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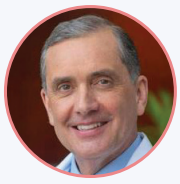
September 2024

UNVEILING IgG4-RELATED DISEASE: Understanding the Systemic Features of the Great Imitator



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Release Date: September 2024
Expiration Date: September 2025

UNVEILING IgG4-RELATED DISEASE: Understanding the Systemic Features of the Great Imitator

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Content Source

This continuing medical education (CME) activity captures content from a live-virtual symposium.

Activity Description

This supplement summarizes a discussion that will help practitioners improve their ability to recognize and diagnose IgG4-related disease.

Target Audience

This certified CME activity is designed for rheumatologists, nurse practitioners, and physician assistants, as well as pathologists and radiologists who diagnose and/or treat patients with IgG4-related disease.

Learning Objectives

Upon completion of this activity, the participant should be able to:

- **Describe** the prevalence, etiology, and pathophysiology of IgG4-related disease
- **Identify** the individual organ manifestations/clinical features that may support a diagnosis of IgG4-related disease
- **Outline** the diseases and/or conditions whose manifestations have substantial overlap with IgG4-related disease
- **Analyze** clinical, serological, histopathological, and radiological findings to facilitate early diagnosis of patients with IgG4-related disease
- **Explain** how patients with IgG4-related disease are currently treated
- **Develop** effective comanagement strategies to improve outcomes for patients with IgG4-related disease

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PRETEST QUESTIONS

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1. Please rate your confidence in your ability to recognize the individual organ manifestations/clinical features that may support a diagnosis of IgG4-related disease (IgG4-RD; based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Which of the following is TRUE in patients with IgG4-RD?

a. Fevers are present in the majority of cases
b. Serum IgG4 levels can be normal
c. Patients frequently do not respond to corticosteroid therapy
d. C-reactive protein is commonly elevated

3. A 67-year-old male was diagnosed with the pancreato biliary phenotype of IgG4-RD about 12 months ago. He was initially treated with high-dose prednisone (1 mg/kg) that led to induction of remission. He has since been tapered down to prednisone 5 mg daily. During the past 3 months, he has noticed increased yellowing of his skin, darker urine, and decreased appetite. He denies abdominal pain. Labs are notable for a serum IgG4 level of 960 mg/dL, direct bilirubin of 3.8 mg/dL, and an alkaline phosphatase of 390 IU/L. Treatment with which of the following is most likely to induce complete remission and prevent future relapses?

a. Adalimumab
b. Anakinra
c. Rituximab
d. Tocilizumab

4. A 56-year-old male is referred to rheumatology for bilateral eyelid swelling, diplopia, and proptosis. Serum IgG4 level is 1203 mg/dL, ANCA serologies are negative, and thyroid studies are normal. Cross-sectional imaging of the chest does not reveal mediastinal or hilar lymphadenopathy. MRI of the orbits reveals gadolinium-enhancing lesions in the extraocular muscles. An orbital biopsy is performed. The presence of which of the following histopathologic components would be expected?

a. Multinucleated giant cells
b. Necrosis
c. Storiform fibrosis
d. Histiocytic infiltrate

5. Which of the following cell types directly contributes to end-organ damage in IgG4-RD?

a. Natural killer cells
b. Memory B cells
c. CD8+ T cells
d. Neutrophils
e. Cytotoxic CD4+ T cells

6. A 64-year-old male presents for lower back pain, decreased urine output, and testicular swelling. Laboratory evaluation is notable for acute kidney injury, erythrocyte sedimentation rate of 42, normal C-reactive protein, and normal serum IgG4 level. A CT of the abdomen and pelvis reveals hydronephrosis and retroperitoneal fibrosis. The patient reports that he is up to date on all age-appropriate cancer screening. Testing for histoplasmosis and tuberculosis is negative. A serum protein electrophoresis shows a normal pattern. Obtaining which of the following is most likely to establish a diagnosis?

a. Retroperitoneal biopsy
b. Repeat serum IgG4 level
c. Serum complements
d. PET scan

UNVEILING IgG4-RELATED DISEASE: Understanding the Systemic Features of the Great Imitator

INTRODUCTION TO IgG4-RELATED DISEASE

John H. Stone, MD, MPH: IgG4-related disease (IgG4-RD) wasn't known to be a unique, distinct disease entity until about 20 years ago.[1] We know now that it is a multiorgan fibroinflammatory disease that can present in a variety of ways. Sometimes it presents with multiple organs involved, either at presentation or presenting in a metachronous fashion, ie, unfolding one organ at a time; and other times it can involve only one organ. It is not entirely clear whether IgG4-RD is an autoimmune disease; although, we suspect that it is because of the important roles of T and B cells in the disease.[2] However, no single autoantibody has been identified as being specific for IgG4-RD.

IgG4-RD is not a new disease. Going back through the medical literature, in 1892, one of the very famous surgeons of the day, Johann Mikulicz, wrote about a 44-year-old German farmer who had enlargement of the lacrimal, parotid, and submandibular glands.[3] Advancing forward, more than a century, to 2001, a group of Japanese investigators reported that high serum IgG4 concentrations differentiated patients with what they called "sclerosing pancreatitis" from other hepatobiliary disorders.[4] Then, in 2003, another group of Japanese investigators recognized this as being a distinct clinicopathological entity, which they termed IgG4-related autoimmune disease.[1] Later, during the first International Symposium on IgG4-RD in 2011, an international group of investigators studying this disease agreed to call it IgG4-RD.[5]

This disease can be challenging because it can potentially involve any organ in the body, although there are 10 or 12 organs that are most commonly involved. These include the pancreas, bile ducts, major salivary glands, submandibular glands, parotid and lacrimal glands, orbits, and aorta and blood vessels of any size.[6] Recently, it has become clear that IgG4-RD is, in fact, a vasculitis. We refer to it as being a variable-vessel vasculitis because it can involve any type and any size of blood vessel.[7]

IgG4-RD has solved a lot of mysteries from the past. Retroperitoneal fibrosis, for example, is often IgG4-RD.[2] Riedel's thyroiditis is IgG4-RD of the thyroid gland, and what was referred to in the past as sclerosing pancreatitis is also often type 1 IgG4-related autoimmune pancreatitis (AIP).[8,9] These different diseases are part of the IgG4-RD spectrum. IgG4-RD can also mimic multiple other diseases.[5,6] Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, particularly granulomatosis with polyangiitis, is a cardinal mimicker of IgG4-RD, and vice versa.[6,10] IgG4-RD can also mimic infections, particularly granulomatous infections, although it is not associated with granulomatous inflammation. It can mimic hematopoietic conditions, including lymphomas, multiple myeloma, and histiocytosis. It can also mimic solid tumors, such as pancreatic cancer and Klatskin tumors, or cholangiocarcinomas. It's important to make the diagnosis of IgG4-RD because it is a treatable condition with specific therapies available. It's very rewarding to make the diagnosis, because we can make a huge difference in these patients' lives.

EPIDEMIOLOGY OF IgG4-RD

Dr. Stone: Over time, we have learned more about the epidemiology of the disease. However, an International Classification of Diseases (ICD)-10 code specific for IgG4-RD only became available in October 2023.[11] The absence of an ICD-10 code has been a major challenge to understanding the epidemiology.

Based on our current understanding, IgG4-RD affects between 5 to 10 out of every 100,000 people, which amounts to about 20,000 cases in the United States, but this is likely an underestimate. IgG4-RD tends to affect middle-aged and elderly individuals, and it is more common and more severe in male patients compared to female patients. In our cohort at the Massachusetts General Hospital (MGH) of 600 patients, 328 of whom fulfilled the American College of Rheumatology-European Alliance of Associations for Rheumatology (ACR-EULAR) classification criteria, almost 70% were male compared to about 30% female.[12] This preponderance is also echoed in a number of other studies, including baseline data from the MITIGATE trial, the world's first multicenter, international, randomized, double-blind, placebo-controlled trial for IgG4-RD,[13] for which topline results have been reported. Males also tend to be about 5 years older at diagnosis compared to women, and more likely to have internal organ disease involving the pancreas, bile ducts, lungs, and kidneys.[12] Women, in contrast, are more likely to have head and neck disease, such as major salivary gland disorders. Males are also more likely to have very elevated serum IgG4 concentrations, often very elevated IgE values, and low complements.[12]

Image courtesy of Yoh Zen, MD, PhD, FRCPath.

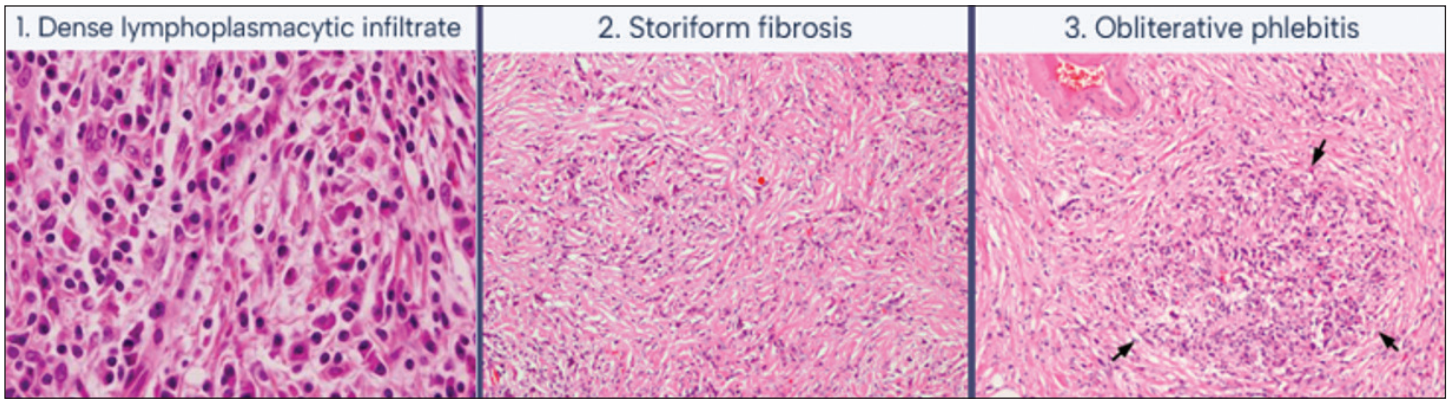

Figure 1. Characteristic morphological features of IgG4-related disease. Key histopathological features include (1) an extensive inflammatory infiltrate consisting of lymphocytes and plasma cells; (2) an irregularly whorled pattern of fibrosis (storiform fibrosis); and (3) obliteration of the vein by aggregated inflammatory cell infiltration (obliterative phlebitis).[5]

MOLECULAR BASIS OF IgG4-RD

Dr. Stone: We have come a long way in understanding the molecular basis of IgG4-RD. Based on research confirmed by a number of different laboratories, the key pathophysiologic interaction is between cells of the B cell lineage, particularly plasmablasts, but also others, and CD4-positive cytotoxic T cells.[2] The available evidence suggests that these B cells continuously present antigen to CD4-positive cytotoxic T cells, which in turn produce a variety of profibrotic mediators, such as interferon (IFN)-gamma, transforming growth factor beta (TGF-β), and interleukin (IL)-1β, leading to the characteristic fibrosis of the disease.[2] These T cells also express cytotoxic molecules that initiate tissue injury. B cells can also perform similar actions. In summary, the key pathophysiologic event in IgG4-RD appears to be the interaction between cells of the B cell lineage and certain T cells, particularly CD4-positive cytotoxic T cells.[2]

PROLIFERATIVE VERSUS FIBROTIC DISEASE

Dr. Stone: One way of classifying IgG4-RD is to think about it as being proliferative versus fibrotic.[2,14,15] This classification is imperfect, but one can typically group patients into one of these subsets. Patients with proliferative disease tend to have disease of specific organs. In contrast, patients with fibrotic disease tend to have involvement of regions of the body, such as the retroperitoneum. Patients with proliferative disease may have disease in multiple organs, such as the pancreas, kidneys, major salivary glands, and lungs, while patients with fibrotic disease tend to have disease in organ regions, such the retroperitoneum, the mediastinum, and the mesentery of the gut.[2,14,15]

The symptoms of patients with proliferative disease result from the organomegaly that ensues and the resulting organ dysfunction of pancreas, kidneys, major salivary glands, etc.[2] In contrast, symptoms in patients with disease in the fibrotic areas, such as the retroperitoneum or the mediastinum, tend to result from the mass effects of the inflammation, which can lead to ureteral obstruction or constriction of one of the major bronchi in the lung.[2,15] Both subsets have a chronic and relapsing natural disease course. Patients with proliferative disease appear to relapse more often, possibly because patients with fibrotic disease have had the disease longer; however, we don't really know that for sure.[2,14,15] Fibrotic disease also seems to recur less often, but more research is needed on this question.

Overall, patients with proliferative disease tend to be very serologically active, with highly elevated concentrations of IgG4 and IgE, peripheral blood eosinophilia, and hypocomplementemia.[2] They don't typically have very elevated C-reactive protein (CRP) values. In contrast, patients with fibrotic disease are less serologically active.[2] They're less likely to have hypocomplementemia.[2] However, a significant subset of them do have elevated acute phase reactants, particularly CRP.[15]

PATHOLOGICAL FINDINGS IN IgG4-RD

Yoh Zen, MD, PhD, FRCPath: The pathological findings of IgG4-RD include unique morphological changes as well as immunohistochemical findings. In terms of morphological changes, we have three key findings—lymphoplasmacytic infiltrate, storiform-type fibrosis, and obliterative phlebitis (Figure 1).[5]

In IgG4-related sclerosing cholangitis, organs affected are typically enlarged, and the bile duct wall becomes very thick, and as seen in Figure 1, this is mainly due to an extensive fibroinflammatory process.[5] If you look closely, there are many infiltrating lymphocytes, mature lymphocytes, and plasma cells in the inflamed area.[5] Another important cellular element is eosinophils.[5] We have a lot of eosinophils in the majority of cases of histology proven IgG4-RD.[5]

Storiform-type fibrosis is a moderately specific finding for this condition, and it's always good to look for this pattern of fibrosis in cases of suspected IgG4-RD. This pattern of fibrosis is unique and resembles straw mat-like architecture, in which collagen fibers are arranged regularly, with slit-like spaces in between (Figure 1).[5]

The last morphological finding characteristic of IgG4-RD is obliterative phlebitis, in which small- or medium-sized veins

Image courtesy of Yoh Zen, MD, PhD, FRCPath.

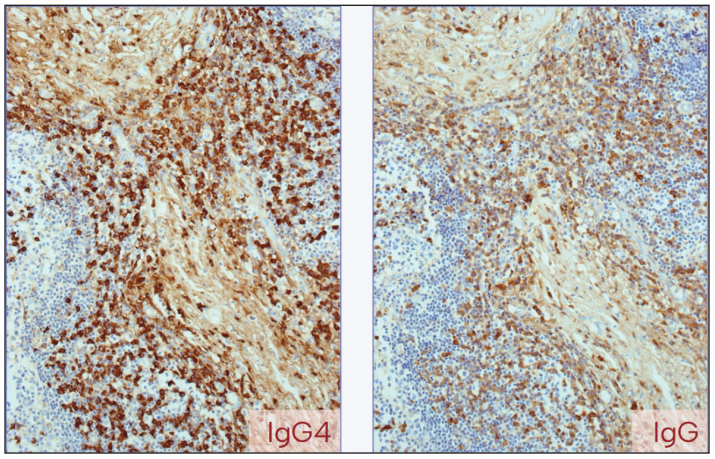

Figure 2. Immunostaining for IgG4 and IgG in IgG4-related disease. Most of the IgG-positive plasma cells are also positive for IgG4.[5]

are partly or completely obliterated by the fibroinflammatory process (Figure 1).[5] Obliterative phlebitis may be difficult to appreciate based on hematoxylin and eosin staining, because veins are completely obliterative and entirely embedded in the adjacent connective tissue. But Elastica van Gieson staining is helpful to identify obliterated venous structures.[16] In obliterated phlebitis, you can see completely obliterated veins next to intact arterial branches.

Immunostaining is also an important part of the histopathological examination of IgG4-RD.[5] The histological hallmark is IgG4-positive plasma cell infiltration. We need to demonstrate three findings in IgG4-positive plasma cell infiltration: (1) diffuse distribution, (2) increased number of IgG4-positive plasma cells, and (3) an IgG4-positive/IgG-positive plasma cell ratio greater than 40%.[5] IgG4-positive plasma cells should be diffusely present in the inflamed area.[5] Focal aggregates of positive cells are not typical for this condition, so diffuse distribution is very important. Therefore, we need to count IgG4-positive cells in at least three different areas.[5] Then we need to count IgG4-positive cells under high-power view, and we typically see significantly increased number of IgG4-positive cells.[5] For the last element, we need to calculate the IgG4-positive versus IgG-positive plasma cell ratio, and therefore, immunostaining for IgG4 as well as IgG is needed.[5] In the case illustrated in Figure 2, the IgG4-positive/IgG-positive plasma cell ratio is close to 100% as the majority of IgG-positive cells are also positive for IgG4.[5]

For diagnosing IgG4-RD, we have different cutoff points for the number of IgG4-positive plasma cells per high-power field based on the organ involved.[5] For instance, we need to document more than 100 IgG4-positive plasma cells for the diagnosis of IgG4-related dacryoadenitis and sialadenitis.[5] In contrast, more than 10 IgG4-positive plasma cells in needle biopsy samples of the pancreas would be enough for the diagnosis of IgG4-related AIP.[5] As the degree of IgG4-positive plasma cell infiltration is variable among organs, different cutoff points have been proposed for the different organs.[5] Additionally, while the IgG4-positive/IgG-positive plasma cell ratio must be over 40% for the diagnosis of IgG4-RD,[5] I want to emphasize that 40% is a minimum criterion and typically cases show a ratio greater than 70%.

Dr. Stone: How easy is it to establish a diagnosis of IgG4-RD based on histopathology?

Dr. Zen: If we have a surgically resected large specimen, for instance, a pancreatic resection specimen, I think microscopic changes are diagnostic. We can make a firm diagnosis purely based on morphological histopathological changes. But the situation is slightly more challenging for biopsy samples. We may have positive findings, but it's really challenging to establish a definitive diagnosis based purely on biopsy histopathological findings.

Dr. Stone: As we've become more aware of IgG4-RD, pathologists are likely receiving more samples from needle biopsies or core needle biopsies than organ resections. I imagine that poses some challenges.

Dr. Zen: Yes, that's right. For instance, we cannot prove the diffuse distribution of IgG4-positive cells in needle biopsy samples, and we may not see obliterative phlebitis or storiform fibrosis. In those cases, diagnosis is based more on immunohistochemical findings, which are IgG4-positive cells. I think the risk of overdiagnosis becomes higher in needle biopsy samples.

THE MANY FACES OF IgG4-RD

Emanuel Della Torre, MD, PhD: In IgG4-RD, affected organs, in general, share common histopathological features. Understanding some of the slight differences among clinical presentations as well as associated histopathological findings may help frame the multiple presentations of IgG4-RD.

If you read the definition of IgG4-RD, you will generally find that the disease is considered a multisystemic or multiorgan disease, which means that different organs across the body might be affected or different organs in the same anatomical systems, such as the pancreatobiliary system or the large vessels.[5,17] Some organs are more frequently affected, such as the pancreas, lacrimal glands, and major salivary glands, while certain organs are less frequently involved, such as the pachymeninges or thyroid gland.[17]

The reasons for why these organs are differentially affected, not only at presentation, but also during the disease course, are only partially understood. It may have to do with slight differences in the histopathological and pathophysiological features and mechanisms. This hypothesis is supported by the fact that clinicians commonly observe clusters of clinical phenotypes, which has been confirmed across different international cohorts.[18,19] In particular, we tend to observe four clinical phenotypes (Figure 3): pancreatobiliary IgG4-RD, large vessel involvement of IgG4-RD with or without retroperitoneal fibrotic tissues surrounding large vessels, head and neck

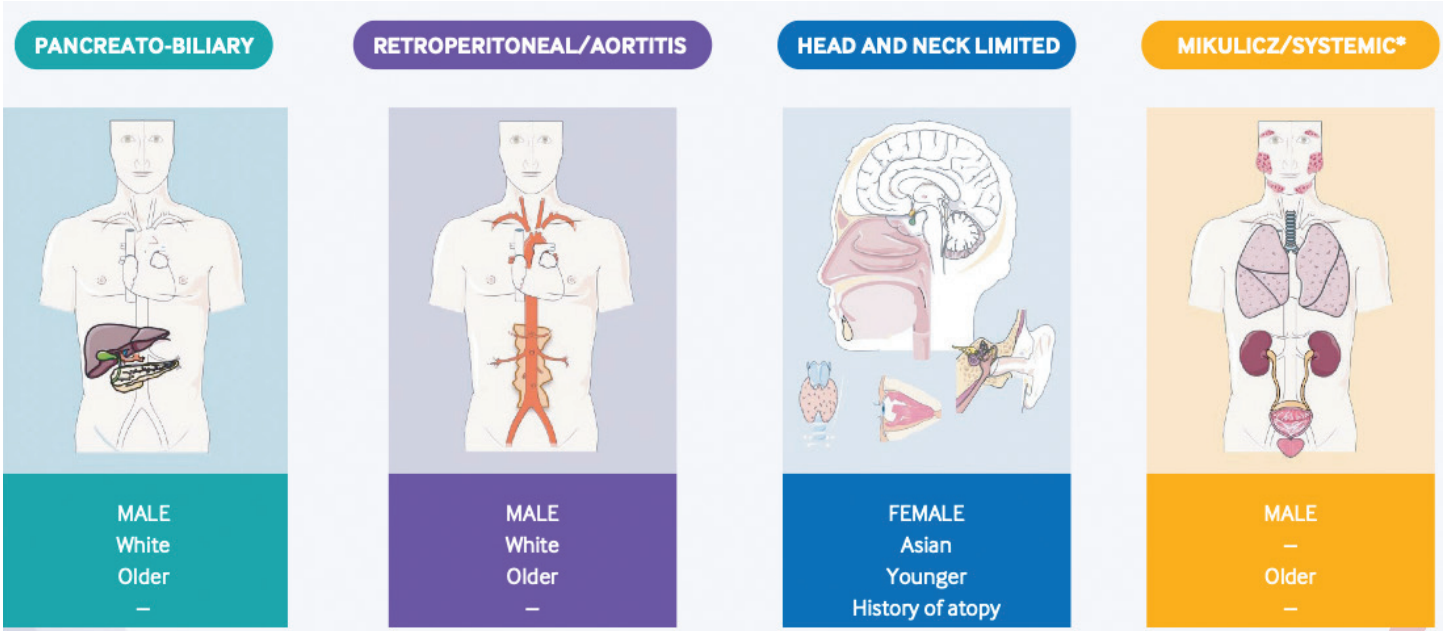

Figure 3. Most frequently observed clinical phenotypes of IgG4-related disease.[18]

limited IgG4-RD without extracranial manifestations, and systemic IgG4-RD that typically also affects the salivary glands and the lacrimal glands.[18,19] There are slightly different epidemiological features across these phenotypes.[18] Awareness of some of the commonly encountered clinical scenarios may help in identifying or raising the suspicion of IgG4-RD across these different phenotypes.

The pancreatobiliary phenotype of IgG4-RD, which includes pancreatic and biliary tract involvement, is IgG4-related AIP.[9] In IgG4-related AIP, the classic lobular structures of the pancreas become swollen. On imaging, you may see a diffuse versus a focal IgG4-related AIP.[9] In the case of focal IgG4-related AIP, differentiating pancreatitis from pancreatic adenocarcinoma is, of course, much more difficult. In the case of a diffuse form, IgG4-related AIP may present with a 'sausage-shaped' pancreas, which is a classic finding for AIP.

IgG4-related AIP can present with symptoms that are difficult to differentiate from pancreatic cancer, namely nausea, fatigue, weight loss, and abdominal pain, with its classic belt distribution. Additionally, when the choledocus, or common bile duct, is entrapped, a patient may come to your attention because of jaundice.[9] In any case, we want to pursue a biopsy to rule out cancer. As previously mentioned, the differential diagnosis is much more difficult when AIP affects the pancreas focally. IgG4-related AIP can involve the biliary tract, which may include the proximal or distal bile ducts, giving rise to some radiological scenarios that can mimic cholangiocarcinoma or primary sclerosing cholangitis.[20] In all these cases, the typical presentation of sclerosing IgG4-related cholangitis is either jaundice or elevation of liver enzymes in a patient that might be otherwise asymptomatic.[20]

In IgG4-RD with large vessel involvement, we may see involvement of the abdominal aorta, with or without surrounding fibrotic tissue, called retroperitoneal fibrosis.[19] In this scenario, the fibrotic tissue might pull the walls of the arteries, which can lead to aortic aneurysms, or extend centrifugally and retract the ureters, leading to hydronephrosis, which might be symmetric or asymmetric, unilateral or bilateral.[2] If this fibrosis extends down to the iliac artery, the patient can also present with intermittent claudication of the lower limbs. Involvement of the thoracic aorta and its branches, which can also affect the proximal walls of the coronary arteries, can lead to different manifestations, including thoracic aortic aneurysms and fibrosing mediastinitis.[2,7] Classic clinical presentations in these cases include thoracic pain or angina, and may include more urgent scenarios such as rupture of aortic aneurysm.[7]

IgG4-related head and neck-limited disease may present with Riedel's thyroiditis, which is now recognized as fibrotic IgG4-related thyroiditis.[2,8,21] Patients with Riedel's thyroiditis typically present with hypothyroidism due to fibrosis of the thyroid gland, with the fibrosis usually extending beyond the thyroid capsule and into surrounding tissues.[8,21] IgG4-related orbital disease can lead to exophthalmos due to orbital soft tissue swelling or vision loss from compression of the optic nerve.[2,22] Diplopia and limited field of vision can also occur from involvement of the orbital (extraocular) muscles.[2,22] In fact, involvement of the lateral rectus muscles of the eye is a classic finding.

Neurological involvement, particularly meningeal involvement, is also important to consider in IgG4-related head and neck-limited disease.[2] The dura mater and leptomeninges may also be affected.[23] The clinical presentation of IgG4-related pachymeningitis would depend on the extent of meningeal involvement and the nerves being compressed, as either cranial nerves or spinal nerves might be affected, and patients can

present with sensory or motor nerve palsies, headache, or other neurological manifestations.[23]

The systemic clinical phenotype of IgG4-RD often includes involvement of the salivary glands (sialadenitis) and lacrimal glands (dacryoadenitis).[2,19] Salivary glands might be affected at the parotid level or submandibular gland level, resulting in conditions historically known as Mikulicz disease (simultaneous involvement of lacrimal, parotid, and submandibular glands) or Küttner's tumor (isolated submandibular gland enlargement).[2,3] It's important to note that in contrast to mimicker conditions such as sarcoidosis or Sjögren syndrome, dryness and pain are not classic clinical features of IgG4-related salivary gland enlargement.[24] A similar consideration might apply to lacrimal gland disease. In general, lacrimal gland involvement leads to swelling of the lacrimal gland and the upper eyelid anatomical area, which is noticed by lifting the eyelid. Again, dryness is not a classic feature of IgG4-RD, unless the diagnosis is made at a late stage when fibrosis has subverted the parenchymal tissue.

Lung involvement in IgG4-RD leads to a variety of pulmonary manifestations that can present concurrently or sequentially during the course of the disease. Potential radiological findings include honeycombing, solid nodules, ground-glass opacities, and thickening of the peribronchovascular bundles, which is a feature included in the ACR-EULAR classification criteria for IgG4-RD.[6,25] Based on findings on computed tomography, the four major subtypes of IgG4-related lung disease are solid nodular, round-shaped ground-glass opacity, alveolar interstitial (characterized by honeycombing, bronchiectasis, and diffuse ground-glass opacity), and bronchovascular (showing thickening of bronchovascular bundles and interlobular septa).[25]

Kidney involvement is also an important consideration in IgG4-RD due to its potential sequela. In general, IgG4-related kidney disease manifests as tubulointerstitial nephritis, with a minority of patients having membranous glomerulonephritis.[26,27] Kidney involvement can lead to mass lesions in the parenchyma, which may be unilateral or bilateral, impaired kidney function, and abnormalities in the urinalysis with variable degrees of proteinuria and hematuria.[26]

MISCONCEPTIONS SURROUNDING IgG4-RD

Dr. Della Torre: I would like to address some misconceptions surrounding IgG4-RD and its clinical manifestations. This disease is usually considered slow progressing, mild, or subtle. However, when looking at our cohort of patients with IgG4-RD, more than half (54%) presented to the emergency department for their first manifestation of the disease.[28] Therefore, to a certain extent, IgG4-RD might be a life-threatening condition. Among the patients presenting to the emergency department, the most frequently affected anatomical sites were the pancreas and/or biliary tract, retroperitoneum, and nervous system.[28]

Dr. Stone: These data suggest that maybe the acuity to the presentation of IgG4-RD is greater than appreciated. How much of that do you think is due to diagnostic delay? For instance, is it that the patient has had the disease for months or years, and then finally gets to a critical point in the disease that requires a visit to the emergency room? Or does this disease begin and present quickly in some cases?

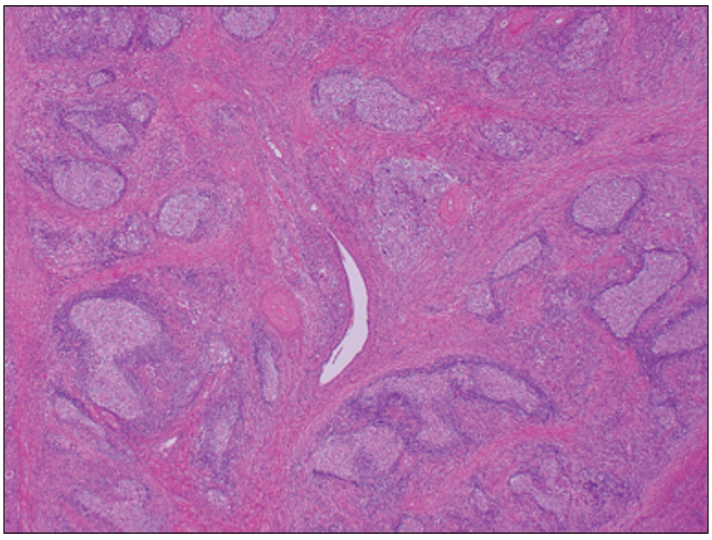

Image courtesy of Yoh Zen, MD, PhD, FRCPath.

Figure 4. IgG4-related dacryoadenitis. Microscopic findings demonstrate extensive lymphoid follicular formation, with germinal center, and significant lymphoid hyperplasia.

Dr. Della Torre: That's difficult to answer. It was also difficult to determine in our cohort because not all patients had imaging performed before being referred to the emergency department. Having said that, in our study, the manifestation that led to the emergency department visit was the first that we could attribute to IgG4-RD.[28] However, I cannot be sure for how long the disease was present. We know, from unpublished data, that the inflammatory wave can be rapid. When retrieving images from patients who had imaging performed up to 6 months before the diagnosis of IgG4-RD, there are cases without any findings and then the disease manifests suddenly. We need prospective cohorts with imaging to appreciate the speed of disease development. It might be that fibrosis develops slowly while inflammation has a more rapid onset, but these are only hypotheses.

A second potential myth that I would like to address is that allergic manifestations are a characteristic feature of IgG4-RD, an association that has been frequently reported in the literature.[29,30] We first need to consider the definition of atopy, which is a genetic tendency to develop allergic manifestations mediated by allergen-specific IgE.[31] Although we may see atopic manifestations such as rhinitis, bronchial asthma, or atopic dermatitis among patients with IgG4-RD, allergic manifestations are not highly prevalent in this patient population.[30] Most patients with IgG4-RD do not have atopic manifestations, with the prevalence of atopy being no higher than what would be expected in the general population.[30] Among patients with IgG4-RD, peripheral blood eosinophilia and

Image courtesy of Yoh Zen, MD, PhD, FRCPath.

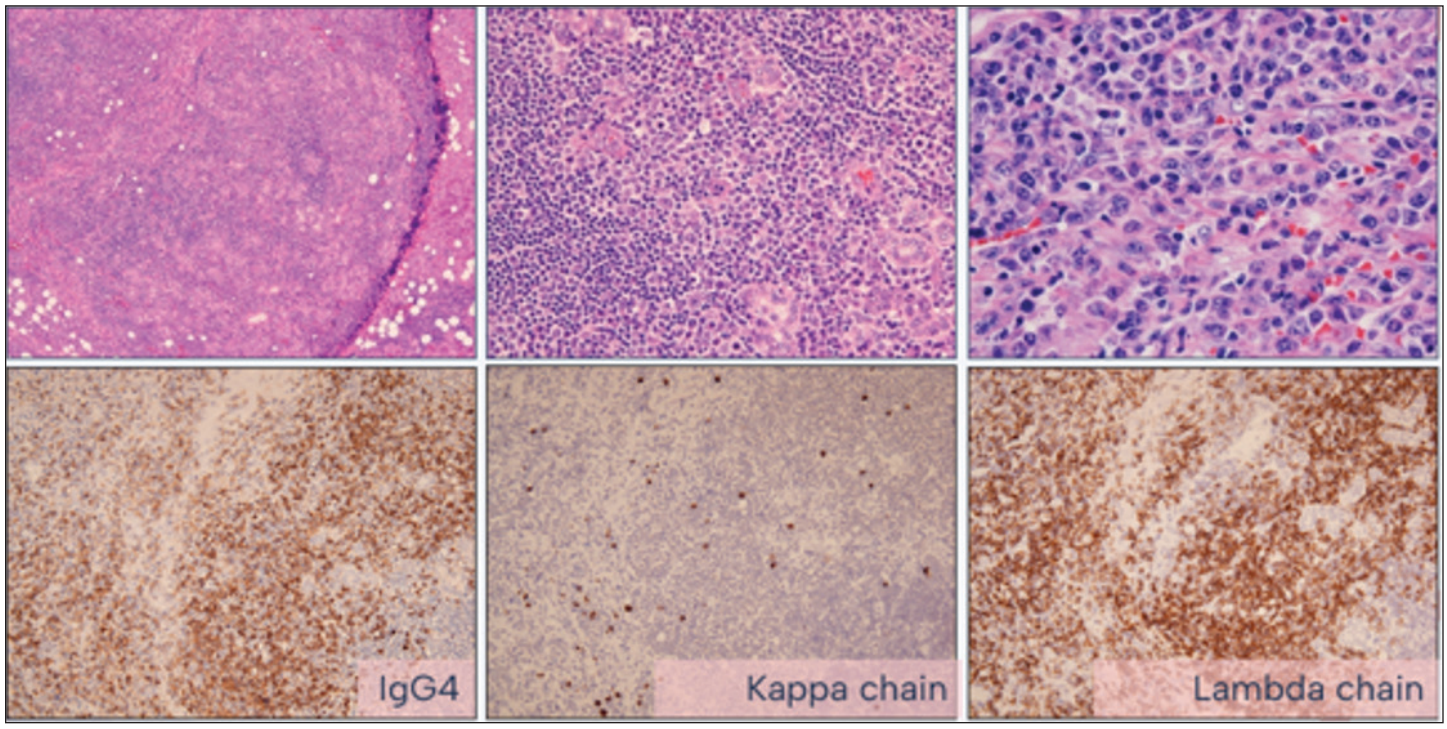

Figure 5. Findings from orbital mass biopsy in a 60-year-old woman. Findings demonstrate fibroinflammatory changes, with many lymphoid cells and mature plasma cells. Samples were strongly positive for IgG4 immunostaining, but additional immunostaining for kappa and lambda chains demonstrated the light chain restriction. Ultimately, the patient was diagnosed with MALT (mucosa-associated lymphoid tissue) type B cell lymphoma with IgG4 production.

elevated serum IgE levels occur more frequently among those with atopy, but these findings are also encountered in a subset of patients without atopy.[30] These findings suggest that processes inherent to IgG4-RD, rather than an underlying atopic condition, lead to elevated IgE concentrations and peripheral blood eosinophilia.[30]

ORGAN-SPECIFIC PATHOLOGICAL CHANGES

Dr. Zen: Although microscopic changes are generally similar in any organ affected by IgG4-RD, there are some organ-specific changes that can be observed. Florid lymphoid hyperplasia can be seen in head and neck manifestations, particularly sialadenitis and dacryoadenitis. In cases of IgG4-related dacryoadenitis, you may see extensive lymphoid follicular formation, with germinal center, and significant lymphoid hyperplasia (Figure 4). In cases with florid lymphoid hyperplasia, it's always important to exclude the possibility of malignant lymphoma and other lymphoproliferative disorders, particularly in this anatomical site, as malignant lymphoma can mimic IgG4-RD.[32]

We had a 60-year-old woman who presented with an orbital mass and biopsy from the mass lesion showed fibroinflammatory changes, with many lymphoid cells and mature plasma cells (Figure 5). Interestingly, the samples were strongly positive for IgG4 immunostaining but additional immunostaining for kappa and lambda chains clearly demonstrated the light chain restriction, consistent with monoclonal B lymphocytes and plasma cells. Ultimately, the patient was diagnosed with MALT (mucosa-associated lymphoid tissue) type B cell lymphoma with IgG4 production, highlighting the need to exclude malignant lymphoma when encountering these presentations.

Another organ-specific change is broad fibrosis in the retroperitoneum, which may be due to the longstanding nature of the disease, but we do not know the exact cause.[2] In a surgically resected biopsy sample you may see fibrosing changes and focal lymphocytic infiltration, with IgG4-positive cell infiltration.

Obliterative arteritis is also an organ-specific change, and is a relatively common microscopic finding in IgG4-related lung disease.[5] As previously mentioned, obliterative phlebitis is a unique morphological change we see in any organ manifestation of IgG4-RD, but, for unknown reasons, obliterative arteritis is only seen with lung involvement. In these cases, you may see complete obliteration of pulmonary artery branches due to the fibroinflammatory process (Figure 6).

DIAGNOSING IgG4-RD

Dr. Stone: Out of all the diversity of organs that IgG4-RD can involve, the histopathology and the immunostaining of the disease is similar from organ to organ, which is one of the key features that makes us understand that this is all one disease. For instance, while the meninges and the pancreas are vastly different organs, histopathology from each site would demonstrate the same classic findings of lymphoplasmacytic infiltrate and storiform-type fibrosis.

Image courtesy of Yoh Zen, MD, PhD, FRCPath.

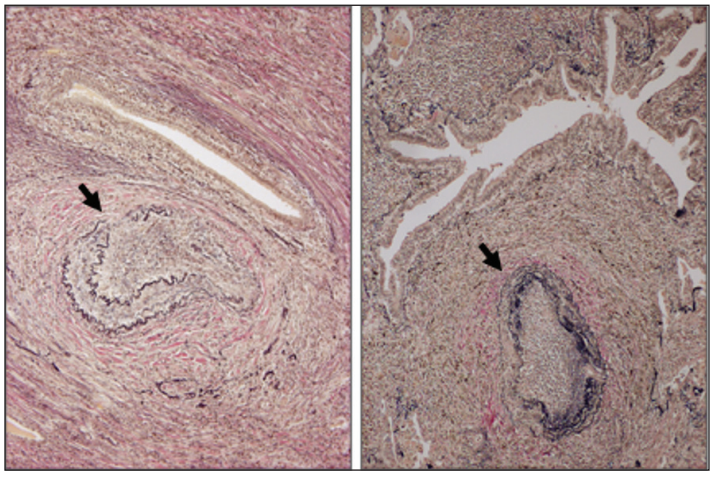

Figure 6. Obliterative arteritis in IgG4-related lung disease. Microscopic findings demonstrate obliteration of pulmonary artery branches due to the fibroinflammatory process.

Additionally, as Dr. Zen has demonstrated, a large proportion of the plasma cells in these biopsies are IgG4-positive.

While certain findings on histopathology and immunostaining are characteristic of IgG4-RD, it is important to remember that pathology doesn't tell the whole story, and that's where classification criteria and collaboration between clinicians, pathologists, and radiologists come into play. None of these different parameters, ie, clinical, serological, radiologic, or pathology, are diagnostic by themselves for IgG4-RD.[6] Therefore, correlation among all four of these parameters is essential for making the diagnosis of IgG4-RD. An analogy that I like to make is with one of the great mimickers of IgG4-RD, granulomatosis with polyangiitis (GPA), which is also a complex disease. Parameters such as hemoptysis, alveolar hemorrhage, necrotizing vasculitis, and ANCA positivity figure into the diagnosis of GPA, but none of these parameters alone are diagnostic of the disease. Diagnosis of GPA requires correlation among all parameters. This is the type of strategy that we aim for when making the diagnosis of IgG4-RD.

Working with an international group of collaborators, we developed and published ACR and EULAR classification criteria for IgG4-RD.[6] These criteria include a three-step process for classifying the disease. The first requirement is to ask, is there a typical organ affected? We've already discussed the organs typically involved. It is problematic to make the diagnosis of IgG4-RD if the pathological findings are in an atypical organ, for example, the breast or skin or lymph node, but if they're in a typical organ, that is extremely helpful. Therefore, the patient needs to have a typical organ affected for the disease to be classified as IgG4-RD.[6]

A second step in making the diagnosis of IgG4-RD is to consider the exclusion criteria, which help us narrow in on the diagnosis (Table).[6] For instance, fever is part of the exclusion criteria as it is very atypical in IgG4-RD. If fever is an important part of the patient's clinical presentation, the diagnosis is probably not IgG4-RD. Similarly, if the patient does not respond to an adequate course of glucocorticoids, then the diagnosis is almost certainly something else. There are serological exclusion criteria as well. Positivity for ANCA or for anti-Ro or anti-La antibodies means that the diagnosis is probably either ANCA-associated vasculitis on one hand or Sjögren syndrome on the other. Radiological exclusion criteria include rapid progression of the radiologic findings over 6 to 8 weeks, which would be atypical for IgG4-RD and more typical for an infection or malignancy. Pathology exclusion criteria are also critical to consider. For example, findings such as necrotizing vasculitis or an overwhelming granulomatous inflammation are atypical for IgG4-RD.

The next step is to apply eight weighted inclusion criteria domains. These include serum IgG4 concentration, the pathology which includes both histopathology and immunostaining, and organ-specific features, including glandular enlargement, chest and thoracic aorta, pancreas and biliary tree, kidney, and retroperitoneum.[6] Each of the items in these domains is weighted for an overall score.

Patients with an elevated serum IgG4 are often referred to me with the question, does this patient have IgG4-RD? To answer this, I ask three key questions. Number one, how high is the serum IgG4 concentration? The higher it is, the more likely it is that IgG4-RD is the diagnosis, but one cannot make the diagnosis based simply on an elevated serum IgG4 concentration. Number two, is there a typical organ involved? Number three, is there another potential explanation? Dr. Della Torre has talked about atopy, and really, just about any other immune-mediated condition can cause at least a mild elevation of serum IgG4. It is critical to remember that the positive predictive value of a serum IgG4 concentration greater than five times the upper limit of normal is only 75% for the diagnosis of IgG4-RD, meaning that 25% of patients with such high serum IgG4 concentrations have an alternative diagnosis.[33] Therefore, the ACR/EULAR classification criteria, which are based on clinical features, serological findings, radiologic data, and pathology findings, are essential to approach the diagnosis of IgG4-RD correctly.[6]

Two mimickers of IgG4-RD, which underscore the importance of considering different parameters for the diagnosis, are ANCA-associated vasculitis and GPA.[10] I had a case of an elderly man who was referred to me for ANCA-negative ANCA-associated vasculitis. The patient had a retrobulbar mass causing proptosis of the right eye, sinus disease, lung disease, and renal dysfunction, and he was ANCA negative. Some clinical features suggested that it might be ANCA-associated vasculitis, and while some of the radiologic findings supported that, the serological data did not. The pathology from the biopsy of the retrobulbar mass did not show granulomatous inflammation but did show a lymphoplasmacytic infiltrate and obliterative phlebitis. Additionally, his serum IgG4 concentration was very high. He was ultimately diagnosed with IgG4-RD. In the case of GPA, biopsy findings can demonstrate IgG4-positive plasma cells and storiform-type fibrosis, making it difficult to distinguish it from IgG4-RD based on pathology findings alone.

We need to consider the findings that would point to an alternative diagnosis. Findings of necrosis are not consistent with

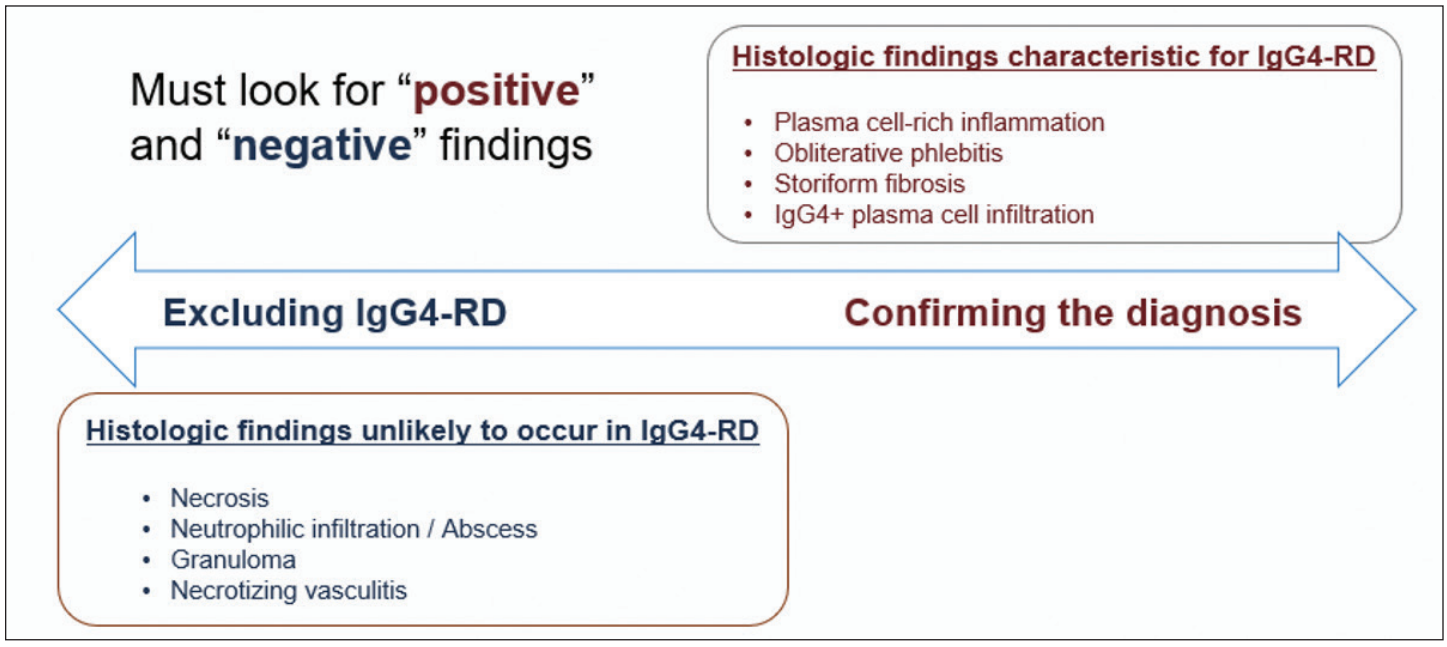

Figure 7. Role of biopsy for suspected IgG4-related disease (IgG4-RD). Both positive and negative histologic findings should be taken into consideration for confirming or excluding the diagnosis of IgG4-RD.

IgG4-RD. Findings of multinucleated giant cells, neutrophilic leukocytosis within tissue, and neutrophilic abscesses are often consistent with ANCA-associated vasculitis, particularly GPA. Additionally, it's important to remember that even a low-titer ANCA can be of significance if it has been performed in a good laboratory, if it is directed against either myeloperoxidase or proteinase 3, and if the patient has other features that are compatible with ANCA-associated vasculitis.

ROLE OF BIOPSY FOR SUSPECTED IgG4-RD

Dr. Zen: When evaluating the biopsy from a patient with suspected IgG4-RD, we need to examine the tissue for both positive and negative findings (Figure 7).[6] Plasma cell-rich inflammation, obliterative phlebitis, storiform fibrosis, and IgG4-positive cell infiltration are positive findings that support the diagnosis of IgG4-RD. At the same time, it is also important to look for negative findings that may help us exclude IgG4-RD since some microscopic findings are unlikely to occur in this condition. These negative histologic findings include necrosis, neutrophilic infiltration/abscess, granuloma, and necrotizing vasculitis. If we have any of these findings in the biopsy sample, a diagnosis of IgG4-RD becomes very unlikely.

We had a case of a 65-year-old man who presented with multiple lung nodules, and IgG4-RD was initially suspected based on imaging findings and mild IgG4 elevation (175 mg/dL; normal range is <135 mg/dL). Biopsy from one of the lung nodules showed extensive lymphoplasmacytic infiltrate and fibrosis, as well as IgG4-positive cell infiltration on immunostaining (Figure 8). However, the biopsy also showed one small focus of necrosis with granulomatous change, which is a negative finding for IgG4-RD, and the patient was ultimately diagnosed with GPA. This case highlights the importance of considering negative histologic findings when evaluating for IgG4-RD.

TREATING IgG4-RD

Dr. Della Torre: We currently rely on two main drugs, glucocorticoids and B cell-depleting agents, for the treatment of patients with IgG4-RD.[34] Diagnosing this condition promptly is important because the clinical phenotypes previously discussed can lead to organ insufficiency and organ failure.[18] For instance, we have had at least one patient with the pancreatobiliary phenotype who underwent liver transplantation, and another one with the systemic disease phenotype who underwent renal transplantation because of late diagnosis.

Considerations for the treatment of IgG4-RD are nicely summarized in the "International consensus guidance statement on the management and treatment of IgG4-related disease," published in 2015.[34] We need to keep in mind that IgG4-RD does not always require treatment. Watchful waiting may be appropriate for some patients with asymptomatic, single organ disease without life-threatening manifestations.[34] Spontaneous remission of IgG4-RD has been reported, although rarely. Symptomatic disease with life-threatening manifestations requires urgent treatment.

The next consideration is the limited window of time for treating the disease before irreversible fibrosis occurs. The longer the disease has been present, the lower the probability of being able to revert the fibrosis and restore organ functionality.[34] Comorbidities are also an important consideration when treating a patient with IgG4-RD, as patients are often elderly individuals

Image courtesy of Yoh Zen, MD, PhD, FRCPath.

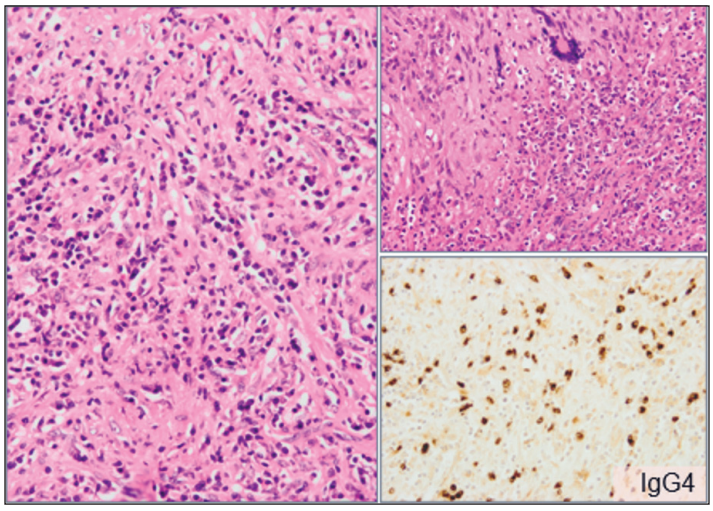

Figure 8. Lung biopsy findings from a 65-year-old man with multiple lung nodules. Findings demonstrate extensive lymphoplasmacytic infiltrate and fibrosis, and IgG4-positive cell infiltration on immunostaining. One small focus of necrosis with granulomatous change was also observed (right upper panel), which is a negative finding for IgG4-RD. The patient was ultimately diagnosed with granulomatosis with polyangiitis.

with previously existing comorbidities as well as comorbidities secondary to IgG4-RD and its treatment. Examples of comorbidities that should be addressed include pancreatic insufficiency, renal insufficiency, osteoporosis, and hypertension.

In general, glucocorticoids are the first-line therapy for IgG4-RD.[34] This condition tends to respond to steroids, and therefore, response to glucocorticoids can be helpful when the diagnosis is uncertain and other disorders, such as cancer, are being ruled out. The typical treatment for induction of remission consists of 0.6-1 mg/kg of prednisone given for 3 to 4 weeks. This is then tapered down over 4 to 6 months, maintaining lower doses of glucocorticoids for a variable period, depending on the organ manifestations.

IgG4-RD is a relapsing-remitting disease, with many patients experiencing relapse within a few years of achieving remission.[35,36] Predictors of disease relapse include multiorgan disease, and baseline elevated serum IgG4 and/or elevated serum IgE.[34,36] Hence, we may want to consider maintenance therapy to sustain disease remission in patients with baseline features associated with higher risk of early disease relapse.[34] If we want to avoid using long-term glucocorticoids as maintenance therapy, steroid-sparing treatments include disease-modifying antirheumatic drugs (DMARDs), which include classic immunosuppressive agents, or B cell depleting agents. Both types of agents have demonstrated to be effective in IgG4-RD to a certain extent.[37-39]

The recent WInS IgG4-RD trial was a prospective study conducted in China in which patients with IgG4-RD who were receiving maintenance treatment with low-dose glucocorticoids plus immunosuppressive therapy were randomized to withdrawal of both treatments, withdrawal of glucocorticoids but continuation of immunosuppressants, or maintenance of

TABLE. VALIDATION COHORT CASES AND MIMICKERS FULFILLING EXCLUSION CRITERIA FROM THE ACR/EULAR CLASSIFICATION CRITERIA FOR IgG4-RD.[6]

Clinical Exclusion Criteria	Mimickers	Cases
Fever	44 (17%)	1 (<1%)
No response to steroids	23 (9%)	1 (<1%)
Leukopenia and thrombocytopenia	19 (7%)	1 (<1%)
Peripheral eosinophilia (>3,000 mm^3)	9 (4%)	4 (1%)
Serological Exclusion Criteria	**Mimickers**	**Cases**
PR3 or MPO-ANCA positive	48 (19%)	2 (1%)
Anti-Ro or La positive	51 (20%)	5 (1%)
Extractable nuclear antibody positive	6 (2%)	0 (0%)
Cryoglobulins	10 (4%)	0 (0%)
Other disease-specific autoantibody	0 (0%)	0 (0%)
Radiological Exclusion Criteria	**Mimickers**	**Cases**
Rapid radiographic progression	5 (2%)	0 (0%)
Long bone abnormalities (eg, Erdheim-Chester disease)	3 (1%)	0 (0%)
Splenomegaly	14 (5%)	3 (1%)
Concern re: infectious/malignancy	4 (2%)	2 (1%)
Pathology Exclusion Criteria	**Mimickers**	**Cases**
Malignant infiltrate	26 (10%)	1 (<1%)
Inflammatory pseudotumor pathology	2 (1%)	0 (0%)
Prominent neutrophilic infiltrate	6 (2%)	0 (0%)
Necrotizing vasculitis	36 (14%)	0 (0%)
Prominent necrosis	2 (1%)	0 (0%)
Primarily granulomatous inflammation	39 (15%)	0 (0%)
Prominent histiocytic infiltrate	7 (3%)	1 (<1%)
Multi-Centric Castleman's Pathology	6 (2%)	0 (0%)

both glucocorticoids plus immunosuppressants.[37] Patients who continued immunosuppressants alone or in combination with glucocorticoids relapsed less frequently.[37] Findings suggest that the use of classic immunosuppressive agents may be helpful in maintaining disease remission in IgG4-RD regardless of the use of glucocorticoids. However, this study does not provide insight into the best immunosuppressive agent to use in this setting. The immunosuppressant therapies used included a variety of agents, such as methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil, and number of patients on each drug are likely too small to draw a conclusion on the relevance of any single drug.

On the other hand, we know that B cell depletion works effectively in IgG4-RD, even without glucocorticoids, for both induction of remission and maintenance of remission.[38,39] This was first demonstrated by a study from Dr. Stone's group years ago, and then confirmed in a number of retrospective and prospective studies that were summarized in a systematic review and meta-analysis.[38,39] This systematic review and meta-analysis of studies assessing the efficacy of rituximab for IgG4-related pancreatobiliary disease demonstrated a 90% rate of complete response at 6 months.[39] However, the relapse rate on rituximab was 21%, with a median time to relapse of 10 months.[39] Based on these data, maintenance therapy with periodical infusion of rituximab may be considered for patients with predictors of relapse.

We have seen impressive responses with rituximab in patients with IgG4-RD, including among those with Mikulicz disease, lung masses, orbital involvement, or pancreatic disease. Complete responses have been observed 4 to 6 months after rituximab administration, following the same dosing schedule as for rheumatoid arthritis (three infusions of 1 g, 15 days apart).

Dr. Stone: Do you have any sense of whether the patients with atopic features respond differently to our conventional or biologic therapies for IgG4-RD compared with patients who do not have atopic features?

Dr. Della Torre: I'm fully convinced that these atopic manifestations in our patients with IgG4-RD are probably supported by different immunological mechanisms. In my experience, both outcomes could happen, either the atopic manifestations in a patient with IgG4-RD respond to rituximab or any other B cell-depleting agent, or these manifestations do not respond in the way we expected, suggesting that probably they are not driven by the same immunological mechanisms that drives IgG4-RD. For these cases, we're starting to also use other biologics in compliance with guidelines for the treatment of severe rhinitis or severe asthma.

Dr. Stone: This is an area of IgG4-RD that needs to be further studied to increase our understanding of these type 2 immune responses that occur in a significant proportion of our patients.

IgG4-RD remains a diagnostic challenge, as it can involve many different organs and mimic several neoplastic, infectious, and inflammatory conditions. It is important to consider IgG4-RD in the differential diagnosis as this is a treatable condition with specific therapies available. Early treatment of IgG4-RD, before irreversible fibrosis occurs, is essential to preserve organ function and optimize patient outcomes. ■

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Unveiling IgG4-Related Disease: Understanding the Systemic Features of the Great Imitator

Release Date: September 2024
Expiration Date: September 2025

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Midwest
___ Northeast
___ Northwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the prevalence, etiology, and pathophysiology of IgG4-related disease	_____	_____	_____
Identify the individual organ manifestations/clinical features that may support a diagnosis of IgG4-related disease	_____	_____	_____
Outline the diseases and/or conditions whose manifestations have substantial overlap with IgG4-related disease	_____	_____	_____
Analyze clinical, serological, histopathological, and radiological findings to facilitate early diagnosis of patients with IgG4-related disease	_____	_____	_____
Explain how patients with IgG4-related disease are currently treated	_____	_____	_____
Develop effective comanagement strategies to improve outcomes for patients with IgG4-related disease	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the activity.

1. Based on this activity, please rate your confidence in your ability to recognize the individual organ manifestations/clinical features that may support a diagnosis of IgG4-related disease (IgG4-RD; based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Which of the following is TRUE in patients with IgG4-RD?

a. Fevers are present in the majority of cases
b. Serum IgG4 levels can be normal
c. Patients frequently do not respond to corticosteroid therapy
d. C-reactive protein is commonly elevated

3. A 67-year-old male was diagnosed with the pancreato biliary phenotype of IgG4-RD about 12 months ago. He was initially treated with high-dose prednisone (1 mg/kg) that led to induction of remission. He has since been tapered down to prednisone 5 mg daily. During the past 3 months, he has noticed increased yellowing of his skin, darker urine, and decreased appetite. He denies abdominal pain. Labs are notable for a serum IgG4 level of 960 mg/dL, direct bilirubin of 3.8 mg/dL, and an alkaline phosphatase of 390 IU/L. Treatment with which of the following is most likely to induce complete remission and prevent future relapses?

a. Adalimumab
b. Anakinra
c. Rituximab
d. Tocilizumab

4. A 56-year-old male is referred to rheumatology for bilateral eyelid swelling, diplopia, and proptosis. Serum IgG4 level is 1203 mg/dL, ANCA serologies are negative, and thyroid studies are normal. Cross-sectional imaging of the chest does not reveal mediastinal or hilar lymphadenopathy. MRI of the orbits reveals gadolinium-enhancing lesions in the extraocular muscles. An orbital biopsy is performed. The presence of which of the following histopathologic components would be expected?

a. Multinucleated giant cells
b. Necrosis
c. Storiform fibrosis
d. Histiocytic infiltrate

5. Which of the following cell types directly contributes to end-organ damage in IgG4-RD?

a. Natural killer cells
b. Memory B cells
c. CD8+ T cells
d. Neutrophils
e. Cytotoxic CD4+ T cells

6. A 64-year-old male presents for lower back pain, decreased urine output, and testicular swelling. Laboratory evaluation is notable for acute kidney injury, erythrocyte sedimentation rate of 42, normal C-reactive protein, and normal serum IgG4 level. A CT of the abdomen and pelvis reveals hydronephrosis and retroperitoneal fibrosis. The patient reports that he is up to date on all age-appropriate cancer screening. Testing for histoplasmosis and tuberculosis is negative. A serum protein electrophoresis shows a normal pattern. Obtaining which of the following is most likely to establish a diagnosis?

a. Retroperitoneal biopsy
b. Repeat serum IgG4 level
c. Serum complements
d. PET scan

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low_____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low_____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____
Change in nonpharmaceutical therapy _____
Change in diagnostic testing _____
Choice of treatment/management approach _____
Change in current practice for referral _____
Change in differential diagnosis _____
My practice has been reinforced _____
I do not plan to implement any new changes in practice _____

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relevant to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
You would recommend this program to your colleagues	___ Yes	___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____

_____