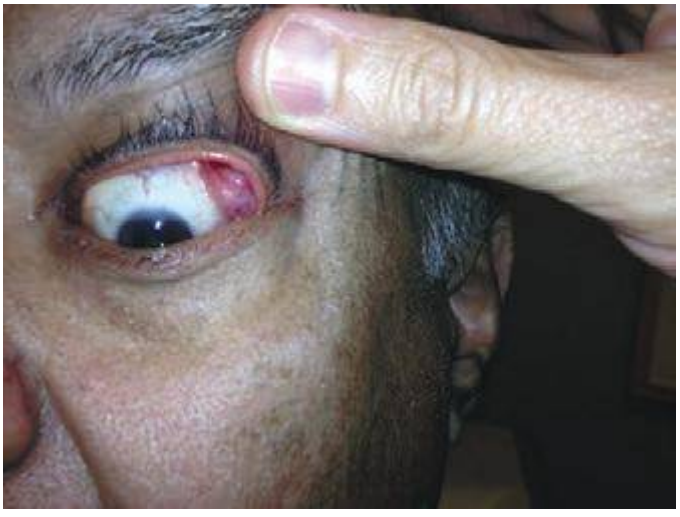
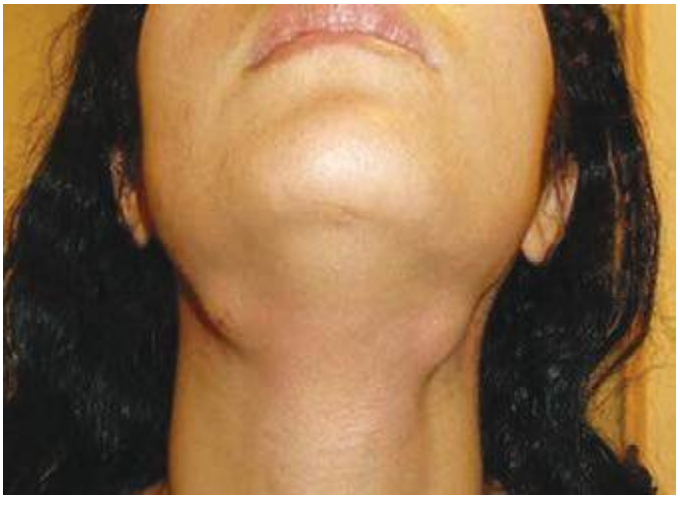
Multiorgan disease may be evident at diagnosis but can also evolve over months to years. Some patients have disease confined to a single organ for many years. Others have either known or subclinical organ involvement at the same time as the major clinical feature. Patients with type 1 AIP may have their major disease focus in the pancreas; however, thorough evaluations by history, physical examination, blood tests, urinalysis, and cross-sectional imaging may demonstrate lacrimal gland enlargement, sialoadenitis, lymphadenopathy, a variety of pulmonary findings, tubulointerstitial nephritis, hepatobiliary disease, aortitis, retroperitoneal fibrosis, or other organ involvement. Spontaneous improvement, sometimes leading to clinical resolution of certain organ system manifestations, is reported in a small percentage of patients.

Two common characteristics of IgG4-RD are allergic disease and the tendency to form tumefactive lesions that mimic malignancies (Fig. 391e-1). Many IgG4-RD patients have allergic features such as atopy, eczema, asthma, nasal polyps, sinusitis, and modest peripheral eosinophilia. IgG4-RD also appears to account for a significant proportion of tumorous swellings—pseudotumors—in many organ systems. Some patients undergo major surgeries (e.g., Whipple procedures or thyroidectomy) for the purpose of resecting malignancies before the correct diagnosis is identified. Frequent sites of pseudotumors are the major salivary glands, lacrimal glands, lungs, and kidneys; however, nearly all organs have been affected with this manifestation.



A



B

FIGURE 391e-1 A major clinical feature of IgG4-related disease is its tendency to form tumefactive lesions. Shown here are mass lesions of the lacrimal glands (***A***) and the submandibular glands (***B***).

IgG4-RD often causes major morbidity and can lead to organ failure; however, its general pattern is to cause damage in a subacute manner. Destructive bone lesions in the sinuses, head, and middle ear spaces that mimic granulomatous polyangiitis (formerly Wegener's granulomatosis) also occur in IgG4-RD; less aggressive lesions are the rule in most organs. In regions such as the retroperitoneum, substantial fibrosis often occurs before the diagnosis is established, leading to ureteral entrapment, hydronephrosis, postobstructive uropathy, renal atrophy, and chronic pain, possibly resulting from the encasement of peripheral nerves by the inflammatory process. Undiagnosed or undertreated IgG4-related cholangitis can lead to hepatic failure within months. Similarly, IgG4-related aortitis, believed to be associated with between 10 and 50% of cases of inflammatory aortitis, can cause aneurysms and dissections. Substantial renal dysfunction and even renal failure can ensue from IgG4-related tubulointerstitial nephritis, and renal atrophy is a frequent sequel to this disease complication.

SEROLOGIC FINDINGS

The majority of patients with IgG4-RD have elevated serum IgG4 concentrations; however, the range of elevation varies widely. Serum concentrations of IgG4 as high as 30 or 40 times the upper limit of normal sometimes occur, usually in patients with disease that affects multiple organ systems simultaneously. Approximately 30% of patients have normal serum IgG4 concentrations despite classic histopathologic and immunohistochemical findings. Such patients tend to have disease that affects fewer organs. Patients with IgG4-related retroperitoneal fibrosis have a high likelihood of normal serum IgG4 concentrations, perhaps because the process has advanced to a fibrotic stage by the time the diagnosis is considered.

The correlation between serum IgG4 concentrations and disease activity and the need for treatment is imperfect. Serum IgG4 concentrations typically decline swiftly with the institution of therapy but often do not normalize completely. Patients can achieve clinical remissions yet have persistently elevated serum IgG4 concentrations. Rapidly rising serum IgG4 concentrations may identify patients at greatest risk for clinical flares and monitoring of serial IgG4 concentrations identifies early relapse in some patients; however, the temporal relationship between modest IgG4 elevations and the need for clinical treatment is poor. Clinical relapses occur in some patients despite persistently normal IgG4 concentrations.

IgG4 concentrations in serum are usually measured by nephelometry assays. These assays can lead to reports of spuriously low IgG4 values because of the prozone effect. This effect can be corrected by dilution of the serum sample in the laboratory. The prozone effect should be considered when the results of serologic testing for IgG4 concentrations appear to be at odds with the patient's clinical features.

EPIDEMIOLOGY

The typical patient with IgG4-RD is a middle-aged to elderly man. This epidemiology stands in stark contrast to that of many classic autoimmune conditions, which tend to affect young women. Studies of AIP patients in Japan indicate that the male-to-female ratio in that disease subset is on the order of 3:1. Even more striking, male predominance has been reported in IgG4-related tubulointerstitial nephritis and IgG4-related retroperitoneal fibrosis. Among IgG4-RD manifestations that involve organs of the head and neck, the sex ratio may be closer to 1:1.

PATHOLOGY

The key histopathology characteristics of IgG4-RD are a dense lymphoplasmacytic infiltrate (Fig. 391e-2) that is organized in a storiform pattern (resembling a basket-weave), obliterative phlebitis, and a mild to moderate eosinophilic infiltrate. Lymphoid follicles and germinal centers are frequently observed. The infiltrate tends to aggregate around ductal structures when it affects glands such as the lacrimal, submandibular, and parotid glands or the pancreas. The inflammatory lesion often aggregates into tumefactive masses that destroy the involved tissue.

Obliterative arteritis is observed in some organs, particularly the lung; however, venous involvement is more common (and is indeed