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Identifying the Great Imitator – Demystifying the Systemic Features of IgG4-Related Disease

**Intro:**
Welcome to CME on ReachMD. This replay of a live broadcast titled: Identifying the Great Imitator – Demystifying the Systemic Features of IgG4-Related Disease, is provided by Evolve Medical Education and is supported by an independent medical education grant from Amgen.

**Dr. Stone:**
Welcome. It's a great pleasure to be with you today and with my good friends and colleagues, Dr. Emanuel Della Torre and Dr. Yoh Zen, to talk to you about our favorite disease, IgG4-related disease and demystifying the great imitator.

Let's get through a couple of preliminaries here. Here are disclosures. And disclosures of Evolve and our learning objectives.

And so I will begin with an introduction to IgG4-related disease. So a little bit of background: IgG4-related disease is a disease that wasn't even known to be a unique, distinct disease entity until just a little bit more than 20 years ago, but 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, and that involvement is obvious at presentation. Other times, it presents in a metachronous fashion, sort of unfolding one organ at a time. And at other times it can involve only one organ. So multiple different ways that this disease can present.

It is not entirely clear that it is an autoimmune disease, although we suspect that it is because of the important roles of T and B cells in the disease, but no single autoantibody has been identified which is specific for IgG4-related disease.

The disease can be challenging because it involves so many different organs, potentially. Indeed, it can involve any organ in the body, but there are 10 or 12 that it involves most commonly. These include the pancreas, bile ducts, the major salivary glands, the submandibular glands, the parotid and the lacrimal glands, the orbits, the aorta, and blood vessels of any size. And recently, it's really become abundantly clear that IgG4-related disease is, in fact, a vasculitis. And we refer to it as being a variable vessel vasculitis, because it can involve any type and any size of blood vessel.

So when should we consider IgG4-related disease in the differential diagnosis? Well, IgG4-related disease, as it turns out, has solved a lot of mysteries from the past. So retroperitoneal fibrosis, for example, is very often actually IgG4-related disease. And Riedel's thyroiditis is actually IgG4-related disease of the thyroid gland. And what was referred to in the past as sclerosing pancreatitis is also very often type 1 IgG4-related autoimmune pancreatitis. So all of these different diseases are part of the IgG4-related disease spectrum.

There are also multiple diseases that IgG4-related disease can mimic, and vice versa, IgG4-related disease can be mimicked by these same conditions. So ANCA-associated vasculitis, particularly granulomatosis with polyangiitis is a cardinal mimicker of IgG4-related disease, and vice versa. And we'll emphasize that over the course of this program. IgG4-related disease can also mimic infections, particularly granulomatous infections, although it is not affiliated, associated with granulomatous inflammation, as Dr. Zen will emphasize. It can mimic hematopoietic conditions, including lymphomas and multiple myeloma and histiocytoses. And it can mimic solid tumors, particularly pancreatic cancer and Klatskin tumors, or cholangiocarcinomas as well.

It's important to make the diagnosis of IgG4-related disease because, increasingly, it has specific therapies and it is a very treatable

condition. So it's very rewarding to make the diagnosis, because we can make a huge difference in these patients' lives.

So a quick timeline of the disease. It's not a new disease, although I indicated that it was recognized really only a little bit more than 20 years ago. But if one goes back through the medical literature, one finds this paper from the German literature in 1892 from one of the very famous surgeons of the day, Johann Mikulicz, who wrote about a 44-year-old German farmer who had enlargement of the lacrimal, parotid, and submandibular glands. Advancing forward quite a bit, more than a century, a group of Japanese investigators published in the *New England Journal of Medicine* in the year 2001 reporting that high serum IgG4 concentrations differentiated patients with what they called sclerosing pancreatitis from other hepatobiliary disorders. And it was a couple of years after that, that another group of Japanese investigators recognized this as being a distinct clinico pathological entity, which they called IgG4-related autoimmune disease. And in 2011 at the time of the first International Symposium on IgG4-related disease, the world group of investigators studying this disease agreed to call this condition IgG4-related disease.

So we've also learned a bit about the epidemiology of the disease. The disease doesn't have an – only had an ICD-10 code as of October which has been a big hurdle. The absence of an ICD-10 code has been a big hurdle to understanding the epidemiology. But suffice it to say that we believe, at the moment, that the disease affects between 5 and 10 out of every 100,000 people, this amounts to about 20,000 cases in the United States. But I feel certain that that estimate is quite an underestimate. We do know that it tends to affect middle-aged and elderly individuals, that it is more common and more severe in male patients compared to female patients. Women can get this disease, no question about it. It can be every bad as – every – as bad as it is in men, but it tends to be more severe in males. Looking at our cohort at the Massachusetts General Hospital of 600 patients, 328 of whom fulfilled the ACR/EULAR classification criteria, almost 70% of them were male compared to about 30% female.

So this 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-related disease, which we'll be reporting out this fall. And interestingly, patients enrolled from all over the world, there's almost the same ratio, 65% male and 35% female.

So males also tend to be about 5 years older at diagnosis compared to women, and they are also more likely to have internal organ disease, pancreatic disease, bile duct disease, lung and kidney disease. Women, in contrast, are more likely to have the head and neck disease, major salivary gland disorders. And males are more likely to be wildly serologically active, by which I mean very elevated serum IgG4 concentrations, often very elevated IgE values, and low complements.

So over 20 years, we have actually come a long way in understanding the molecular basis of IgG4-related disease. And it is very clear from research done at a number of labs and confirmed at a number of labs across the world that the key interaction is between cells of the B cell lineage, particularly plasmablasts, but also others and a CD4-positive cytotoxic T cell. Most of the evidence thus far really indicates that the B cell is a critical player in this disease, and we know this from treatment studies which Dr. Della Torre will describe at the end of the presentation. But we believe that these B cells are continuously presenting antigen to this CD4-positive cytotoxic T cell, which in turn is elaborating a variety of mediators that are fibrogenic, interferon gamma, TGF beta, and IL-1 beta, contributing to the characteristic fibrosis of the disease which Dr. Zen will describe. And these T cells also elaborate cytotoxic molecules that initiate tissue injury. B cells, it turned out, can do a lot of the same things. So in summary, the key interaction in this disease appears to be between cells of the B cell lineage and certain T cells, particularly this CD4-positive cytotoxic T cell.

We've begun to think about identifying subsets of disease, and we'll talk about that at a variety of points in the presentation. Suffice it to say, for now, that one way of breaking the disease down, which is imperfect, is to think about disease as being proliferative or fibrotic. And there – one can group patients typically into one of these subsets or another. The proliferative patients 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. So the proliferative patients may have disease in multiple organs: the pancreas, the kidneys, the major salivary glands, the lungs. And the fibrotic patients tend to have disease in the retroperitoneum, the mediastinum, the mesentery of the gut.

The symptoms of patients with proliferative disease result from the organomegaly that ensues and the resulting organ dysfunction of pancreas, of kidneys, of major salivary glands, etc. In contrast, patients with disease in the fibrotic areas, the retroperitoneum, the mediastinum, etc., these tend to result from the mass effects of the inflammation, leading to ureteral obstruction or constriction of one of the major bronchi in the lung.

The natural history of both of these subsets really is to be chronic and relapsing. The proliferative patients appear to relapse more often, perhaps because the fibrotic patients have had disease longer. We don't really know that for sure, but it's possible that they have had more longstanding disease. Their disease seems to recur less often, but we really need more studies on that question. So I can summarize the differences between the proliferative and the fibrotic subsets by saying that the proliferative patients tend to be very serologically active, very elevated concentrations of IgG4, IgE, they often have an eosinophilia in the peripheral blood, and they're

hypocomplementemic. They don't typically have very elevated C-reactive protein values. In contrast, the patients with fibrotic disease are less serologically active. They're less likely to be hypocomplementemic, a significant subset of them, however, do have elevated acute phase reactants, particularly the C-reactive protein.

So that's enough for background to get us started, and now I'd like to hand it over to Dr. Yoh Zen from King's College London to discuss the key pathology findings in this disease.

**Dr. Zen:**
Thank you. Thank you very much. So I'll just explain in the pathological findings of this particular condition, IgG4-related disease, showed a very unique morphological changes, as whereas immunohistochemical findings. So in terms of morphological changes, we have three important key findings, which are lymphoplasmacytic infiltrate storiform type fibrosis and obliterative phlebitis. I'll explain these three findings in the next slide.

So I typically speak to the flow of the case of IgG4-related sclerosing cholangitis. So basically, organs affected by this condition are typically enlarged, and in the bile duct, bile duct wall becomes very thick, as you can see here, it is mainly due to extensive fibroinflammatory process. And if you look at closely many infiltrating lymphocytes and mature lymphocytes and plasma cells, we have a lot of mature plasma cells in the inflamed area. Another important cellular element is eosinophils. We have a lot of eosinophils in a great majority of cases of histology proven IgG4-related disease.

So in terms of fibrosis, the pattern of fibrosis in this condition is unique, and it's called storiform type fibrosis. So collagen fibers are arranged regularly with slit-like spaces, and this is now called storiform type fibrosis. And storiform fibrosis is moderately specific finding for this condition. So it's always good to look for this particular pattern of fibrosis in cases of suspected IgG4-related disease.

Then the last microscopic finding which is characteristic for this condition, is obliterated phlebitis, small or medium sized veins are partly or completely obliterated by the fibroinflammatory process, as you can see in this picture.

So what is a storiform pattern? So storiform pattern is something like straw mat-like architecture, as you can see here. Collagen fibers are arranged regularly, and we have slit-like spaces in between, and that combination gives us straw mat-like appearance. That's why we call this unique pattern fibrosis as storiform fibrosis. As I already mentioned, this is a moderately specific finding, so it's always good to look for this finding.

Obliterative phlebitis may be a little bit difficult to appreciate based on H and E stained slide, because veins are completely obliterated and entirely embedded in the adjacent connective tissue. But if elastic stain is always helpful for us to identify obliterated venous structures. As you can see here, these two cases, we have completely obliterated veins next to intact arterial branches. So this is obliterated phlebitis.

And immunostaining is also important part for the histopathological examination of IgG4-related disease. And a histological hallmark is, of course, IgG4-positive cell infiltration. And we need to prove three aspects in an IgG4-positive cell infiltration. Number one is distribution. Number two is increased number of positive cells. And the number three is ratio. So the IgG4-positive cells should be diffusely present in the inflamed area. Focal aggregates of positive cells are not typical for this condition, so diffuse distribution is really important. Therefore, we need to count IgG4-positive cells at least three different areas. Then we need to count IgG4-positive cells under high power view. And typically we have significantly increased number of IgG4-positive cells. And then the last element is ratio. We need to calculate IgG4-positive versus IgG-positive cell ratio. Therefore we need to do immunostaining for IgG4 as well as IgG. In this particular case, as you can see here, great majority of IgG-positive cells are also positive for IgG4. So the ratio is close to 100%.

We have a different cutoff point for IgG4-positive cell count for the diagnosis of this condition. For instance, we need to prove more than 100 IgG4-positive cells for the diagnosis of IgG4-related dacryadenitis and sialadenitis. But probably more than 10 cells should be enough for the diagnosis of autoimmune pancreatitis in needle biopsy samples. So the idea behind is that the degree of IgG4-positive cell infiltration is variable among organs; therefore, we proposed different cutoff points based on the organs. And as I already mentioned, this ratio should be over 40% but I want to emphasize that 40% is minimum criterion, and typical cases show greater than 70 or greater than 70% of the ratio.

**Dr. Della Torre:**
Thank you, Yoh. Good morning or good afternoon to everybody. As you have heard from my colleagues, IgG4-related disease is a proteiform condition in which every affected organ basically share, in general, common histopathological features. So in the next slides, we will try to dive into some slight differences among clinical presentation and also histopathological findings that might help framing the multiple IgG4 disease presentations.

In general, if you read the definition of IgG4-related disease, you will always find that IgG4 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. In general, we have organs that are more frequently affected, such as the pancreas, the lacrimal glands, the salivary glands, and organs that are less frequently encountered, such as the pachymeninges or the thyroid gland.

The reasons for which these organs are differentially affected, not only at presentation, but also during the disease course, are partially understood. Probably the reason relies on different and or slightly different histopathological and also pathophysiological features and mechanisms that we still poorly understand. And this hypothesis is kindly of – kind of supported by the fact that it's common experience among clinicians to observe clusters of clinical phenotypes in our clinics. And this is confirmed across different international cohorts. In particular, we use observe four clinical phenotypes. Type 1 clinical phenotypes, which is the pancreatobiliary IgG4-related; the large vessel involvement of IgG4-related disease, which is type 2 with or without retroperitoneal fibrotic tissues surrounding large vessels; head and neck limited IgG4-related disease without extracranial manifestations and systemic IgG4-related disease that typically also affects the salivary glands and the lacrimal glands.

There are slightly different epidemiological features across these phenotypes, but will not go into these differences right now, because our priority today was to provide some scenarios that might help in identifying or raising the suspect of IgG4-related disease across these different phenotypes. So in the next couple of slides, we will go through these phenotypes and see and look into some selected scenarios that may be of common encounter.

The first scenario is the pancreatobiliary phenotype of IgG4-related disease, which includes pancreatic and biliary tract involvement. This is autoimmune IgG4-related pancreatitis which it's with its classic features. On the right – on the left panel, you can appreciate the normal pancreas, which it's with its classic lobular structures, and on the two right-hand panels, you can appreciate how the pancreas become swollen when it's affected by IgG4-related disease. In the center, you see a diffuse autoimmune IgG4-related pancreatitis. On the right-hand, you see a focal autoimmune related IgG4-related pancreatitis. In this case, in this later case, differential with pancreatic adenocarcinoma is, of course, much more difficult. While in this center image, you can clearly appreciate the so-called sausage-like shape pancreas with the diffuse from infection. And this is kind of classic of autoimmune pancreatitis. In this case, IgG4-related disease presents with symptoms that are very clinical manifestation that are very difficult to differentiate from pancreatic cancer, namely nausea, fatigue, weight loss, abdominal pain, with its classic belt distribution. And also when the choledocus is entrapped, a patient might come to your attention because he's jaundiced. And in any case, we want to pursue a biopsy to rule out, of course, that this could be a cancer. And the differential, as mentioned earlier on, is much more difficult when autoimmune pancreatitis affects the pancreas in a focal way, rather than in a diffuse way.

In 12% of the cases, autoimmune pancreatitis is contained by an involvement of biliary tract, which is again very proteiform in terms of involvement of the proximal or distal bile ducts, giving rise to some scenarios, radiological scenarios, that might mimic, of course, cholangiocarcinoma or primary sclerosing cholangitis. In all these cases, the typical presentation of sclerosing IgG4-related cholangitis is either joints or elevation of liver enzymes in a patient that might be otherwise asymptomatic.

For the large vessel involvement, we selected two main clinical scenarios, which is involvement of the abdominal aorta, with or without surrounding fibrotic tissue, called retroperitoneal fibrosis. And this tissue might pull the walls of the arteries, leading to aneurysms, the so-called inflammatory aortic aneurysms, or extend centrifugally and retract the ureters, leading to hydronephrosis, which might be symmetric or asymmetric, unilateral or bilateral. And when this fibrosis extends down to the iliac artery, patients can also present with claudication intermittence of the lower limbs.

When the disease affects the thoracic aorta and its branches, again, you might encounter different manifestations, ranging from fibrotic heart bulk planes, to involvement of the proximal walls of the coronary arteries, and also to scenarios and clinical pictures like the one I'm showing in the lower pictures of real fibrosing mediastinitis. And also in this case, thoracic pain or angina are classic clinical presentations, if not urgent scenarios like ruptures of aortic aneurysms.

For the head and neck limited disease, we selected a number of scenarios shown here. Like Riedel thyroiditis, as already mentioned by Professor Stone, this is really fibrosing thyroiditis, typically presented in hypothyroidism due to the submersion of the tissue by this fibrosis that fully affect the thyroid gland. And also orbital disease. Orbital disease leads to exophthalmos, or when compressing the optic nerve to reduction of the visual acuity, or diplopia, one affects the orbital muscles again. And in this case, it's kind of classic, the involvement of the lateral rectus muscles of the eye. For the head and neck limited disease neurological involvement is also important to consider, in particular the meningeal involvement. The dural mater, and also the leptomeninges might be affected either supratentorially or subtentorially. And the clinical presentation depends, in general, on the nerve that is compressed, either cranial nerves or spinal nerves when the pachymeninges extends down the spine on the spinal cord. And patients might present with either sensory pulses or motor pulses, together with headache or other neurological manifestations.

When we move to the systemic phenotype of IgG4, we can now consider the sialadenitis or dacryadenitis, which means the involvement of the salivary gland and the lacrimal gland. Salivary glands might be affected either at the parotid level or submandibular gland level. These conditions were known for centuries as Mikulicz disease or Kuttner's tumor, respectively. And it's important to notice that in contrast with mimicker conditions such as sarcoid or Sjogren's syndrome, in patients with IgG correlate disease, dryness is not a classic features, and also pain is not classic of this salivary gland enlargement.

A similar consideration might apply to lacrimal gland disease. In general, lacrimal gland involvement leads to swelling of the lacrimal gland and to swelling of this upper eyelid anatomical area. In general, you don't appreciate lacrimal gland, but if you lift up the upper eyelid in this set, lacrimal set might fall down part and indicating swelling of this gland. And again, dryness is not classic of IgG4-related disease presentation, unless you make a diagnosis at least late stages when fibrosis has subverted the parenchymal tissue.

Lung disease is as well very proteiform in its manifestations. According to the radiological pattern, we can distinguish four types of manifestations of IgG4 that have been described. And these manifestations might appear all together, or one by one, probably during the course of the disease. We might observe either honeycombing manifestations, namely pulmonary fibrosis, single, isolated, or multiple solid nodules, ground-glass opacities, and a characteristic feature that has also been included among the ACR/EULAR classification criteria, which is this thickening of the peribronchovascular bundles.

Kidney disease is also very important for its potential sequela. In general, kidney IgG4-related disease is mainly tubulointerstitial disease, rather than a glomerular nephritic disease. And this also leads to the mass forming lesions in the kidney parenchyma, which might be either unilateral or bilateral, shown in these pictures. And of course, variable abnormalities in the urinalysis might also contain these masses, ranging from variable degrees of proteinuria and, of course, hematuria, or impaired kidney function and serum protein level increase.

Before passing the mic to Dr. Zen, I would like to spend 2 minutes around IgG4-related disease and its clinical manifestation. The first is that IgG4 is usually considered a slow progressing disease, a mild disease, a subtle disease. But when looking into our cohorts of patients, we realize that more than half of our patients presented to the emergency department for their first manifestation of IgG4-related disease, meaning that to a certain extent, IgG4 might be a life-threatening condition. And if we look at those organs that were more frequently reported by patients presenting at the emergency department, pancreato biliary manifestation, retroperitoneal involvement, and neurological involvement were the most frequently affected anatomical sites.

The second myth I would like to dispel is an association that is reported frequently in the literature about allergic manifestations being a characteristic feature of IgG4-related disease. Well, probably this is not completely wrong, but it is if we consider the definition of atopy. Atopy is basically a genetic tendency to develop allergic manifestations mediated by allergen-specific IgE. And this is something that we can tell do not encounter classically in IgG4-related disease. We for sure encounter manifestations such as rhinitis, bronchial asthma, or atopic dermatitis, such as in this case, a patient with orbital disease and also massive sinusitis, shown here in this magnetic resonance. But if we look at allergen-specific IgE, we discovered that allergic manifestations are not so prevalent in IgG4- related disease, at least at lower frequency compared to the general population. And also, if we look at these manifestations, they are equally found in patients who have a history of atopy, and in those who have not. Similar consideration might apply to elevation of serum Ig and eosinophils, which might be equally found in allergic patients with IgG4 and in non-allergic patients with IgG4. This means probably that this kind of atopic, or similar to atopic manifestation shown and found in many IgG4-RD, on one hand, are probably part of the immunologic background of the disease. On the other hand, if the patients with IgG4 also has allergic manifestation, they may probably be more moderate or severe than without IgG4, probably again to some immunological background.

So I'm happy now to pass the mic to Dr. Zen to look into slight differences in the pathology of organs affected by IgG4.

**Dr. Stone:**
Emanuel, before Yoh goes, there are a couple of questions from the audience directed to both of you that I think we should take now. So the first one is actually for Yoh, for his – for the first part of his presentation. Dr. Zen, could you tell us if there is a diagnostic histopathology or pathology picture of IgG4-related disease, a diagnostic histopathology for this condition?

**Dr. Zen:**
So if we have a surgically resected large specimen, for instance, 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 a little bit more challenging for biopsy samples. We may have positive findings, but it's really challenging to establish a definitive diagnosis purely based on biopsy histopathological findings.

**Dr. Stone:**
And sort of following up on that, I think as we've become more aware of IgG4-related disease, less often are we giving you organ

resection samples, modified Whipple procedures, which is a ton of tissue. And it's more common, and needle biopsy or a core needle biopsy, and that poses some challenges to the pathologists, I guess.

**Dr. Zen:**
Yes, that's right. For instance, we cannot prove the diffuse distribution of IgG4 positive cells in needle biopsy samples and also, we may not see obliterative phlebitis or storiform fibrosis. So diagnosis is more based on immunohistochemical findings, which is IgG4-positive cells. So I think the risk of overdiagnosis becomes higher in needle biopsy samples. I think we can discuss it, how to interpret biopsy samples later.

**Dr. Stone:**
Yeah, we'll get a little bit more into the discussion of how to make the diagnosis, but I think that's very important.

And Emanuel, there are a couple of questions for you about the data from the emergency room suggesting maybe greater than appreciated acuity to the presentation. How much of that do you think is due to diagnostic delay? So the patient has had the disease for months or years, and then finally gets to a critical point in the disease which lands them in the emergency room – do you think that's an issue, or does this disease begin and present quickly in some cases?

**Dr. Della Torre:**
Thank you, John, for this question. It's difficult to answer. We try to look into that in our cohort, but it was very difficult to go back, especially because not all patients had an imaging done before being referred to the emergency department. What I think is actually in the study we performed, that was the first manifestation that we could attribute to IgG4-related disease, the one which led patient to the emergency department. So that was day 1 for us, the day in which IgG4-related disease presented. But I cannot be sure for how long it was there. From unpublished data, we can tell that probably the formation of this inflammatory wave is kind of rapid, because it's common sense that actually it might be, when retrieving images from patient who had images before the diagnosis of IgG4, even 6 months or 4 months before, there are cases in which there was nothing there, and then the disease come up all of a sudden. But I cannot also prove that the opposite is correct. So I think we really need prospective cohorts and imaging to realize how fast this tissue growth. But I think that it might be some something rapid, like an inflammation, but then some fibrosis. So fibrosis like being slower while inflammation being some more rapid. But these are only hypotheses.

**Dr. Stone:**
Thank you very much. There's another question about the atopic patients, but we'll get to that when we talk about treatment.

So Yoh, why don't you go ahead now and talk about the organ-specific changes in this disease?

**Dr. Zen:**
Okay, so I think microscopic changes are basically similar in any organ manifestations, but there are a couple of organ-specific changes.

So one is a florid lymphoid hyperplasia in the head and the neck manifestations, particularly sialadenitis and dacryadenitis. As you can see here, this is a case of IgG4-related dacryadenitis with extensive lymphoid follicular formation, with germinal center, so there is a significant lymphoid hyperplasia in this case. Because of florid lymphoid hyperplasia, it's always important to exclude the possibility of malignant lymphoma and other lymphoproliferative disorders in this particular anatomical site. And the malignant lymphoma may mimic IgG4-related disease. This is a good example of malignant lymphoma mimicking IgG4-related disease, a 60-year-old woman presented with orbital mass. We had biopsy from the mass lesion, which showed fibroinflammatory changes. We have quite a lot of lymphoid cells, and also we have a lot of mature plasma cells in the right upper panel. And interestingly, this case was strongly positive for IgG4 immunostaining. But additional immunostaining for kappa and the lambda chains clearly demonstrated the light chain restriction. So basically infiltrating lymphocytes and plasma cells are monoclonal. So this is a case of MALT type B cell lymphoma with IgG4 production. This case is nothing related to IgG4 disease; this is just a MALT type lymphoma with IgG4 class switch. So it's always important to exclude malignant lymphoma in this particular anatomical site.

Another organ-specific change is a broad fibrosis in the retroperitoneum. This may be due to longstanding nature, but we still do not know the exact cause. This is a surgically resected biopsy sample, and the most part showed just fibrosing changes. And we have only focal lymphocytic infiltration. And nevertheless, we have at least a capable foresight of IgG4-positive cell infiltration. So this is another organ-specific change.

The final organ-specific change is obliterative arteritis. As I already mentioned, obliterative phlebitis is a unique morphological change we see in any organ manifestations, but obliterated arteritis can be seen in only the lung manifestations. As you can see here, pulmonary artery branches next to bronchs, showed complete obliteration due to fibroinflammatory process. We still do not know why it

occurs only in the lung manifestations, but this is relatively common microscopic finding in lung manifestations.

I think we can hand over the mic to Dr. Stone?

**Dr. Stone:**
Yes, thank you. So we'll talk about making a diagnosis of IgG4-related disease. Dr. Zen and Dr. Della Torre have given you some great background for this. I would point out that out of all the diversity of organs that IgG4-related disease can involve, the meninges, shown here with this classic histopathology, lymphoplasmacytic infiltrate, swirling storiform fibrosis is a very different organ from the pancreas. This is the central pancreatic duct here, but it shows the same histopathology of the meninges, the storiform fibrosis, the periductal lymphoplasmacytic infiltrate. So the histopathology and the immunostaining of the disease is similar from organ to organ to organ, one of the key features that makes us understand that this is all one disease. And as Dr. Zen has demonstrated, a large proportion of the plasma cells in these biopsies are IgG4-positive.

But it is important to remember that pathology doesn't tell the whole story, and that's where classification criteria and collaboration between clinician and pathologist and radiologist come into play. So none of these different parameters, the clinical parameters, the serological parameters, the radiology findings, or the pathology features is diagnostic in and of itself for this condition. So correlation among all four of these is really essential to making the diagnosis. An analogy that I like to make is with one of the great mimickers of IgG4-related disease, namely granulomatosis with polyangiitis, or GPA. So GPA is also a complex disease. All four of these parameters figure into the diagnosis ultimately, but all patients with hemoptysis don't have GPA; neither do all patients with alveolar hemorrhage have GPA. Some do. All patients with necrotizing vasculitis don't have GPA. But if you take all three of those, and you add to that positivity for a serum assay for ANCA, then the diagnosis really can't be anything other than GPA. So this is the type of strategy that we aim for in making the diagnosis, in triangulating on the diagnosis of IgG4-related disease.

So working with an international group of collaborators, including Dr. Della Torre and Dr. Zen and multiple others from all over the world, we developed and published ACR and EULAR classification criteria for IgG4-related disease. There are really three features of these criteria that are essential, and I think contribute to making these criteria very good for the purpose of classifying the disease. The first is the criteria to ask, is there a typical organ affected in the patient? And I've already mentioned what these typical organs are. It is problematic to make the diagnosis of IgG4-related disease if the pathology findings are in an atypical organ, for example, the breast or the skin or the lymph node. But if it's in a typical organ, that is very helpful. So the patient needs to have that in order to be classified as IgG4-related disease.

Then there are a number of exclusion criteria which really are very effective in helping to narrow in on the diagnosis, and these exclusion criteria include fever. So fever is very atypical of IgG4-related disease. If fever is an important part of the patient's presentation, the diagnosis is probably not IgG4-related disease.

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 Sjogren syndrome on the other.

There are also radiology exclusion features, so rapid progression of the radiology findings over 6 to 8 weeks is very atypical for IgG4-related disease, more typical of an infection or a malignancy.

And then finally, there are a number of pathology exclusion criteria that are really critical. So if one sees a necrotizing vasculitis with the emphasis on the necrosis, it's not IgG4-related disease. If there is an overwhelming granulomatous inflammation, that is also atypical of IgG4-related disease.

So finally, after getting through the question of whether there's a typical organ involved and whether the patient fulfills or does not fulfill exclusion criteria, we get to the inclusion criteria. And there are eight domains for the ACR/EULAR classification criteria. Serum IgG4 concentration, the pathology which includes both histopathology and immunostaining, and then the organ-specific features, the glandular enlargement, the chest and thoracic aorta, the pancreas and biliary tree, the kidney and the retroperitoneum. Each of the items in these domains is weighted.

And so speaking a little bit further about the serum IgG4 concentration, because all the time I get referred to me patients with an elevated serum IgG4 and the question is asked, Does this patient have IgG4-related disease? So there are three questions that I ask. Number one, how high is the serum IgG4 concentration? The higher it is, the more likely it is that IgG4-related disease 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? And I've mentioned what those are. And 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. So these

are three very important questions. And it is critical to remember that even a patient who has an elevated serum IgG4 greater than five times the upper limit of normal, the positive predictive value of that elevated serum IgG4 is only 75%, which means that 1 patient in 4 who has a serum IgG4 concentration elevated to five times the upper limit of normal has another diagnosis, not IgG4-related disease.

So these classification criteria, which are based on clinical features, serological findings, radiologic data, and pathology findings are really critical to approaching the diagnosis of IgG4-related disease correctly.

This patient makes this point well. He's an elderly man who was referred to me to treat his ANCA-negative ANCA-associated vasculitis. It was thought that because he had this proptosis, because of a retrobulbar mass causing proptosis of the right eye, and he had sinus disease, and he had lung disease, and he had renal dysfunction, that he had granulomatosis with polyangiitis, even though he was ANCA negative. So there were some clinical features that suggested that it might be ANCA-associated vasculitis. There were radiologic findings that supported that. The serological data, however, did not. And ultimately, the pathology biopsy of the retrobulbar mass did not show granulomatous inflammation. It showed a lymphoplasmacytic infiltrate and obliterative phlebitis and the classic, albeit not diagnostic features of IgG4-related disease, which was the correct diagnosis. And his serum IgG4 concentration was actually quite high. So this case underscores the point that ANCA-associated vasculitis and IgG4-related disease can mimic each other very closely.

Underscoring that point a little bit more, because this comes up all the time clinically, on the left is a biopsy from a patient with IgG4-related disease. Lots of IgG4-positive plasma cells on the left. There is storiform fibrosis. And on the right, one sees a biopsy from a patient with granulomatosis with polyangiitis, lots of IgG4-positive plasma cells and also storiform fibrosis. So one cannot base the diagnosis exclusively on any of these parameters, including the pathology findings.

And so the pertinent positives are also important. If there is necrosis, it's not IgG4-related disease. Multinucleated giant cells and neutrophilic leukocytosis within tissue, neutrophilic abscesses, this really speaks to another disease; namely, very often, ANCA-associated vasculitis, particularly GPA. And it's important to remember that even a low titer ANCA can be important if it has been performed in a good lab, and if it is directed specifically against either myeloperoxidase or proteinase 3, and if the patient has other features that are compatible with ANCA-associated vasculitis.

So I'll turn it back to Dr. Zen now to talk again about the role of biopsy for suspected IgG4-related disease.

**Dr. Zen:**
Yeah. Thank you very much. Yeah. So I think if we take a biopsy from the patient with suspected IgG4-related disease, we need to examine the tissue from two aspects. One is we need to look for positive findings. So basically, we need to find histological findings that are characteristic for this condition. If we have plasma cell rich inflammation, obliterative phlebitis, storiform fibrosis, and IgG4-positive cell infiltration, I think these findings are clearly supporting the diagnosis of this condition.

But at the same time, it is also important to look for negative findings that may help us to exclude this condition. This is possible because we already know some microscopic findings are unlikely to occur in this condition. So negative findings include necrosis, neutrophilic infiltrate, abscess granuloma, and necrotizing vasculitis. If we have any of these findings in the biopsy sample, the possibility of IgG4-related disease becomes very, very low.

So my message is to look for not only positive but also negative findings.

I skipped this case, and I just want to briefly discuss this 65-year-old man who presented with multiple lung nodules. We initially suspected that IgG4-related disease because of imaging findings, as well as IgG4 elevation, mildly elevated IgG4. And we took a biopsy from one of the nodules, which showed extensive lymphoplasmacytic infiltrate and fibrosis, and also immunostaining confirmed a lot of IgG4-positive cell infiltration. But there was one minute focus of necrosis with granulomatous change. So basically, this is a negative finding, and we could entirely exclude the possibility of IgG4-related disease based on this finding, and we made his diagnosis of granulomatosis with polyangiitis in this particular case.

So it's really important to look for negative findings in a biopsy sample, which is taken from a patient with suspected IgG4-related disease.

So I'll hand over the mic to Emanuel, I think. Yeah.

**Dr. Della Torre:**
I was saying that we're moving towards our last slide deck and on the treatment of IgG4, and hopefully succinct also, because while we wait eagerly for mechanistic therapies that might expand our therapeutic armamentarium for patients with IgG4-related disease. Nowadays, we only rely on two main drugs, which are glucocorticoids and B cell-depleting agents.

And it's important to diagnose IgG4-related disease promptly, as mentioned already by Dr. Stone and Dr. Zen, because each of the

phenotypes if are presented early on, might down the road, lead to organ insuffificiency and organ failure. And here, you have a list of examples of this very severe potential organ failure. We have at least one patient from the pancreatobiliary phenotype that underwent liver transplantation. And also one from the systemic disease that underwent renal transplantation because of late diagnosis.

So how do we treat IgG4-related disease nowadays? First of all, we might want to consider some preliminary aspects of the disease which are nicely recapitulated and summarized in the International Consensus Guidance statement on the management and treatment of IgG4 that was published 10 years ago nearly. First of all, we want to consider that IgG4 probably not always requires treatment, especially in organs that are non-life-threatening manifestations, so those that are basically asymptomatic with single organ disease. So in this case, we might want to watchfully wait for progression of the disease, because cases of spontaneous remission have been described, although rarely. If the disease, of course, is symptomatic and affects life-threatening manifestations, then we want to treat patients urgently. So depending on the presentation, we might want to decide on the intensity of the treatment and then on the drug that we want to use.

Second consideration is that probably because of this, also we have a limited window of time for treating disease, because before irreversible fibrosis succeeds. So the longer the disease, probably the lower the probability of revert these active fibrosis, and restore the organ functionality.

Third, we want to consider that, because we don't know what is the driver, the trigger of the disease, IgG4 is a relapsing disease. Once we put it into remission, the disease will ultimately come back in most patients. So we want to consider first an induction of remission treatment and then a maintenance of this reduction of this remission, especially in patients who present baseline with features that might predict an early relapse of the disease. And we will see these predictors later on.

So the first treatment is, in general, glucocorticoids, which can be used also as a next line therapy, because IgG-4 related disease is a very steroid responsive treatment. So even if we don't get to a final diagnosis, response to glucocorticoids might be a very helpful tool to rule out cancer, for instance.

And finally, because IgG4 affects elderly individuals with potentially already existing comorbidities, if we're also part of these comorbidities with our glucocorticoid therapy, we might want also to support our patients with collateral site treatments for pancreatic insufficiency, for renal insufficiency, or for osteoporosis or for blood hypertension. So as I said, glucocorticoids are the first line therapy. Typical scheme of induction of remission consists in 0.6 or 1 mg/kg of prednisone given for 3 to 4 weeks, and then taper this down over 4 to 6 months, maintaining lower doses of glucocorticoids for a variable period of time, depending on the school, on the experience, and of the organ manifestations. But IgG4-related disease has anticipated relapse in nearly all patient up to the 3 years. And predictors of relapse include multiorgan involvement at baseline, elevated serum IgG4 at baseline, and/or elevated serum IgE at baseline.

At this point, we want to consider also treatments for maintaining disease remission. And if we want – if we don't want to use glucocorticoids, we can only look into alternatives, such as DMARD, classic immunosuppressive agents, or B cell-depleting agents. Both of them have been demonstrated to be effective to a certain extent.

So I would like to mention just two studies. The first is this recent study, a prospective, randomized study conducted in China, where researchers randomized three arms, patients with IgG4-related disease receiving maintenance treatment with glucocorticoids plus immunosuppressive therapies, with only immunosuppressive therapies, or with no drugs. So basically kept on follow-up.

And they demonstrated that patients on maintenance treatment with either immunosuppressive agents alone or in combination with glucocorticoids, relapse less frequently, suggesting, on one hand, that immunosuppressive treatment with classic immunosuppressive agents might be helpful in maintaining disease remission regardless of the use of glucocorticoids.

On the other hand, this study does not clearly explain what is the best immunosuppressive agent to be used, because immunosuppressant therapies included a variety of combination of methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil. So basically, numbers are still probably low to draw a conclusion on the relevance of each single immunosuppressive drug.

What we know for sure, on the other hand, is that B cell depletion works effectively, even without glucocorticoids for both induction of remission and maintenance of the remission. 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 was summarized in a systematic meta-analysis, showing a 90% rate of complete response at 6 months, even in the absence of concomitant glucocorticoid therapy. Nevertheless, also patients on B cell depletion relapsed, at least in 20% of cases of the median of 10 months from this meta-analysis. So patients with predictors of relapse might also be kept on maintenance treatment with periodical infusion of rituximab.

And on the right, you can see examples of the impressive response of Mikulicz disease or lung masses that disappear after 4 to 6 months from the injection of rituximab, which is at least in IgG4-related disease given with the rheumatoid arthritis scheme, so three

infusions of 1 gram, 15 days apart. And these are examples of orbital and pancreatic disease, as we mentioned then earlier on in Dr. Stone's examples, showing how an orbital pseudotumor might improve, again 4 to 6 months after the rituximab infusion, and similarly, autoimmune pancreatitis with the diffuse pancreatic swelling that basically goes back to normality after treatment.

So this was my last slide. And if we still have time. John, I'll turn the mic to you for questions.

**Dr. Stone:**
Thank you very much, Emanuel. So IgG4-related disease is such a fascinating condition. I think we could go on for a couple of more hours about the pathology features and about the treatment features, but we are just a little bit over time. So I will ask Emanuel one question that was asked earlier that we didn't get to and that relates to the response of the patients who have atopic features to treatment for IgG4-related disease. Emanuel, do you have any sense of whether the patients with atopic features respond differently to our conventional or biologic therapies for IgG4-related disease and patients who do not?

**Dr. Della Torre:**
This is a very tricky question. As I was saying before, I'm fully convinced that these atopic manifestations in our IgG4 patients are probably supported by different immunological mechanisms. So myexperience, it might occur that both things happen, either that the atopic manifestations in a patient with IgG4-related disease, or at least the so-called atopic manifestation, nicely responds to the rituximab or any other B cell-depleting agent, but also that these manifestations do not respond in the way we expected, suggesting that probably they are not part or driven by the same immunological mechanisms that drives IgG4 in general. So in these cases, we're starting to also use other biologic drugs in compliance with guidelines for the treatment of severe rhinitis or severe asthma. So in my experience, there are two clusters depending on this atopic manifestation probably; one who responds to B cell depletion and the other who do not respond, probably because of difference underlying immunological mechanisms.

**Dr. Stone:**
Wonderful. Thank you very much for that thoughtful and detailed response about an area where I think we still need a lot of work in IgG4-related disease, understanding these sort of type 2 immune responses that happen in a very significant proportion of our patients.

I'd like to thank you both for joining today. Yoh, the conversation with you is always enlightening and underscores for me the great pleasure I've taken over the years in working with pathologists to understand IgG4-related disease.

**Dr. Zen:**
Thank you.

**Dr. Stone:**
So I'd like to thank our audience for joining in. There is CME credit available for this. We ask that you complete the post test. Hopefully you'll get all the answers right and then submit for credit. So thank you very much. Have a pleasant day or evening, wherever you are, and we look forward to talking with you in the future.

**Conclusion:**
You've been listening to a replay of a live broadcast this activity titled: Identifying the Great Imitator – Demystifying the Systemic Features of IgG4-Related Disease, is provided by Evolve Medical Education and is supported by an independent medical education grant from Amgen. To receive your free CME credit or to download this activity, go to reachmd.com/cme. This is CME on ReachMD. Be part of the knowledge.