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potentially has higher rates of infectious complications. Other medications that can be considered second-line treatment include leflunomide or mycophenolate mofetil. Hydroxychloroquine can also be an effective immunomodulator, particularly for skin disease or hypercalcemia, but is not recommended for lung disease.

If all second-line therapies have been exhausted due to intoler ance, inefficacy, or inability to taper corticosteroids, tumor necrosis factor (TNF) inhibitors can be considered. TNF-α is produced by the activated macrophages of the granuloma and contributes to propagation of inflammation in sarcoidosis. Infliximab and adali mumab are monoclonal antibodies that target TNF-α. Infliximab has garnered the most supporting data, with randomized controlled trials and larger case series showing positive effects on pulmonary function, imaging, and inflammatory cytokine levels, particularly in those with more severe disease. Adalimumab has shown efficacy in smaller series, particularly in ocular sarcoidosis. Etanercept, on the other hand, a TNF receptor antagonist, has been shown to be ineffective for sarcoidosis and should not be used for treatment. Other therapies targeting different aspects of the immune response are also considered at times in refractory cases including anti-B-cell therapy and antifibrotic medications. IMMUNOSUPPRESSIVE MONITORING While on immunosuppressive therapy, close attention to preven tion of toxicity is important in the care plan, and monitoring should follow published rheumatologic guideline recommenda tions. Bisphosphonates should be considered to minimize steroidinduced osteoporosis, and regular eye exams should be obtained with corticosteroid use and hydroxychloroquine. When assessing a medication choice, it is also important to consider pregnancy risk, as many second-line agents have adverse reproductive effects. DURATION OF TREATMENT The exact duration of treatment may differ between individuals based on severity of disease but is ~1 year for most patients. Shorter courses of therapy have been associated with higher relapse rates, although they can be considered for particularly responsive cases. For pulmonary involvement, the greatest amount of improvement is seen within the first weeks to months of therapy; therefore, tapering of corticosteroids to a lower maintenance dose should be considered with early follow-up to minimize long-term toxicity. Longer courses of treatment may be necessary for life-threatening or refractory disease. Relapses are treated with the last known effec tive dosing regimen. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders APPROACH TO THE PATIENT Sarcoidosis Comprehensive treatment of the patient with sarcoidosis includes not only suppression of granulomatous inflammation but also consideration of medication side effects and evaluation of fatigue, psychological health, and pain. Up to 80% of patients with sarcoid osis experience

multifactorial fatigue, which can persist even after treatment and remission. Fatigue can be due to medications, sleep disorders, pain, and the granulomatous inflammation itself. It is associated with extrapulmonary involvement. Neuropathic pain or autonomic dysfunction may require symptomatic care. Formal ized physical training has been shown to improve exercise capacity, strength, and fatigue in patients with sarcoidosis. Depression is also highly prevalent in chronic sarcoidosis, associated with female sex, dyspnea, and poor access to care. Cognitive impairment contribut ing to decreased quality of life is well-noted but poorly understood. Patient-centered care of the entire constellation of effects of sarcoid osis can include neuropsychiatric evaluation, sleep therapy, exercise therapy, pain relief, and lifestyle modifications. An individualized plan is necessary for every patient to address the benefits of antiinflammatory treatments, associated comorbidities, and mainte nance of quality of life while living with sarcoidosis.

■ ■FURTHER READING Baughman RP et al: Clinical characteristics of patients in a case con trol study of sarcoidosis. Am J Respir Crit Care Med 164:1885, 2001. Baughman RP et al: European Respiratory Society clinical practice guidelines on treatment of sarcoidosis. Eur Respir J 58: 2004079, 2021. Crouser ED et al: Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 201:e26, 2020. Drent M et al: Challenges of sarcoidosis and its management. N Engl J Med 385:1018, 2021. Judson MA: Environmental risk factors for sarcoidosis. Front Immu nol 11:1340, 2020. John H. Stone

IgG4-Related Disease IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by a tendency to form tumefactive lesions. The clinical manifestations of this disease, however, are protean, as IgG4-RD can affect virtually any organ system. The disease has a particular predilec tion for targeting blood vessels of any size on either the venous or arte rial side of the circulation and is therefore regarded as a variable-vessel vasculitis. Commonly affected organs are the pancreas, biliary tree, major salivary glands (submandibular, parotid), periorbital tissues, kidneys, lungs, lymph nodes, and retroperitoneum. In addition, IgG4RD involvement of the meninges, aorta, prostate, thyroid, pericardium, skin, and other organs is well described. The disease affects the brain parenchyma, the joints, the bone marrow, and the bowel mucosa only rarely. The pathologic findings are consistent across all affected organs. These findings include a lymphoplasmacytic infiltrate with a high percentage of IgG4-positive plasma cells; a characteristic pattern of fibrosis termed “storiform” (from the Latin storea, for “woven mat”); a tendency to target blood vessels, particularly veins, through an oblit erative process (“obliterative phlebitis”); and a mild to moderate tissue eosinophilia. Although the pathology is consistent from organ to organ, it is essentially never diagnostic in and of itself. Classification criteria emphasize the importance of careful correlation among clinical, sero logic, radiologic, and pathologic findings in deciding whether a patient should be classified as having IgG4-RD. Biopsy is not required in order to establish the diagnosis in classic cases, but most patients undergo a biopsy at some point in the evaluation in order to exclude malignancy. IgG4-RD encompasses a number of conditions previously regarded as separate, organ-specific entities. A condition once known as “lym phoplasmacytic sclerosing pancreatitis” became the paradigm of IgG4RD in 2000, when Japanese investigators recognized that these patients had elevated serum concentrations of IgG4. This form of sclerosing pancreatitis is now termed type 1 (IgG4-related) autoimmune pancre atitis (AIP). By 2003, extrapancreatic disease manifestations had been identified in patients with type 1 AIP, and descriptions of IgG4-RD in other organs followed. Mikulicz’s disease, once considered to be a subset of Sjögren’s syndrome that affected the lacrimal, parotid, and subman dibular glands, is one

of the most common presentations of IgG4-RD. ■ ■CLINICAL FEATURES The major organ lesions are summarized in Table 380-1. IgG4-RD usually presents subacutely, and even in the setting of multiorgan dis ease, most patients do not have fevers or high elevations of C-reactive protein levels. Some patients, however, experience substantial weight loss over periods of months. This is generally because of exocrine

TABLE 380-1 Organ Manifestations of IgG4-Related Disease ORGAN MAJOR CLINICAL FEATURES Orbits and periorbital tissues Painless eyelid or periocular tissue swelling; orbital pseudotumor; dacryoadenitis; dacryocystitis; orbital myositis; and mass lesions extending into the pterygopalatine fossa and infiltrating along the trigeminal nerve Ears, nose, and sinuses Allergic phenomena (nasal polyps, asthma, allergic rhinitis, peripheral eosinophilia); nasal obstruction, rhinorrhea, anosmia, chronic sinusitis; occasional bone-destructive lesions Salivary glands Submandibular and/or parotid gland enlargement (isolated bilateral submandibular gland involvement more common); minor salivary glands sometimes involved Meninges Headache, radiculopathy, cranial nerve palsies, or other symptoms resulting from spinal cord compression; tendency to form mass lesions; magnetic resonance imaging (MRI) shows marked thickening and enhancement of dura Hypothalamus and pituitary Clinical syndromes resulting from involvement of the hypothalamus and pituitary, e.g., anterior pituitary hormone deficiency, central diabetes insipidus, or both; imaging reveals thickened pituitary stalk or mass formation on the stalk, swelling of the pituitary gland, or mass formation within the pituitary Lymph nodes Generalized lymphadenopathy or localized disease adjacent to a specific affected organ; the lymph nodes involved are generally 1–2 cm in diameter and nontender Thyroid gland Riedel’s thyroiditis; fibrosing variant of Hashimoto’s thyroiditis Lungs Asymptomatic finding on lung imaging; cough, hemoptysis, dyspnea, pleural effusion, or chest discomfort; associated with parenchymal lung involvement, pleural disease, or both; four main clinical lung syndromes: inflammatory pseudotumor, paravertebral mass often extending over several vertebrae, central airway disease, localized or diffuse interstitial pneumonia; pleural lesions have severe, nodular thickening of the visceral or parietal pleura with diffuse sclerosing inflammation, sometimes associated with pleural effusion Aorta Asymptomatic finding on radiologic studies; surprise finding at elective aortic surgery; aortic dissection; clinicopathologic syndromes described include lymphoplasmacytic aortitis of thoracic or abdominal aorta, aortic dissection, periaortitis and periarteritis, and inflammatory abdominal aneurysm Retroperitoneum Backache, lower abdominal pain, lower extremity edema, hydronephrosis from ureteral involvement, asymptomatic finding on radiologic studies. Classic radiologic appearance is periaortic inflammation extending caudally to involve the iliac vessels. Kidneys Tubulointerstitial nephritis; membranous glomerulonephritis in a small minority; asymptomatic tumoral lesions, typically multiple and bilateral, are sometimes detected on radiologic studies; renal involvement strongly associated with hypocomplementemia Pancreas Type 1 autoimmune pancreatitis, presenting as mild abdominal pain; weight loss; acute, obstructive jaundice, mimicking adenocarcinoma of the pancreas (including a pancreatic mass); between 20 and 50% of patients present with acute glucose intolerance; imaging shows diffuse (termed “sausage-shaped pancreas”) or segmental pancreatic enlargement, with loss of normal lobularity; a mass often raises the suspicion of malignancy Biliary tree and liver Obstructive jaundice associated with autoimmunity in most cases; weight loss; steatorrhea; abdominal pain; and new-onset diabetes mellitus; mimicker of primary sclerosing cholangitis and cholangiocarcinoma Other organs involved Gallbladder, liver (mass), breast (pseudotumor), prostate (prostatism), pericardium (constrictive pericarditis), mesentery (sclerosing mesenteritis),

mediastinum (fibrosing mediastinitis), skin (erythematous or flesh-colored papules), peripheral nerve (perineural inflammation) pancreatic failure and the resulting inability of the pancreas to produce sufficient quantities of digestive enzymes. Failure of the endocrine pancreas, resulting in diabetes mellitus, is also common. Clinically apparent disease can evolve over months, years, or even decades before the manifestations within a given organ become sufficiently severe to bring the patient to medical attention. Some patients have disease that is marked by the appearance and then resolution or temporary improvement in symptoms within a particular organ. Other patients accumulate new organ involvement as their disease persists in previ ously affected organs. Initial misdiagnosis, particularly of cancer, is extremely common because of the disease's tendency to cause mass lesions in the organs it affects. IgG4-RD is also often identified inci dentally through radiologic findings. Multiorgan disease may be evident at diagnosis but can also evolve over months to years. Some patients, however, have disease that appears to be confined to a single organ at the time of diagnosis. Others have subclinical involvement of other organs when the major clini cal feature presents. For example, patients with type 1 AIP may have their major disease focus in the pancreas, but thorough investigation through the history and physical examination, blood tests, and crosssectional imaging may demonstrate disease in multiple other organs. Two common characteristics of IgG4-RD are allergic disease and the tendency to form tumefactive lesions that mimic malignancies (Fig. 380-1). 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 propor tion of tumorous swellings—pseudotumors—in many organ systems (Fig. 380-2). Some patients undergo major surgeries (e.g., modified Whipple procedures or thyroidectomy) for the purpose of resecting malignancies before the correct diagnosis is identified. IgG4-RD often causes major morbidity and can lead to organ failure; however, its general pattern is to cause damage in a subacute manner.

CHAPTER 380 IgG4-Related Disease Destructive bone lesions in the sinuses, head, and middle ear spaces that mimic granulomatosis with polyangiitis occur occasionally in IgG4-RD, but 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, and renal atrophy. Undiag nosed or undertreated IgG4-related sclerosing cholangitis can lead to hepatic failure within months. Similarly, IgG4-related 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 even following apparently effective immunosuppressive therapy. IgG4related membranous glomerulonephropathy, a less common renal manifestation than tubulointerstitial nephritis, must be distinguished from idiopathic membranous glomerulonephropathy. As a variablevessel vasculitis, IgG4-RD can target small-, medium-, and large-sized arteries and veins. Patients with longstanding IgG4-RD marked by substantial elevations of serum IgG4 concentrations and other bio markers are at risk for developing coronary arteritis, marked by wall thickening, periarterial soft tissue encasement, stenosis, calcification, and aneurysms or ectasia. ■ ■SEROLOGIC FINDINGS The majority of patients with IgG4-RD have elevated serum IgG4 con centrations; however, the range of elevation varies widely. Serum con centrations 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 often have normal serum IgG4 concentrations, perhaps because the

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders A B FIGURE 380-1 A major clinical feature of IgG4-related disease is its tendency to form tumefactive lesions. Shown here are mass lesions of the lacrimal glands, causing supraorbital swelling (A) and the submandibular glands (B). process has advanced to a fibrotic stage by the time the diagnosis is considered. Correlations between serum IgG4 concentrations, disease activity, and the need for treatment are 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. Following treatment and a disease response, however, steadily rising serum IgG4 concentra tions are useful in identifying patients at risk for clinical flares who should be considered for re-treatment. Clinical relapses occur in some patients despite persistently normal IgG4 concentrations. IgG4 concentrations in serum are usually measured by nephelome try assays. In the setting of extremely high serum IgG4 concentrations, these assays can generate spuriously low IgG4 values because of the prozone effect. Failure to identify dramatic serum IgG4 elevations can have a substantial impact on patients, because that subset of patients is at greatest risk for multiorgan disease and substantial end-organ injury. The prozone effect should be considered when the results of serologic testing for IgG4 concentrations are normal despite the presence of clinical features that strongly suggest IgG4-RD. This effect can be cor rected by dilution of the serum sample in the laboratory. ■ ■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. Male patients are approximately 5 years older at the time of diagnosis com pared to female patients and have higher degrees of serologic activity, e.g., IgG4 hypergammaglobulinemia or hypocomplementemia. The male-to-female ratio appears to be on the order of 2:1, with even more striking male predominance reported in certain types of internal organ

A B FIGURE 380-2 Thickening of extraocular muscles and meninges. (A) Magnetic resonance imaging study of the orbits, showing enhancement and enlargement of extraocular muscles in a patient with IgG4-related orbital disease (orbit axial T1 postcontrast fat-saturated image). (B) Magnetic resonance imaging study of the brain, showing thickening of the pachymeninges. There is nodular pachymeningeal enhancement at the base of the brain (blue dot), anterior to the pons. There is also abnormal enhancement and thickening of the tentorium cerebelli, interposed between the superior cerebellum and the occipital lobes (sagittal MPRAGE volumetric T1 postcontrast image). involvement (e.g., the pancreas, kidneys, or retroperitoneum). Among IgG4-RD manifestations that involve organs of the head and neck—the orbits, lacrimal glands, and major salivary glands—the sex ratio may be closer to 1:1. ■ ■PATHOLOGY The key histopathology characteristics of IgG4-RD are a dense lym phoplasmacytic infiltrate (Fig. 380-3) that is organized in a storiform pattern, 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. 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 a hall mark of IgG4-RD). Several histopathology features are uncommon in IgG4-RD and, when detected, mitigate against the diagnosis of IgG4-RD. These include intense neutrophilic infiltration,

leukocytoclasis, granulo matous inflammation, multinucleated giant cells, and fibrinoid necrosis.

FIGURE 380-3 Hallmark histopathology characteristics of IgG4-related disease (IgG4-RD) are a dense lymphoplasmacytic infiltrate and a mild to moderate eosinophilic infiltrate. The cellular inflammation is often encased in a distinctive type of fibrosis termed “storiform,” which often has a basket weave pattern. Abundant fibroblasts and strands of fibrosis accompany the lymphoplasmacytic infiltrate in this figure. Outlined by the arrowheads is a vein demonstrating obliterative phlebitis, underscoring the vascular tropism of this disease, which is classified as a variable-vessel vasculitis. This biopsy is from a patient with IgG4related hypertrophic pachymeningitis. However, the findings are identical to the pathology found in the pancreas, kidneys, lungs, salivary glands, and other organs affected by IgG4-RD. The inflammatory infiltrate is composed of an admixture of B and T lymphocytes. B cells are typically organized in germinal centers. Plasma cells staining for CD19, CD138, and IgG4 appear to radiate from the germinal centers. In contrast, the T cells, usually CD4+, are distributed more diffusely throughout the lesion and generally represent the most abundant cell type. Fibroblasts, histiocytes, and eosinophils can all be observed in moderate numbers. Some biopsy samples are particularly enriched with eosinophils. In other samples, particularly from longstanding cases, fibrosis predominates. The histologic appearance of IgG4-RD, although characteristic, should be supplemented by immunohistochemical stains for IgG4 and IgG. IgG4-positive plasma cells predominate within the lesion, but plasma cells containing immunoglobulins from each subclass can be found. The number of IgG4-positive plasma cells can be quantified by either counting the number of cells per high-power field (HPF) or by calculating the ratio of IgG4- to IgG-bearing plasma cells. Tissue fibrosis predominates in the latter phases of organ involvement, and in this relatively acellular phase of inflammation, both the IgG4:total IgG ratio and the pattern of tissue fibrosis are more important than the number of IgG4-positive cells per HPF in establishing the diagnosis. No matter how strongly the histopathology and immunohistochem istry studies favor a diagnosis of IgG4-RD, however, the pathology findings must always be interpreted in the context of clinical, serologic, and radiologic findings. Pathology findings alone are never sufficient for the diagnosis. ■

■PATHOPHYSIOLOGY Despite the emphasis of IgG4 in the name of this disease, the IgG4 molecule is not believed to play a direct role in the pathophysiology of disease within most organs. The IgG4 molecule can undergo Fab exchange, a phenomenon in which the two halves of the molecule dis sociate from each other and reassociate with hemi-molecules of differ ent antigen specificity that have originated from other dissociated IgG4 molecules. Partly as a result of this Fab exchange, IgG4 antibodies do not bind antigen tightly. Moreover, the molecules have low affinities for Fc receptors and C1q and are regarded generally as noninflammatory immunoglobulins. The low affinities for Fc receptors and C1q impair the ability of IgG4 antibodies to induce phagocyte activation, antibodydependent cellular cytotoxicity, and complement-mediated damage. It

is possible, therefore, that the role of IgG4 in this disease is actually as a counterregulatory mechanism rather than part of the primary inflam matory process.

Next-generation sequencing studies of CD4+ effector T cells have demonstrated a unique CD4+ cytotoxic T cell. This cell, also found in abundance at tissue sites of disease, makes interferon gamma, T-cell growth factor-beta, and interleukin-1, all of which may contribute to the storiform fibrosis found in this condition. The cells also elaborate per forin, granzyme A and B, and granulysin, products capable of inducing cytotoxicity. The pronounced oligoclonal expansion of this CD4+ cyto toxic T cell at tissue sites suggests that this cell is a major disease driver. CHAPTER 380

IgG4-Related Disease Oligoclonal expansions of plasmablasts are also present within the blood of patients with IgG4-RD. Continuous antigen presentation by B cells and plasmablasts may support CD4+ cytotoxic T cells, which in turn produce profibrotic cytokines and other molecules, thereby directly mediating tissue injury. ■ ■TREATMENT Vital organ involvement must be treated aggressively, because IgG4-RD can lead to serious organ dysfunction and failure. Aggressive disease can lead quickly to end-stage liver disease, permanent impairment of pancreatic function, renal atrophy, aortic dissection or aneurysms, and destructive lesions in the sinuses and nasopharynx. Not every disease manifestation of IgG4-RD requires immediate treatment, however, because the disease may take an indolent form in some patients. IgG4related lymphadenopathy, for example, can be asymptomatic for years, without evolution to other disease manifestations. Watchful waiting is prudent in some cases, but monitoring is essential because serious organ involvement may evolve over time, particularly in the setting of persistently rising serum IgG4 concentrations. Glucocorticoids are the first line of therapy. Treatment regimens, extrapolated from experience with the management of type 1 AIP, generally begin with 40 mg/d of prednisone, with tapering to dis continuation or maintenance doses of 5 mg/d within 2 or 3 months. Although the clinical response to glucocorticoids is usually swift and striking, prolonged steroid-free remissions are uncommon and the risk of steroid-induced morbidity in this middle-aged to elderly patient population is high, particularly in those with baseline comorbidities and pancreatic involvement by IgG4-RD. Few data exist to support the utility of conventional glucocorticoid-sparing agents in this disease. For patients with relapsing or glucocorticoid-resistant disease, B-cell depletion with rituximab is an excellent second-line therapy. Ritux imab treatment (two doses of 1 g IV, separated by ~15 days) leads to a swift decline in serum IgG4 concentrations, suggesting that rituximab achieves its effects in part by preventing the repletion of short-lived plasma cells that produce IgG4. More important than its effects on IgG4 concentrations, however, may be the effect of B-cell depletion on T-cell function. Specific effects of rituximab on the CD4+ cytotoxic T cell described above have been documented in IgG4-RD. The rapidly evolving understanding of the pathophysiology of IgG4-RD suggests several novel targeted approaches to treating the disease, some of which are in clinical trials. Phase 3 clinical trials of treatments target ing CD19+ B lymphocytes are now at advanced stages of recruitment. B-cell–targeted treatment strategies may be appropriate first-line ther apy options for some patients following confirmation of their efficacy in clinical trials, particularly for patients at high risk for glucocorticoid toxicity and for those with immediately organ-threatening disease. ■ ■FURTHER READING Jha I et al: Sex as a predictor of clinical phenotype and determinant of immune response in IgG4-Related disease: A retrospective study of 328 patients fulfilling the American College of Rheumatology/ European League Against Rheumatism classification criteria. Lancet Rheumatol 6:E460, 2024. Katz G et al: IgG4-related disease as a variable-vessel vasculitis: A case series of 13 patients with medium-sized coronary artery involvement. Semin Arthritis Rheum 60:152184, 2023. Katz G et al: Proliferative features of IgG4-related disease. Lancet Rheu matol 6:e481, 2024.

Revision #1
Created 2026-01-06 16:34:58 UTC by Omar Ayman
Updated 2026-01-06 16:34:58 UTC by Omar Ayman