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IgG4-RD Case Conversations: Using Thoracic CT as a Diagnostic Clue

Dr. Sharma:
Hello, everyone. My name is Amita Sharma, and I am a Thoracic Radiologist at Massachusetts General Hospital. I'm also the Medical Director of CT in the Department of Radiology, and an Associate Professor at Harvard Medical School.

Dr. Katz:
Hello. My name is Dr. Guy Katz. I'm a Rheumatologist also at the Massachusetts General Hospital and an Instructor at Harvard Medical School.

Here are our disclosures.

We're looking forward to speaking today about IgG4-related disease, and the insights we can get from thoracic radiology as part of the diagnostic process in this disease.

We're going to review two cases today. The first is a 53-year-old man who presents with chronic dyspnea on exertion, wheezing, and dry cough. He also had lateral eye swelling, nasal congestion, and lower urinary tract symptoms that occurred around the same time that he started developing his pulmonary symptoms. He had a longstanding history of known diffuse lymphadenopathy. And on physical exam, he was found to have bilateral submandibular gland enlargement, bilateral parotid gland enlargement, and left lacrimal gland enlargement, with some periocular swelling that was visible on exam as well. We obtained some radiology, and Dr. Sharma, it would be great if you could walk us through what we see.

Dr. Sharma:
Thanks, Guy. So these are some selected axial images through a contrast-enhanced chest CT, and I put some arrows to help us identify some abnormalities here. The image on your left shows that there is enlargement of a right paratracheal lymph node, and the image on your right shows enlargement of a right hilar lymph node and a right subcarinal lymph node. So generally, when we measure lymph nodes, we measure them in their short axis diameter. But in the chest, the short axis diameter should be less than 1 cm. And all of these are larger than 1 cm in short axis. So that largest one in the right hilum was actually about 1.6 cm in short axis diameter. So there's evidence of generalized lymphadenopathy in this patient.

And then on the next image, we have some selected images through the chest, now on lung windows. So this window setting allows us to see the lungs and the airways. And the first finding when we look at the airways is that the shape of the trachea is actually abnormal. Normally, the trachea should have a nice horseshoe shape that has relatively equivalent levels of diameter for the sagittal and coronal diameter. But you can see in this example that the coronal diameter is severely narrowed, and the sagittal diameter is increased relative to that. So this is what we call a saber-sheath trachea. And that really tells us that there's remodeling of the trachea. When we go from the top to the bottom of the trachea, the intrathoracic portion becomes this shape in a saber-sheath trachea, but above the level of the thorax, the trachea is of normal shape.

And what this indicates, Guy, is that there is increased intrathoracic pressure. So typically, we see this with chronic obstructive pulmonary disease. So that's usually how it's been described. So it's interesting that your patient has this because, looking in the lungs,

there's no real evidence of emphysema. But when we look at the bronchi, there is this very diffuse bronchial wall thickening. So if you follow the airway wall in the right upper lobe, where the arrow is on that image on the right, you can see thickening that's very sort of nodular in its appearance along the whole length of that right anterior segmental airway.

And then on the next image, we actually see that this bronchial wall thickening is really quite diffuse. So the image on the left shows a segmental airway in the right lower lobe. And notice how that wall is really very prominent, because it has nodular thickening along the wall. These bronchial walls are thickened quite proximally, because as we get to the distal portion, there isn't such obvious bronchial wall thickening.

And then as part of chest CT, because we perform volumetric imaging, we can actually do multiplanar reformatted imaging. And so this coronal reformatted image really shows quite nicely, that nodular thickening in the right upper lobe segmental airway. But if you look at the other more central airways in the left lung and also in the right lower lobe, you can see that that's really quite diffuse bronchial wall thickening throughout the lungs. So a very interesting finding, that combination.

Dr. Katz:
Thanks, Amita, that was really helpful and really explains why the patient might have been having such significant dyspnea on exertion and wheezing with all that bronchial wall thickening.

So we did some additional workup. His complete blood count showed eosinophilia. The comprehensive metabolic panel was normal. His inflammatory markers showed that the ESR, the sedimentation rate, was elevated at 86 whereas the CRP, C-reactive protein, was normal at less than 3. He had an elevated total IgG. And his IgG subclasses showed that the IgG1 was elevated, IgG3 was elevated, and IgG4 was markedly elevated at over 10 times the upper limit of normal. IgE was also markedly elevated, at over 3000. His C3 was normal, whereas his C4 complement level was low at 5. And finally, he had a lymph node biopsy that showed lymph node – lymphoid hyperplasia, a plasma cell ratio of IgG4-positive cells to IgG-positive cells that was greater than 80% with over 100 IgG4-positive cells per high-powered field.

Overall, these serologies, in combination with the patient's enlargement of the glands of the head and neck, and the bronchial wall thickening that was seen on the imaging, are strongly suggestive of a diagnosis of IgG4-related disease.

So let's take a step back and talk about IgG4-related disease for a second. This is a systemic autoimmune disease that causes, typically, multiorgan involvement, though single organ involvement can rarely occur. There's a broad range of intrathoracic manifestations that can be seen in this disease. In fact, perhaps more variety in the thorax than we can see just about anywhere else. It's a chronic and relapsing disease. And unlike many other systemic autoimmune diseases, it's very indolent, where symptoms tend to develop very slowly over time, and patients can have largely asymptomatic disease, even when they have quite active disease. And as a result of that, clinically significant damage is very common in the disease.

So we're going to spend a lot of time talking about the thoracic manifestations, but it's really important to recognize that this is a systemic disease, and it can involve a wide variety of extrathoracic sites as well. Lacrimal and major salivary gland enlargement is one of the most common presentations of the disease. And other manifestations that we can see in the head and neck include orbital inflammation, pachymeningitis, and Riedel's thyroiditis. In the abdomen, autoimmune pancreatitis is one of the most common manifestations as well, and is very commonly seen in conjunction with IgG4-related cholangitis. Retroperitoneal fibrosis, or periaortitis, is an inflammatory condition of soft tissue surrounding the infra-abdominal aorta, often leading to obstruction of the ureters and hydronephrosis, and is also one of the most common manifestations of IgG4-related disease. In the kidneys, we frequently see tubulointerstitial nephritis, and prostatitis is actually a common manifestation as well.

IgG4-related disease is very much a clinical pathologic diagnosis. It's important for clinicians considering the diagnosis to recognize the typical clinical manifestations as we just went over and will continue to go over throughout this talk. The laboratory markers are a very important part of the diagnostic process. Most patients have elevated serum IgG4, though other markers that can be elevated include IgG1, IgG3, IgE, eosinophils. And many patients have C3 and/or C4 hypocomplementemia. As was seen in our patient, ESR is typically elevated, where a CRP is typically normal or only mildly elevated.

Radiologic findings are critical for the diagnosis in most cases. And also critical in most cases is histopathology, where we look for evidence of a dense lymphoblastic infiltrate, a high number of IgG4-positive cells per high-powered field, with a high ratio of IgG4-positive to IgG-positive cells. Storiform fibrosis is another typical histopathologic finding in IgG4-related disease, as is obliterative phlebitis.

Importantly, there are certain elements of the presentation that we really don't see in IgG4-related disease, and strongly suggest a mimicking condition. For example, fever and a lack of response to glucocorticoids are very unusual in IgG4-related disease, and really

suggest an alternative diagnosis. Disease-specific autoantibodies, such as the PR3 or MPO ANCA antibodies or the Ro antibody of Sjogren syndrome, typically suggest that those are the diagnoses. Radiologic abnormalities such as rapid progression or long bone abnormalities suggestive of Erdheim-Chester disease are also atypical of IgG4-related disease. And certain features on pathology are really atypical, such as neutrophilic infiltrate, granulomatous inflammation, necrosis or necrotizing vasculitis, and features of histiocytic disorders. When we see any of these features in a patient presenting with what otherwise looks like IgG4-related disease, it is important to consider the many other diseases that can look similar and are treated differently.

Back to our case. So he was treated with prednisone and rituximab, and he had complete resolution of all symptoms, including the enlargement of the glands of the head and neck, as well as his chest symptoms. So in this case, we were able to see that chest CT was really helpful in understanding why the patient was having symptoms and understanding that that was a manifestation of his underlying IgG4-related disease.

In contrast, I'd like to go through a case in which the patient really didn't have chest symptoms. So this was a 57-year-old man who presented with chronic bilateral eye swelling as well as submandibular gland enlargement. This was associated with mild dry eyes and dry mouth, and as I mentioned, he had no dyspnea, no cough, or no chest pain, really was asymptomatic from a chest perspective. Previously, his gland enlargement and eye swelling was responsive to multiple courses of prednisone, but he frequently had return of symptoms after the glucocorticoids were discontinued.

So we obtained a CT chest in this case more as part of the diagnostic workup to see if we could find other clues to what the diagnosis could be, with the idea that IgG4-related disease was high on our differential, as you can imagine from the similarity in the presentation to the previous case.

Dr. Sharma:
So we had done a chest CT as part of his evaluation. And I just have some limited views, just to show you the main findings and to just talk about the sort of differential diagnoses.

You can see on these lung windows that there is evidence of diffuse bronchial wall thickening, very much like the second – or the first case that we had with nodularity along the bronchial walls. We see it best in the right upper lobe on these two sets of images. But also, even though this is a lung window setting, you can see within the mediastinum that there are quite markedly in large paratracheal lymph nodes, in the high right paratracheal region and in the low right paratracheal region.

And if we go on to the next slide, the lymphadenopathy again, extends along the airway walls centrally extending along these segmental airways in this kind of diffuse thickening that has this nodular appearance. So really very marked bronchial wall thickening in this patient.

And then on the next image, we have some mediastinal windows that, again, show that mediastinal paratracheal lymphadenopathy I had mentioned before. But in addition, if we look carefully around the ascending aorta, there's evidence of some periaortic soft tissues and periarteritis surrounding the ascending aorta.

And then on the next image, we can actually appreciate that even at the level of the main pulmonary artery, there's some soft tissue thickening around the ascending aorta. And on that same image, on the left, if you're looking in the paravertebral region, there is some paravertebral soft tissue bilaterally, which really is outside the pleural surface, so it's extrapleural in its position. The image on the right is through the level of the coronary arteries. And if you focus on the left anterior descending coronary artery and the circumflex artery, you can see that there is soft tissue surrounding the wall of the coronary arteries. There's some fusiform dilatation of the right coronary artery as well. And this is very abnormal.

So this finding is really quite unusual. When we see this combination of periaortitis with this paravertebral mass and the coronary artery involvement, it really limits our diagnosis. So if you just saw one finding, you might have quite a long differential diagnosis, but I must say that this combination of findings I really only ever see in patients with IgG4-related disease. So that really is suggestive of IgG4-related disease.

And the next image, these are images that we see – in the chest CT, we always go through the upper abdomen, and so this provides clues of upper abdominal involvement in this patient. And if you focus on the pancreas, the pancreas has lost its normal shape. It has a very sausage shape here. It's lost its normal outline. So there's enlargement and thickening of the pancreas. And then the second image on the right, around the aorta, you can appreciate involvement of the periaortic tissue. There's soft tissue surrounding the aorta that's inseparable from the wall. So really, very characteristic of an associated aortitis.

Dr. Katz:
Thanks for that. Amita.

So we performed a laboratory evaluation on this patient as well. Like the previous patient, he had mild eosinophilia, and his total IgG

was elevated. His IgG1 and IgG3 concentrations were normal, whereas his IgG4 was also markedly elevated, at over 900. His IgE was 258, and his complements were normal, and Ro and La were negative.

He had a submandibular gland biopsy, which I will point out is a better place to biopsy than a lymph node, because we can see more specific pathologic findings for IgG4-related disease. And what was seen was chronic sialadenitis with a dense lymphoplasmacytic infiltrate containing over 100 IgG4-positive plasma cells per high-powered field, and an IgG4-positive to IgG-positive ratio of 60%. There was storiform fibrosis and obliterative phlebitis.

Overall, this constellation of clinical, radiologic, laboratory, and submandibular gland biopsy findings is entirely diagnostic of IgG4-related disease.

Dr. Sharma:
Yeah, he was a very interesting case, and it shows the importance of looking outside the lungs. And so there are many intrathoracic manifestations that you can pick up in patients with IgG4-related disease. And one of those is enlargement or masses within the thyroid gland, secondary to Riedel's thyroiditis. So this was a different case where there was a large mass in the left thyroid lobe secondary to biopsy-proven Riedel's thyroiditis.

And then the next image shows just some other manifestations within the lung. The combination of pleural thickening and lung nodules or consolidation that's typically very peripheral in its distribution, as you see here in the left upper lobe, can be seen in patients with IgG4. They also can get other lung manifestations with septal thickening and ground-glass opacity, as you see on the image on the right, in the lower lobes. There can also be evidence of pleural thickening, as you see in this case on the left, where there is thickening of both pleural surfaces. But notice that there's also involvement of the periaortic tissue. So that combination of multiregional findings is very typical for IgG4-related disease.

And then another case, the one on the right, demonstrates these multiple quite remarkable fusiform aneurysms of the pulmonary artery. And IgG4-related disease is really a mid and large vessel vasculitis, so multiple vessels can be involved within the chest.

There can be pericardial thickening, unusual in IgG4, but certainly can occur, as you see in the image on the left. And then on the image on the right, often these patients also have paravertebral mass and large masses, as you see in this case, do not cause encasement or narrowing of the adjacent aorta, and that's a typical way of us differentiating that from other possible etiologies that can cause paravertebral masses.

So really, it's hard to define a specific finding in IgG4-related disease, many of them are nonspecific. And if we look at this chart, starting from the left, lung nodules and bronchial wall thickening is really common in this condition, but also common in other diseases. We can also see in pleural thickening or effusion, thyroid enlargement. And then as we go towards the right, some findings that are less common with other conditions, such as peribronchovascular and septal thickening, large and medium vessel vasculitis, fibrosing mediastinitis, and then pancreatic enlargement, coronary artery involvement, periarteritis, or aneurysms of the coronary arteries, and paravertebral soft tissue masses; these occur less commonly in other conditions and so really become more specific, particularly if associated with other findings of a diagnosis of IgG4-related disease.

Dr. Katz:
Thanks for that, Amita.

So we treat IgG4-related disease using a number of medications. This disease is really universally responsive to glucocorticoids. However, there is a high relapse rate after treatment, and there's a really high risk of glucocorticoid toxicity, because this is a disease in which largely or more commonly elderly individuals are affected. And very often patients have endocrine, pancreatic insufficiency leading to diabetes as a result of autoimmune pancreatitis. So they're at high risk for glucocorticoid toxicity.

Unfortunately, there is limited efficacy of conventional synthetic disease-modifying anti-rheumatic drugs, though occasionally we do use mycophenolate, methotrexate, or azathioprine, and they can help decrease the relapse rate in some patients. Like glucocorticoids, there's a virtually universal response in this disease to B cell depletion, and rituximab tends to be our first-line treatment for severe or relapsing disease.

Because this is a chronic disease, it's so important to recognize that patients with this disease need to be monitored over time. It is a relapsing disease, and it can relapse long after the patient is treated either with glucocorticoids or rituximab. So it's important for these patients to be monitored over time. Disease biomarkers can be really helpful in monitoring this disease. In most patients who have elevations or abnormalities in these disease biomarkers at baseline before treatment, a subsequent rise of those markers or return of hypocomplementemia, for example, can predict a disease flare and usually should be taken seriously. And patients who have those serologic abnormalities should be re-examined to see if they have return of the symptoms that they previously had. Imaging should be

considered to identify other areas of asymptomatic disease, as our second case demonstrated the importance of. And very often, the serial imaging will need to be done over time to evaluate what happens to the disease manifestations and to screen for new manifestations over time. But this really needs to be individualized to every individual patient.

In this particular patient, we treated with B cell depletion, and he had normalization of glands and marked improvement in all of the radiologic abnormalities that he had that were so important in getting to the diagnosis, despite the fact that most of them were asymptomatic.

Dr. Sharma:
And this just shows how his bronchial wall thickening really improved. So pretreatment, there was a lot of thickening, and posttreatment much better. And this was seen in the upper lobes. And then the lymphadenopathy was also far reduced when we treated this patient. And then posttreatment, his paravertebral masses decreased in size, and the diffuse bronchial wall thickening also significantly improved. So he definitely showed a response on imaging biomarkers as well. The pancreatic mass decreased in size posttreatment, and the soft tissue surrounding his aorta also almost completely resolved. So he had an excellent response on CT following his treatment.

Dr. Katz:
In summary, IgG4-related disease is a systemic, chronic, relapsing autoimmune disease, and it has a broad diversity of manifestations in the chest. It's important to consider clinical, laboratory, imaging, and histopathologic findings in the diagnostic process for this disease. And chest imaging really should be obtained in all patients, regardless of the presence or absence of symptoms, because it can be so helpful in identifying severe manifestations and helping to get to the diagnosis. Glucocorticoids are effective, but most patients do benefit from treatment with B cell depletion in this disease.

Thank you very much.

Dr. Sharma:
Thank you.