# Ophthalmology

# 12

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## 12.1 Introductory Remarks

Mikulicz's disease, which is characterized by symmetrical swelling of the lacrimal and salivary glands, is a representative IgG4-related disease (IgG4-RD), for which the initial patient sketched in the "portrait of a farmer" by Mikulicz in his original publication has subsequently served as a virtual advertising poster for this disease. Because lacrimal glands are relatively easy to biopsy, basic research and pathological and clinical studies on IgG4-RD in the ophthalmic region have focused to a large extent on lesions in these organs. Recently, however, a growing understanding has developed of the frequency with which IgG4-RD involves not only the lacrimal gland but also other ocular adnexa such as the extraocular muscles and orbital nerves. Lacrimal gland lesions are described in detail in other chapters of this book. We therefore concentrate on orbital lesions other than the lacrimal gland.

Manifestations of IgG4-RD in the ophthalmic region are recognized with a frequency that is now surprising, given that IgG4-RD was identified as a distinct disease entity only within the past decade. In our collective experience, IgG4-RD appears to account for approximately 25 % of cases in which patients present with proptosis, eyelid swelling, and other features of orbital inflammation.

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## 12.2 IgG4-RD in Orbital Inflammatory Disease

The most prominent pathological feature in IgG4-RD is lymphoplasmacytic cell infiltration. The differential diagnosis of orbital inflammatory and lymphoproliferative lesions includes malignant lymphoma, "reactive lymphoid hyperplasia," "idiopathic orbital inflammation," and "orbital pseudotumor." Inflammatory and lymphoproliferative conditions comprise the largest group of mass-forming diseases in the orbit and account for more than 40 % of such lesions in Japan [1, 2]. Data available from the United States suggest a somewhat lower percentage, but the figure is still on the order of 20 % [3–5].

The most common lymphomas among the lymphoproliferative disorders that affect the orbit are MALT lymphomas (i.e., extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue), diffuse large B-cell lymphomas (DLBCL), and follicular lymphomas [4]. These low- and medium-grade tumors originate in the ophthalmic region and tend to preserve the shape of the eyeball and orbital bones, demonstrating a predilection for infiltrating the gaps between them (Fig. 12.1d, e).

Computed tomographic (CT) and magnetic resonance imaging (MRI) studies in orbital lymphoma typically demonstrate an absence of globe compression and bone destruction. The absence of destructive lesions facilitates differentiation of lymphomas from the other common orbital tumors such as pleomorphic adenoma (Fig. 12.1a), lacrimal gland cancer (Fig. 12.1b), and hemangioma (Fig. 12.1c). In contrast, the differentiation between lymphomas and nontumorous lesions diagnostic imaging is sometimes difficult (Fig. 12.1d–f), and histopathological confirmation of the diagnosis, often aided by gene rearrangement studies, is essential.

A breakdown of the orbital inflammatory and lymphoproliferative disorders seen at the authors' institutions is shown in Fig. 12.2. IgG4-RD accounts for approximately

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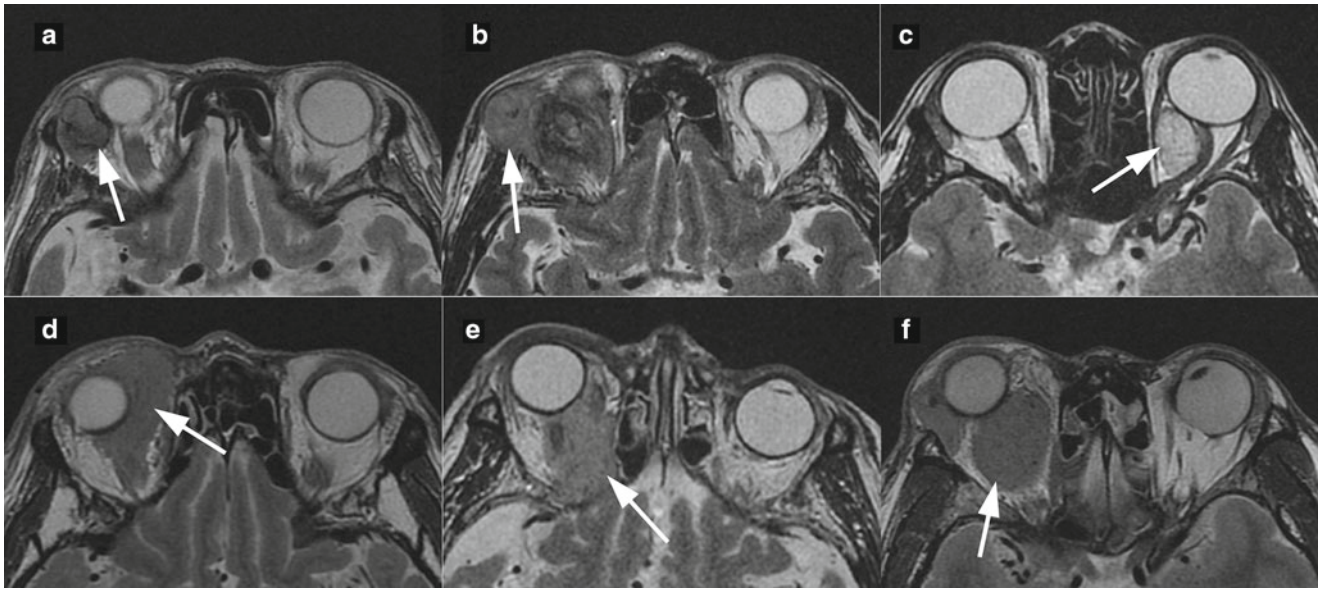


**Fig. 12.1** Representative orbital tumor and lymphoproliferative disorders. (**a**) Right lacrimal gland pleomorphic adenoma (81-year-old man). The tumor is clearly demarcated and spherical and strongly compresses the eyeball. (**b**) Right lacrimal gland adenoid cystic carcinoma (60-year-old man). Destruction of the lateral wall of the orbit (zygomatic bone) is seen. (**c**) Cavernous hemangioma (38-year-old woman). The tumor is spherical and occurs preferentially in the muscle cone. The diagnosis is relatively easy to establish from the pattern of enhancement. (**d**) Right orbital MALT lymphoma (77-year-old man). The tumor infiltrates the eyeball as if encircling it. (**e**) Right DLBCL (85-year-old man). The tumor infiltrates up to the orbital apex in the muscle cone. (**f**) IgG4-related orbital lesions (44-year-old man). Right lacrimal gland swelling and a mass in the muscle cone are seen

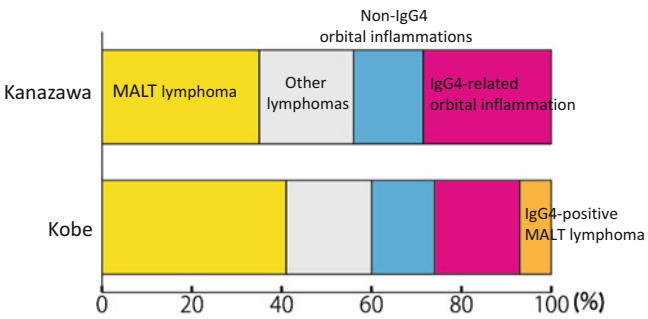


**Fig. 12.2** IgG4-related disease as a percentage of orbital inflammatory and lymphoproliferative disorders. Breakdown of pathologically diagnosed orbital lymphoproliferative disorders cases at the authors' institutions. At Kanazawa University, there were 71 cases from November 2005 to November 2011, and at Kobe University and Kobe Kaisei Hospital, 58 cases from March 2008 to June 2011

one quarter of the total. In general, serum IgG4 values are low and tissue immunostaining for IgG4 is negative in MALT lymphoma. However, prominent IgG4 staining has been reported in some cases of MALT lymphoma (Fig. 12.2). In addition, both the development of malignant lymphoma against a background of IgG4-related dacryoadenitis [6–8] and IgG4-producing MALT lymphomas [9] have also been described.

## 12.3 Diversity of IgG4-Related Lesions in the Ophthalmic Region

A pivotal event in the elaboration of the IgG4-RD concept was the discovery that serum IgG4 values are elevated in autoimmune pancreatitis. Subsequently, Mikulicz's disease was reported to be IgG4-related [10, 11], prompting attention to be focused on systemic IgG4-related lesions in other organs. We focus the majority of our attention on IgG4-related involvement of orbital structures other than the lacrimal gland.

### 12.3.1 Extraocular Myositis

Extraocular muscle swelling is one of the most common IgG4-related orbital lesions after dacryoadenitis [12, 13]. Figure 12.3 illustrates representative cases of IgG4-related extraocular myositis. Swelling is seen in the superior, inferior, medial, and lateral rectus muscles and in the inferior oblique muscle (Fig. 12.3a–d). The pathology findings in the extraocular muscle are similar to those of IgG4-related dacryoadenitis, i.e., an IgG4-positive lymphoplasmacytic infiltrate associated with follicle formation and fibrosclerosis (Fig. 12.3e, f). The frequency of IgG4 extraocular

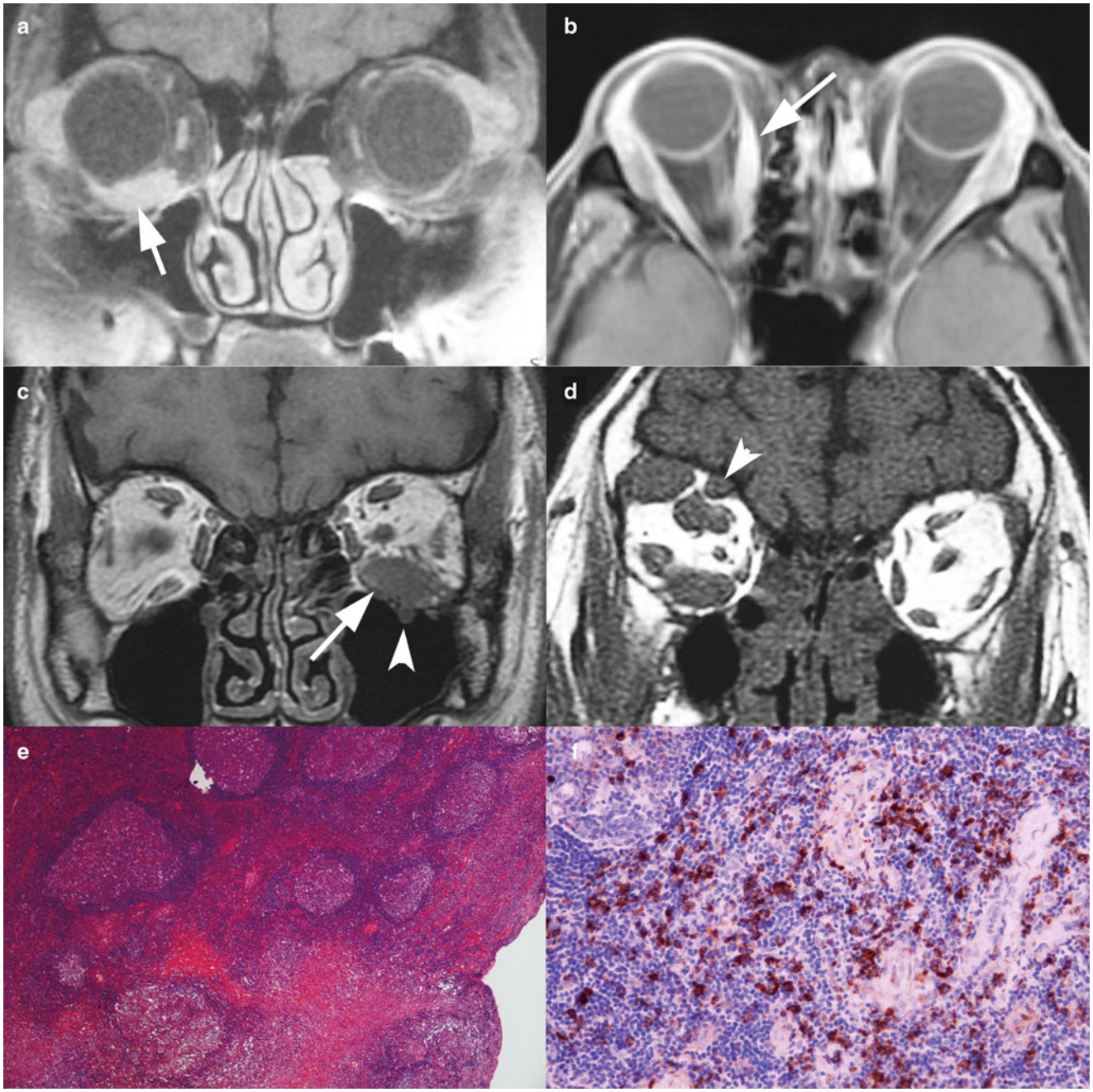


**Fig. 12.3** MRI and pathological findings of IgG4-related extraocular myositis. (**a**) A 46-year-old woman. Serum IgG4 value 209 mg/dL. In addition to bilateral lacrimal gland swelling, right inferior oblique muscle swelling (*arrow*) is seen. (**b**) A 45-year-old man. Serum IgG4 value 914 mg/dL. In addition to bilateral lacrimal gland swelling, right medial rectus muscle swelling (*arrow*) is seen. (**c**) A 65-year-old man. Serum IgG4 value 404 mg/dL. Left inferior rectus muscle swelling (*arrow*) and lesions around the infraorbital nerve (*arrowhead*) are seen. (**d**) A 74-year-old woman. Serum IgG4 was not measured, (**e**, **f**) but IgG4-related lesions were diagnosed pathologically. Right lacrimal gland and right superior and inferior lateral rectus muscle swelling and right supraorbital nerve enlargement (*arrowhead*) are seen. (**e**) Pathological picture of H-E staining in case (**d**). Lymphoplasmacytic infiltration with follicle formation and fibrosis is seen. (**f**) IgG4 staining picture in case (**d**). Numerous IgG4-positive cells are seen

myositis among patients with IgG4-related ophthalmic disease requires further investigation of larger numbers of patients. Biopsy of the extraocular muscles is seldom performed.

Graves' ophthalmopathy, which can also affect multiple extraocular muscles, must be distinguished from IgG4-RD in this setting. Kubota et al. have reported a case in which IgG4-related orbital inflammation and thyroid

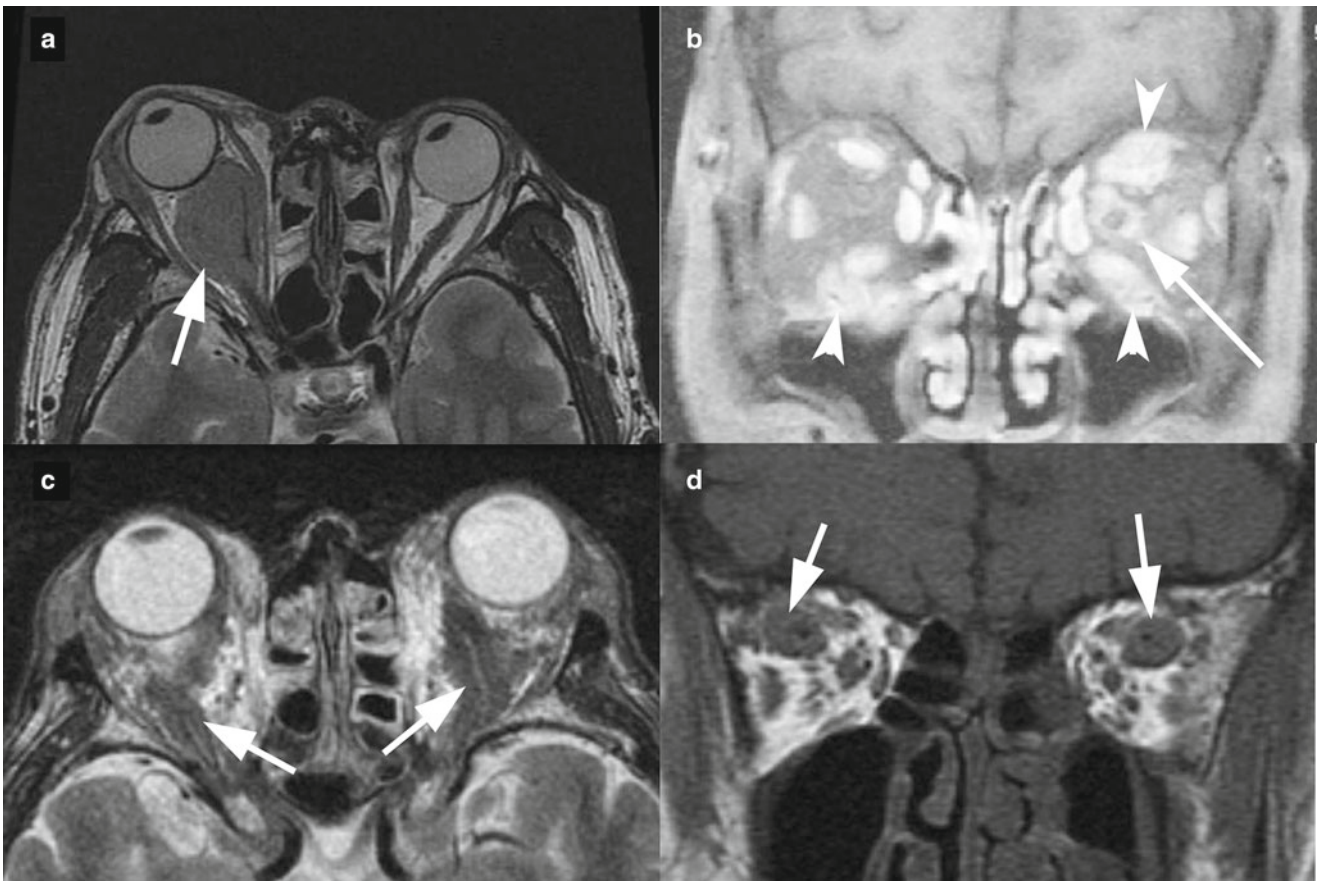


**Fig. 12.4** IgG4-related orbital lesions extending into the muscle cone. (**a**) A 44-year-old man. Serum IgG4 value 599 mg/dL. A tumor is seen around the right optic nerve (*arrow*). (**b**) A 60-year-old man. Serum IgG4 value 463 mg/dL. In addition to mild swelling of the left extraocular muscle, lesions (*arrowhead*) are present around the optic nerve (*arrow*), supraorbital nerve, and infraorbital nerve. (**c**) A 54-year-old man. Serum IgG4 value 1,950 mg/dL. Bilateral lacrimal gland swelling and lesions (*arrow*) along the bilateral superior ophthalmic veins are seen. (**d**) Coronal plane findings in case (**c**). In this case, the perivascular lesions (*arrow*) are more prominent than the extraocular muscle swelling

ophthalmopathy occurred concomitantly [14], but this occurrence is considered to be coincidental.

### 12.3.2 Supraorbital and Infraorbital Nerve Swelling

In IgG4-RD, enlargement of the infraorbital nerve as well as of the infraorbital canal has recently been reported [13, 15, 16]. Lesions around the infraorbital nerve (Figs. 12.3c and 12.4b) and supraorbital nerve are seen in some cases (Figs. 12.3d and 12.4b). Although nerve tissue for pathological examination is difficult to obtain, Katsura et al. reported a perineural lymphoplasmacytic infiltration with foci of IgG4-positive plasma cells and fibrosis [16]. Numbness of the affected nerve appears to be common, but most patients are asymptomatic.

### 12.3.3 Lesions in the Muscle Cone

IgG4-RD lesions are sometimes seen in the muscle cone (the portion surrounded by the four rectus muscles) and around the optic nerve (Fig. 12.4a, b). Patients with such lesions are prone to exophthalmos (Fig. 12.4a). These lesions have been interpreted both as inflammation of the tissues surrounding the optic nerve (i.e., the optic nerve sheath) and as inflammation of the adipose tissues [13]. Perivascular lesions also form in the muscle cone in some patients (Fig. 12.4c, d).

### 12.3.4 IgG4-Related Optic Neuropathy

When lesions of IgG4-RD form near the optic canal, visual acuity and/or visual field impairment due to optic neuropathy may occur. Although this is attributed to compression near

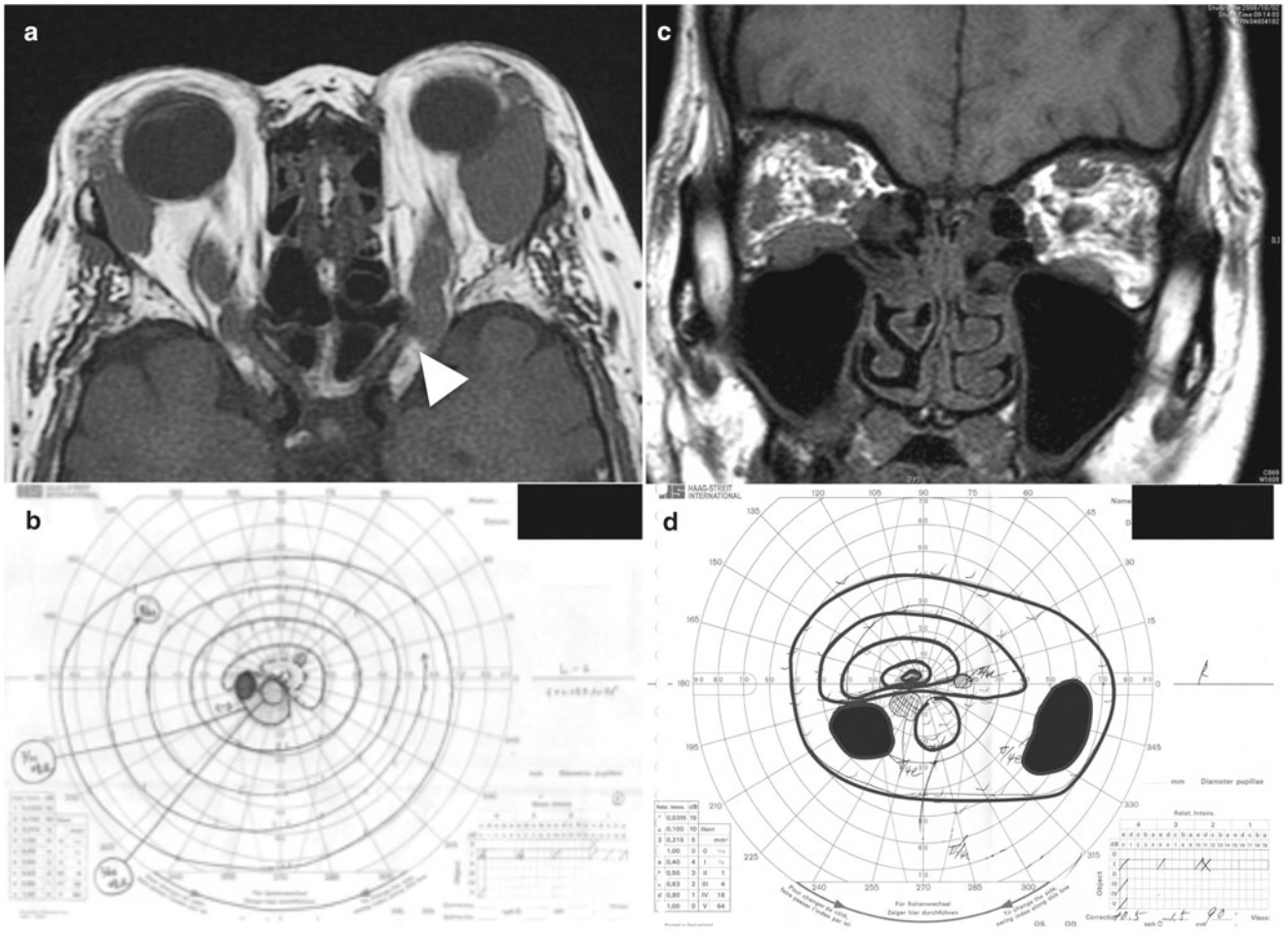


**Fig. 12.5** IgG4-related optic neuropathy. Two cases complicated by optic neuropathy. (**a**) A 60-year-old woman. In addition to bilateral lacrimal gland involvement, supraorbital nerve enlargement is also seen bilaterally. The *arrowhead* indicates the site where the left optic nerve is compressed from above. (**b**) Goldmann kinetic perimetry reveals lower altitudinal hemianopia. Left corrected visual acuity was 0.1. (**c**) A 53-year-old woman. Enlargement of the right infraorbital nerve is seen. A cord-like shadow is seen in the muscle cone, but no masses are identified. (**d**) Altitudinal (horizontally) visual field impairment is seen. Corrected visual acuity of the right eye was 1.0

the optic canal (Fig. 12.5a, b), cases without masses are also encountered (Fig. 12.5c, d). Multiple mechanisms may contribute to this type of optic neuropathy.

## 12.4 Gray Zone of IgG4-Related Lesions in the Ophthalmic Region

The diagnosis of IgG4-RD requires the synthesis of clinical, serological, radiologic, and pathology data from a variety of potential organs that can be involved. As described elsewhere in this book, the pathology of IgG4-RD consists of foci of marked lymphoplasmacytic infiltration associated with fibrosclerosis, and a high percentage of plasma cells stain for IgG4. The serum IgG4 concentration is elevated in the majority of patients, but not all. It must be emphasized, however, that elevations neither in tissue nor in serum are diagnostic of IgG4-RD in and of themselves. For example, typical lacrimal gland cyst cases (Fig. 12.6a–d) can be associated with inflammatory cell infiltration by numerous IgG4-positive cells. This tissue specimen contains none of the other histopathological features of IgG4-RD, however, and it would therefore be erroneous (and dangerous) to render the diagnosis of IgG4-RD in this setting.

The majority of cases diagnosed with IgG4-related Mikulicz's disease or IgG4-related dacryoadenitis are straightforward, demonstrating both serological and pathology characteristics that are strongly suggestive or diagnostic of IgG4-RD. In some patients, however, the diagnosis of IgG4-related dacryoadenitis is predicated upon pathological findings on biopsy in the setting of normal serum IgG4 concentrations (Fig. 12.6e, f).

The case shown in Fig. 12.6g, h illustrates the clinical variability of IgG4-RD. This 65-year-old diabetic man

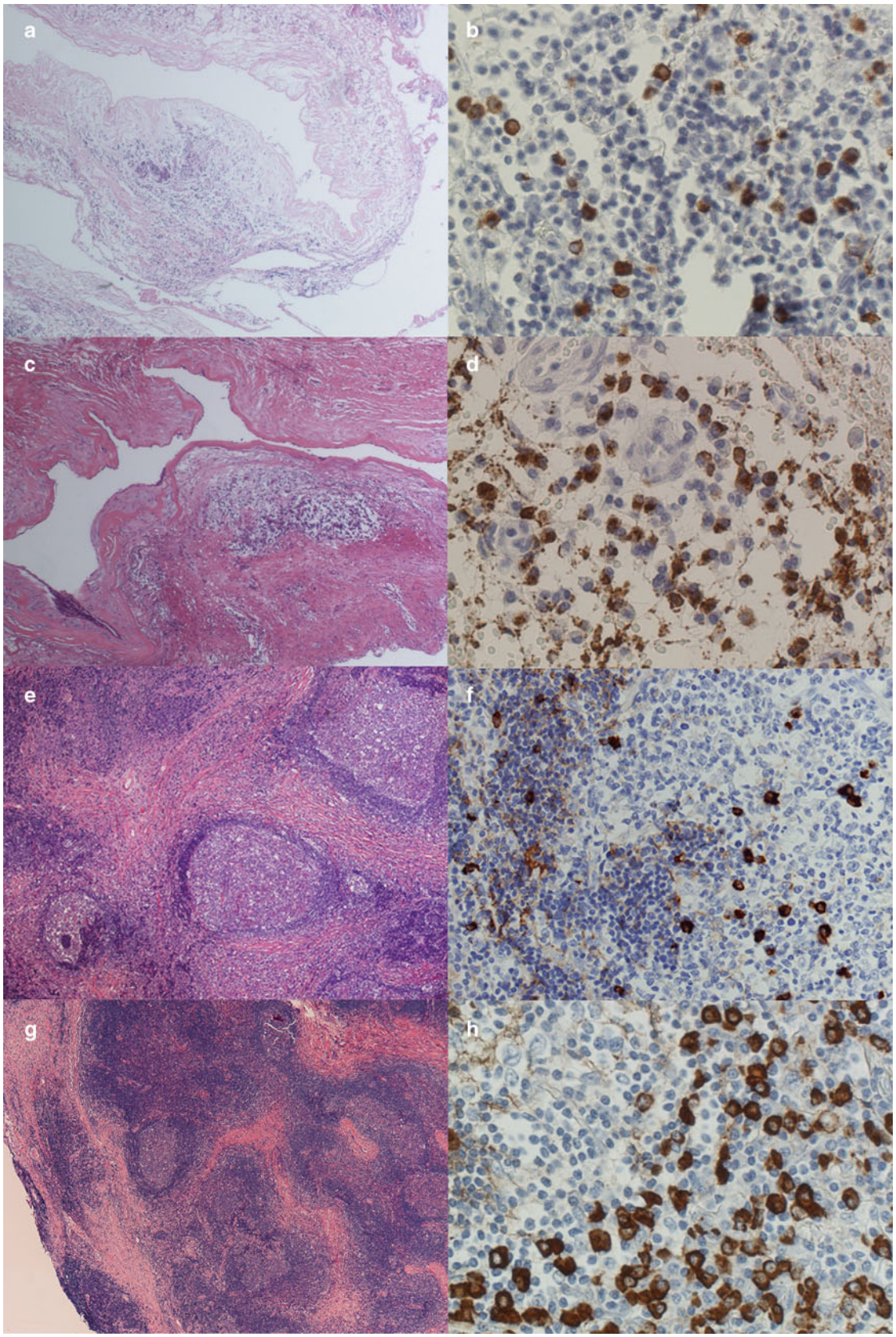


**Fig. 12.6** Pathological and IgG4 staining findings of various orbital lesions. (**a**, **b**) A 51-year-old woman with a left lacrimal gland retention cyst. IgG4 staining-positive cells are seen at sites of lymphocyte infiltration. (**c**, **d**) A 53-year-old man with left conjunctival cyst. Similar IgG4-positive staining sites are seen. (**e**, **f**) A 62-year-old woman with serum IgG4 of 29 mg/dL. In this case with right lacrimal gland swelling, lymphoplasmacytic cell infiltration associated with follicle formation and fibrosis is seen. IgG4-positive cells exceed 30/HPF, and so this patient could be diagnosed with IgG4-RD histologically. (**g**, **h**) A 65-year-old man. IgG4-positive lymphoplasmacytic infiltration associated with follicle formation and fibrosis was seen. Initially, serum IgG4 was 164 mg/dL, and typical IgG4-related Mikulicz's disease was diagnosed, but 5 years later in the untreated state serum IgG4 normalized to 55 mg/dL

was diagnosed with IgG4-related dacryoadenitis on the basis of histopathological and immunostaining features of a lacrimal gland biopsy. At the time of diagnosis, his serum IgG4 concentration was 164 mg/dL (normal <121 mg/dL). Glucocorticoid treatment was withheld because of concern about its effects on his glucose metabolism, and he was followed with expectant management. Five years later, his serum IgG4 concentration had normalized (55 mg/dL) and the bilateral lacrimal gland swelling also decreased. This case demonstrates the variable natural history of IgG4-RD, its prolonged course, and its potential for spontaneous improvement in some patients. It also indicates that the diagnosis of IgG4-RD should be considered in the appropriate clinical setting despite normal serum IgG4 concentrations.

At the First Boston International Symposium on IgG4-RD, Cheuk et al. reported cases of chronic dacryoadenitis in which the serum IgG4 values were normal and IgG4-immunostaining was negative, but hematoxylin and eosin studies revealed a pathological picture of fibrosclerosis and lymphocyte infiltration with follicle formation (Cheuk et al., unpublished observation). We have also observed such cases. Cheuk et al. have referred to such cases as "IgG4-negative IgG4-RD." Further investigation is required to understand the relationship of such cases, if any, to IgG4-RD.

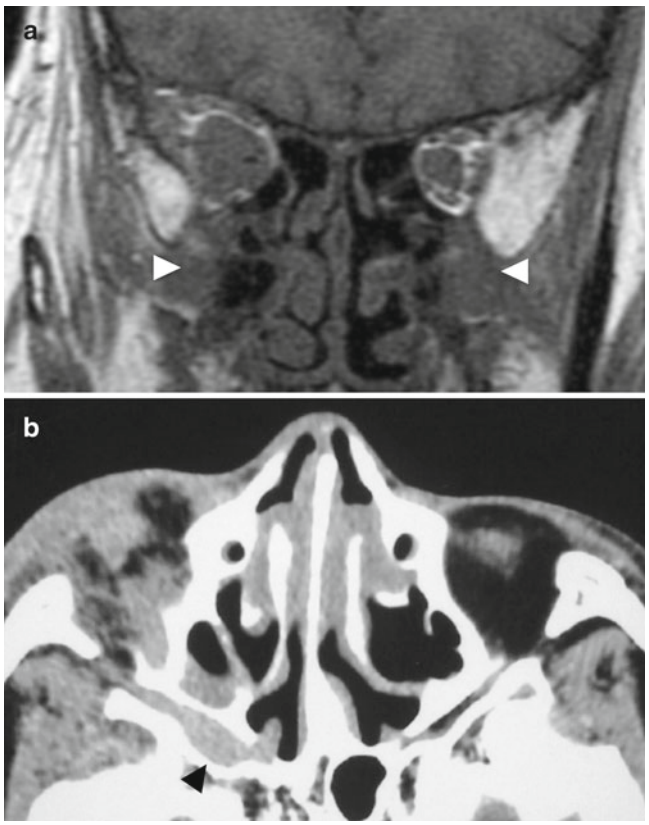


**Fig. 12.7** Lesions from the orbital apex to adjacent structures of the orbit. (**a**) A 64-year-old man. Serum IgG4 value 816 mg/dL. Lesions are seen around the bilateral optic nerves and also extend to the lateral paranasal sinus (*white arrowhead*). (**b**) A 63-year-old man. Serum IgG4 value 860 mg/dL. Lesions are seen near the right inferior orbital fissure and right pterygopalatine fossa (*black arrowhead*)

### 12.4.1 Dacryocystitis and Lacrimal Ducts

Recently, cases of IgG4-related lacrimal duct lesions [17] and IgG4-related dacryocystitis [18] have been reported. Perhaps because lacrimal duct occlusive disease is not usually subjected to pathological examination, we have not encountered such cases at our institutions. More scrutiny needs to be devoted to these potential lesions in the future. Some cases of IgG4-RD are known to be complicated by sinusitis, and lacrimal duct lesions may develop in some of these cases similar to the manner observed in granulomatosis with polyangiitis (formerly Wegener's).

### 12.4.2 Eyeball Lesions

In posterior scleritis, extreme inflammatory thickening of the sclera is sometimes seen. The pathophysiology of this lesion has not been adequately explained. Recently, a case with a prominent intraocular protrusive lesion that was subjected to enucleation because of a suspicion of malignant tumor was reported at a Japanese meeting (unpublished observation by Tsuji). Marked scleral thickening and IgG4-positive plasma cell infiltration were demonstrated on the enucleated eye, and a serum IgG4 concentration >130 mg/dL was documented. The fact that this patient had a history of retroperitoneal fibrosis was also consistent with the diagnosis of IgG4-RD. Another case with IgG4-related intraocular lesion was also reported [19]. In this case, enucleation of the eyeball was performed for the preliminary diagnosis of choroidal tumor.

### 12.4.3 Lesions of the Orbital Apex and Adjacent Structures of the Orbit

Cases are encountered in which extension of the disease to the orbital apex or other adjacent structures of the orbit occurs (Fig. 12.7a, b). When no superficial orbital lesions are present, histopathological diagnosis is extremely difficult to achieve. In this sense, these cases must be considered to have "gray zone" lesions. Depending on the degree of inflammatory cell infiltration into these tight spaces, marked visual impairment can result. Anecdotal reports have described cases in which excessive therapy such as enucleation of the eyeball or orbital exenteration was performed because of a suspicion of malignancy. Determination of the serum IgG4

value can be extremely important in such cases, but even a normal serum IgG4 concentration does not necessarily rule out IgG4-RD.

## 12.5 Nomenclature Encompassing All Lesions in the Ophthalmic Region: IgG4-Related Ophthalmic Disease

Bilateral lacrimal gland swelling is indisputably a typical manifestation of IgG4-RD in the ophthalmic region. However, it has become apparent that IgG4-related lesions exhibit diverse infiltrative patterns and can also involve the extraocular muscles, nerves, and other structures. Although the assignment of names to each of these lesions would be possible—e.g., "IgG4-related extraocular muscle lesions" or "IgG4-related orbital nerve lesions"—the proliferation of names would merely complicate issues of nomenclature, to little purpose. An international consensus document on the nomenclature of IgG4-RD recently recommended "IgG4-related ophthalmic disease" as the broader name for all complications of this disease occurring in this region [20]. However, this summary term does not preclude the use of more precise terminology, e.g., IgG4-related dacryoadenitis, when such anatomic specificity is required.

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