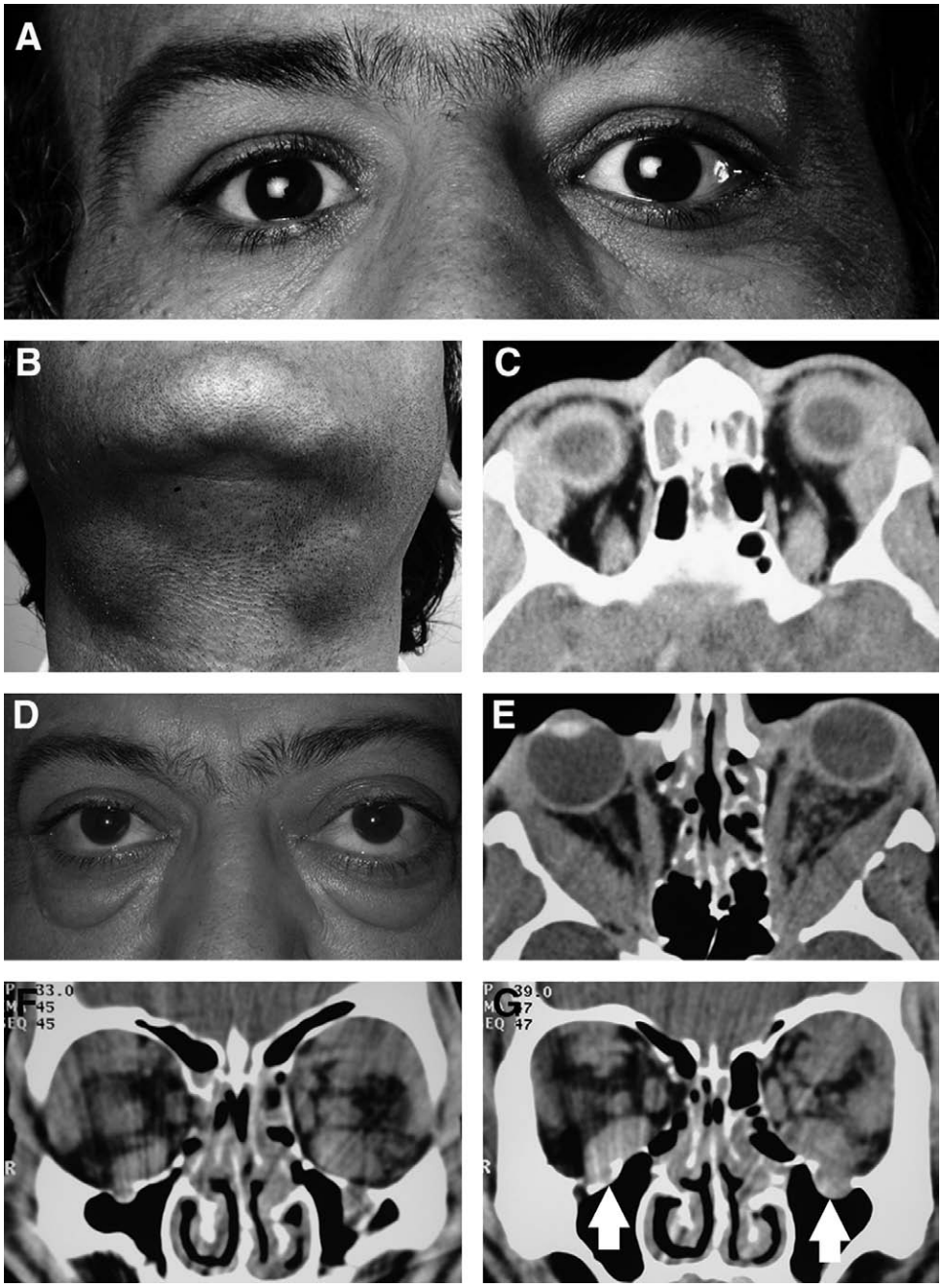

FIG. 6. Case 5. Initial presentation with "Mickulicz disease" pattern and evolved into extraocular muscle disease, enlarged infraorbital nerves, sinus disease. **A** and **B,** A 37-year-old man presented in 1991 with bilateral lacrimal and submandibular gland enlargement. **C,** An axial CT scan showed the enlarged lacrimal glands which on biopsy were reported to show reactive lymphoid hyperplasia. He responded to a short course of oral steroids and was lost to follow up. **D,** He returned in 2001 with 2 to 3 years increasing bilateral proptosis and eyelid swelling. **E, F,** and **G,** CT scans now showed enlarged extraocular muscles, disease in the lacrimal glands and superior orbits, and definite enlargement of the infraorbital nerves and canals (*arrows*). Biopsies from the orbit showed reactive lymphoid hyperplasia again. He responded to oral steroids, but moved overseas and was again lost to follow up. These biopsies were reviewed in 2007 and he had IgG4+ plasma cells of 150 per hpf and an IgG4+/IgG+ plasma cell ratio of 300%.

imaging, and histopathology, the question arises as to whether the patient should be examined for other organ involvement, and if so, what is the best method of looking for disease elsewhere.

It has been shown that about half the patients presenting with IgG4-ROD will have disease in other organs. The first step is to arrange for a physician such as a rheumatologist with an interest in the disease to clinically assess the patient. Salivary gland enlargement and lymphadenopathy should be clinically detectable in most instances. Lung disease may occur in IgG4-RD, and symptomatology may be mild.[51] Liver and renal function should be biochemically assessed. AIP can lead to bile duct stenosis or obstruction with abnormal liver function. Retroperitoneal fibrosis can lead to ureteric obstruction and hydronephrosis. In addition, IgG4-RD can lead to

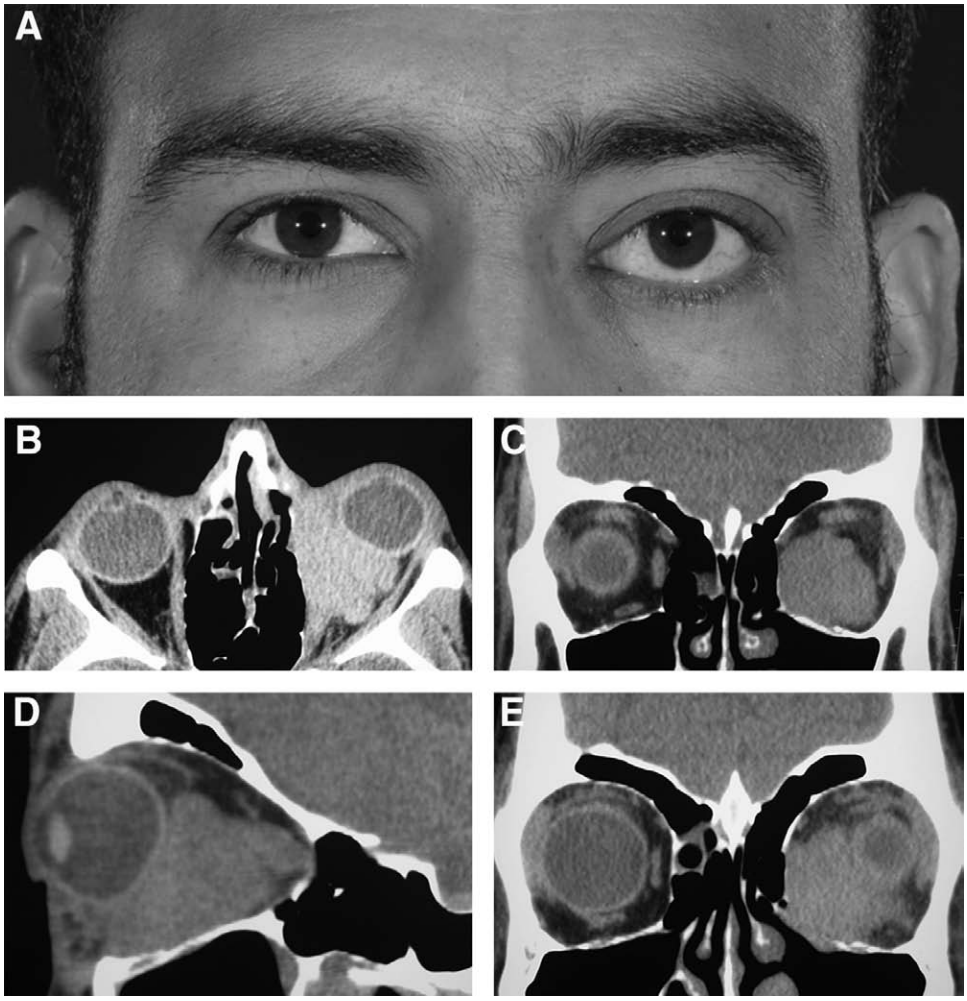

FIG. 7. Case 6. Sclerosing orbital, lacrimal system and nasal disease, formerly known as eosinophilic angiocentric fibrosis. **A,** A 25-year-old man presented in 2008 with 6 months left epiphora and proptosis, with a lacrimal mucocele. There was a hard inferomedial orbital mass. **B, C, D,** and **E,** CT scans showed a large dense mass involving the inferomedial orbit compressing and displacing the globe. A biopsy diagnosed eosinophilic angiocentric fibrosis (an image of this can be seen in Part 1 of this review). He then underwent a DCR with repeat biopsy of the orbit and thickened nasal mucosa. There was dense fibrosis with large numbers of IgG4+ plasma cells and a mild increase in serum IgG4. He was commenced on oral steroids and methotrexate with stabilization of disease. Rituximab is being considered if his disease worsens.

tubulointerstitial nephritis[51,52] and IgG4-RD can also affect the prostate gland, mimicking benign prostatic hypertrophy. Serum IgG4 levels should be obtained, even though normal levels do not exclude the diagnosis, and IgG4 levels may be high in other diseases. Serum IgG4 levels may add weight to the diagnosis and may be a means of following response to treatment.

The simplest and most readily available form of imaging is CT scanning. A CT scan of the head and neck, chest, abdomen, and pelvis should show any mass lesions, including features of retroperitoneal obstruction and hydronephrosis. MRI can provide similar information with more detailed soft-tissue features.

Whole-body fluorodeoxyglucose (FDG) PET/CT is probably the most useful modality for staging IgG4-RD.[53–57] This has most usually been in the setting of patients with AIP, looking for extrapancreatic lesions, but is equally useful in patients with IgG4-ROD, when looking for other organ involvement. FDG-PET/CT has also been shown to be more sensitive in detecting disease in arteries, salivary glands, and lymph nodes compared with other imaging modalities.[56] FDG-PET and PET/CT has also been shown to be useful in assessing response to corticosteroid treatment.[53–56]

A case where FDG-PET/CT was useful in staging IgG4-RD and assessing response to treatment is illustrated in Figure 8.

IMAGING

MRI features of 15 patients with IgG4-RD of the head and neck have been reported.[23] Eight had bilateral lacrimal gland enlargement, 5 had other areas of the orbit affected, and 5 had orbital nerve enlargement (4 ION, 1 frontal nerve). The lacrimal gland lesions showed a homogeneous signal on T1- and T2-weighted images, with homogeneous gadolinium enhancement, without any adjacent bone destruction or enhancement.

Ginat et al.[36] described the radiographic patterns of IgG4-ROD in 9 patients. Patterns of involvement included lacrimal gland enlargement in 5 (bilateral in 4), EOM thickening in 4, orbital fat involvement in 5, neural involvement in 3, and lacrimal sac and duct involvement in 2. All had CT, and 4 had MRI.

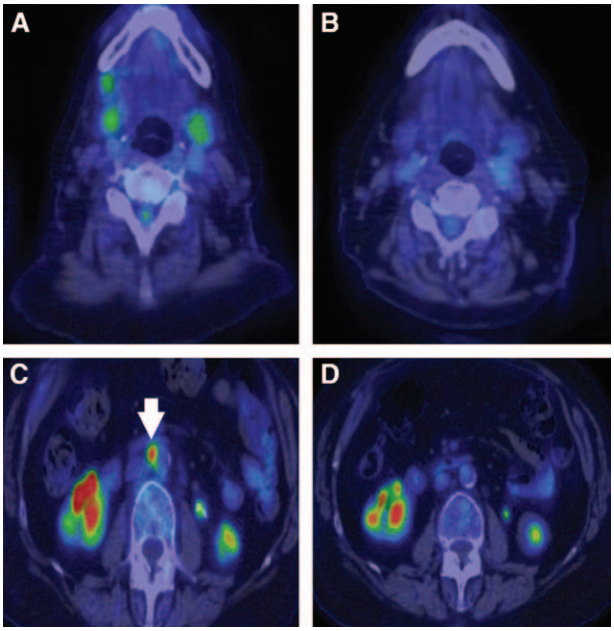

FIG. 8. Case 7. FDG-PET/CT Images in IgG4-RD. An 80-year-old woman with diagnosed IgG4-RD (orbital, paranasal sinuses, and lymph nodes) responded well to oral steroids and methotrexate, but developed severe back pain when the methotrexate was ceased. She had developed left ureteric obstruction due to retroperitoneal and pelvic IgG4-RD, but a FDG-PET/CT also showed disease in cervical lymph nodes (**A**) and the thoracic and abdominal aorta (**C**). Azathioprine was added to her low dose oral prednisolone and the FDG-avid disease resolved (**B** and **D**)

Song et al.[58] reported CT and MRI findings in18 patients with ocular adnexal IgG4-RD. Sixteen of 18 had lacrimal gland disease, 2 had extraconal lesions, and 1 had bilateral enlargement of the ION and frontal nerves. All lesions were well defined, and showed isointensity on T1-weighted images and hypointensity on T2-weighted lesions, which were all homogeneous. There was some bone remodeling but no bone destruction. Pterygopalatine fossa and cavernous sinus disease was also seen in 1 case.

As noted in the section on staging of IgG4-RD, whole-body FDG-PET/CT is a good means of showing areas of disease activity and also the response to treatment, and has been shown to be more sensitive than other imaging modalities for some organs, particularly arteries, lymph nodes, and salivary glands.[56] There is currently no clear guidance as to how frequently FDG-PET/CT scanning should be performed, and each case should be managed individually.

LYMPHOMA AND IGG4-RD

A small number of cases of lymphoma arising in patients with IgG4-ROD have been described, and it seems likely that IgG4-RD, like a number of other chronic inflammatory disorders, increases the risk of development of lymphoma.

Cheuk et al.[59] described 3 cases of ocular adnexal lymphoma arising in patients with IgG4+ sclerosing dacryoadenitis. Two of these were marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue type (extranodal marginal zone lymphoma [EMZL]), and 1 was follicular lymphoma. They also described 3 additional cases of ocular adnexal EMZL, which were distinctive in that the neoplastic cells expressed IgG4. It was unclear whether these cases had arisen de novo or within already established IgG4-ROD. Further cases of ocular adnexal EMZL have been described,[60,61] but in most instances, lymphoma occurring in association with IgG-ROD has not had IgG4-producing neoplastic cells.

Sato et al.[62] described 2 of 17 patients with ocular adnexal IgG4-RD with immunoglobulin heavy chain rearrangement that were diagnosed with EMZL. Kubota et al.[63] found 1 of 10 patients with IgG4-related ocular adnexal disease had B-cell clonality. A study of 14 cases of ocular adnexal IgG4-RD found 2 with monoclonal B-cell proliferations, 1 of which had features of EMZL.[7]

A case of EMZL occurring in the setting of IgG4-ROD has described different densities on MRI of the inflammatory lesion and the EMZL, with the EMZL showing greater density (higher signal).[64] The authors suggested taking representative biopsies from areas with different signal characteristics to avoid missing a diagnosis of EMZL.

A study of 111 patients with IgG4-RD (101 of whom had AIP) found 3 developed non-Hodgkin lymphoma 3 to 5 years after the diagnosis of IgG4-RD, suggesting an increased risk of non-Hodgkin lymphoma in these patients.[65]

Malignancies other than lymphoma may also be commoner in IgG4-RD patients. A study of 106 Japanese patients with IgG4-RD found 11 developed malignancies in the follow-up period of 3.1 years, which was a standardized incidence ratio higher than the general population. The malignancies included lung cancer, colon cancer, and also lymphoma.[66]

Our own experience has mirrored that reported above. We have seen 4 patients with EMZL arising in patients with IgG4-ROD (Figs. 9 and 10). In 2, the lymphoma developed after previously diagnosed IgG4-ROD, and the other 2 had concurrent EMZL at the time of diagnosis of IgG4-ROD. One patient developed diffuse large B-cell lymphoma, which developed 20 years after initial presentation with lacrimal gland disease. (Fig. 5)

TREATMENT

Treatment of IgG4-RD has been reported in small numbers of cases in retrospective series, and there are no prospective long-term studies looking at response to treatment. Against this background is the fact that spontaneous improvement has been reported in a proportion of patients with AIP and in IgG4-RD of other organ systems, including the orbit.[62,67] Many of these may relapse in time, but clear data are lacking on this.

Another consideration in the decision to treat IgG4-RD is the risk of not treating. With IgG4-ROD, irreversible damage may occur in the affected lacrimal glands leading to lifelong dry eye problems. Mass effect from IgG4-RD affected orbital tissues may lead to visual loss,[68,69] which in some cases has been irreversible. In other organ systems, irreversible damage may also occur, such as liver cirrhosis and portal hypertension, retroperitoneal fibrosis with obstructive nephropathy and renal impairment, aortic aneurysm and dissection. The risk of developing lymphoma is small and there is no data on whether treatment influences this risk.

Corticosteroids have been the mainstay of treatment. The response is often excellent, but relapse is common.[70] Japanese researchers have published a consensus on corticosteroid treatment of AIP and recommend commencing treatment at 0.6 mg/kg/day, tapering 5 mg every 1 to 2 weeks.[71] IgG4-related pancreatitis however has a high relapse rate once steroids are stopped and there is evidence that a low maintenance dose of 5 mg/day reduces this relapse rate significantly.[71,72]

A report from the Mayo Clinic has recommended a starting dose of 40 mg/day for 4 weeks, tapering by 5 mg/week, with the course complete after 11 weeks. On this

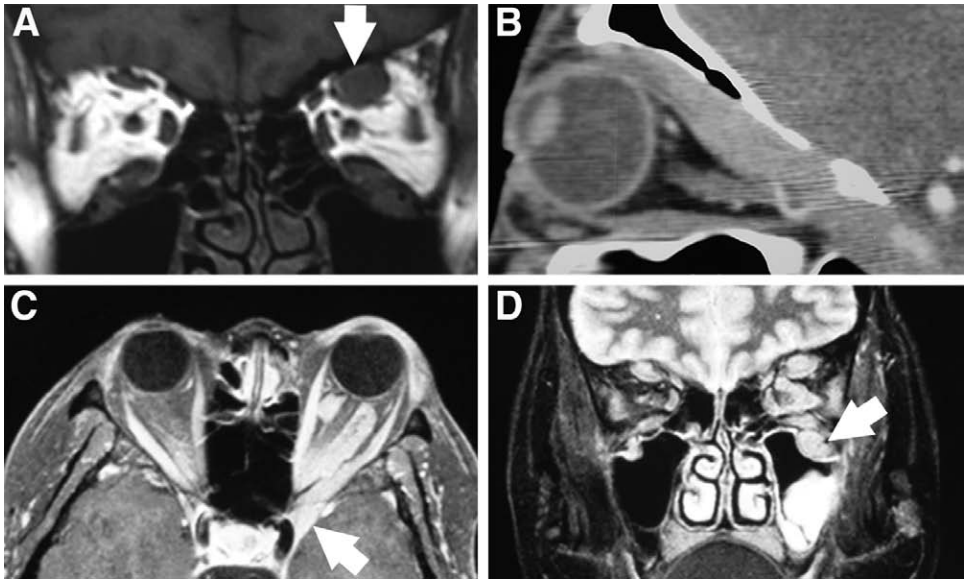

FIG. 9. Case 8. Enlarged lacrimal glands and frontal and infraorbital nerves, cervical lymphadenopathy, enlarged parotid glands and submandibular glands, primary biliary cirrhosis, developed left perioptic nerve disease, which on rebiopsy was found to be marginal zone lymphoma of mucosal-associated lymphoid tissue type. **A,** A 52-year-old woman presented in 2008 with a 1 year history of bilateral lacrimal gland enlargement, cervical lymphadenopathy, and salivary gland enlargement. She had a history of primary biliary cirrhosis, and atypical "Sjögren syndrome" with negative serology. MRI scans showed an enlarged left frontal nerve (*arrow*). **B,** A sagittal CT scan showed the frontal nerve enlargement extending through the superior orbital fissure into the cavernous sinus. The left lacrimal gland and frontal nerve were biopsied. They showed reactive lymphoid hyperplasia with large numbers of IgG4+ plasma cells, and a ratio of IgG4+/IgG+ plasma cells of 80%, and a markedly elevated serum IgG4 level. She was treated with low dose prednisolone and hydroxychloroquine by her rheumatologist with minimal response. **C,** Two years later, she developed worsening vision in the left eye and a repeat MRI showed disease surrounding the optic nerve, and also extending through the superior orbital fissure into the cavernous sinus (*arrow*). **D,** A coronal MRI showed definite enlargement of the left more than right frontal nerves, and the left infraorbital nerve and canal (*arrow*). A rebiopsy showed transformation to marginal zone lymphoma of mucosal-associated lymphoid tissue type. She was treated with low dose orbital irradiation with improvement in vision and proptosis and significant reduction in tumor bulk.

regimen, relapse occurs in over 50% of AIP patients, and at this institution, this is the trigger to move to other nonsteroid immunosuppressants.[73]

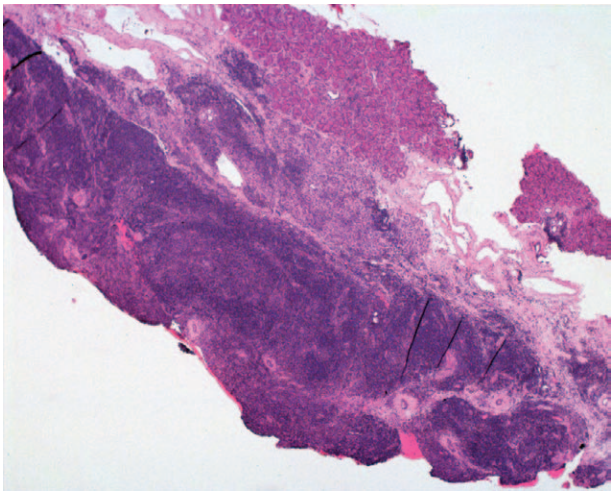

FIG. 10. Low power view of lacrimal gland with marginal zone lymphoma developing in IgG4-related disease. At the top of the field is the relatively normal lacrimal gland, in the center is the IgG4-related plasmacytic infiltrates, and at the bottom the dense diffuse infiltration of small lymphocytes and plasma cells of marginal zone lymphoma. Hematoxylin and eosin ×40 magnification.

Intravenous steroid pulse therapy has been compared with oral steroids in a small Japanese study of 21 patients with AIP, and those receiving pulsed IV steroids (11 cases) showed a more dramatic response to treatment, but with a short follow up.[74]

Serum IgG4 levels may fall with treatment of IgG4-RD, but this is variable, and not all patients' serum IgG4 levels will return to normal with treatment.[71] The same study also showed that elevations of serum IgG4 after treatment may correspond to disease relapse, but not universally. Those with higher levels of serum IgG4 levels after treatment were more at risk of disease relapse also.

Other immunosuppressants have been used in the treatment of IgG4-RD. These include azathioprine, methotrexate, and mycophenolate.[62,70] These are often used after clinical relapse on tapering or stopping corticosteroids. There is limited published data on their use.

Perhaps the most dramatic clinical responses reported with treatment of IgG4-RD have been with the anti-CD20 monoclonal antibody Rituximab.[47,48] Nine of 10 patients treated with Rituximab for systemic IgG4-RD responded dramatically within 1 month of commencement of treatment. Five of these patients had orbital disease as part of their IgG4-RD. Two patients had disease relapse when their B-cells recovered after 6 months, and responded well to a repeat course of Rituximab.[48] Therapeutic responses were matched by dramatic falls in serum IgG4 levels in this and a smaller, earlier study.[47] Single case reports of IgG4-ROD responding well to Rituximab have also been published.[75,76]

Radiotherapy in low dose has been reported in the treatment of IgG4-ROD in a small number of cases.[7,62,63,77]

Response has been variable. The rationale for treatment of IgG4-RD with low dose radiotherapy is the observed response seen in patients with reactive lymphoid lesions and low-grade lymphoma in the orbit.

There is currently no current agreement on defining response to treatment, and different endpoints have been used in different studies. Carruthers et al.[78] have proposed a standardized IgG4-RD responder index to help researchers compare results and outcomes of treatment.

CONCLUSIONS

IgG4-related disease has protean manifestations and is responsible for a significant proportion of orbital inflammatory disease, which was previously labeled idiopathic orbital inflammation or reactive lymphoid hyperplasia. The role of IgG4 or IgG4+ plasma cells in the disease process remains unclear. Orbital and ocular adnexal involvement is relatively common, and may precede, occur at the same time, or follow the development of IgG4-RD elsewhere, and the orbital disease may evolve over time. Diagnosis depends on finding appropriate features on tissue biopsy, and correlating these with clinical assessment, serum IgG4 levels, and imaging. Treatment is usually initially with corticosteroids, but relapse is common on ceasing or tapering treatment, and other immunosuppressants have a role in these patients. Rituximab shows promise as an effective therapeutic agent. There is an increased risk of the development of lymphoma, usually of low grade.

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