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IgG4-RD Case Conversations: Diagnosing Pancreaticobiliary Manifestations and Ruling Out Malignancy

Dr. Hernandez-Barco:
Hello, my name is Yasmin Hernandez-Barco, and I'm a medical pancreatologist at Massachusetts General Hospital in Boston, Massachusetts, and it's my pleasure to introduce my colleague, Dr. Avinash Kambadakone, who is the Chief of Abdominal Radiology here at Massachusetts General.

Dr. Kambadakone-Ramesh:
Thank you, Yasmin. It's my pleasure to be doing this with you.

Dr. Hernandez-Barco:
We're very glad to be here with you today, and we're very excited about what we're going to share with you. Our disclosures are on the next slide.

Today we look forward to sharing a case with you on IgG4-related disorders, specifically related to the pancreas and biliary manifestations of this disease, and important thoughts about ruling out malignancy. So the case we're going to share with you today is a patient of mine. He's a 77-year-old male who presented to the emergency room in November of 2018. He had some abdominal discomfort and on presentation, he was noted to have jaundice and elevated liver function test. He also had slightly elevated lipase. Some important points of his history was that he was previously fairly healthy, and the week prior he presented to his primary care doctor with abdominal discomfort, had blood work done and was diagnosed with acute pancreatitis based on an elevated lipase level and this abdominal discomfort. He also had history of poorly controlled diabetes and atrial flutter on warfarin, and he did have an ICD in place. In the emergency room, his labs were notable for a supratherapeutic INR, a lipase level of 189, and as you can see, in just one week his liver function test had gone from completely normal to quite elevated, showing features of an obstructive pattern.

Dr. Kambadakone-Ramesh:
Thank you, Yasmin. I'm happy to share the imaging findings in this patient. The first imaging study was an ultrasound, which showed that there was gallstones and sludge within the gall bladder, and also dilated intra and extrahepatic bile ducts. The CBD was dilated up to 11 millimeters, and the distance EBD could not be visualized. So typically in these cases, we get a CT scan to evaluate for the pancreatic head, and on the CT scan which was done with oral intravenous contrast, the key findings were focused on the pancreas.

As you can see in the images, the pancreas was diffusely edematous. There was loss of normal pancreatic lobulations. With mild hypoenhancement of the pancreas in the early phase, and also mild . The pancreatic head also looked a little bulky. The Edison findings on the CT were also some scattered pancreatic calcifications in the pancreatic head, which indicates sequalae of prior inflammation. And also, the common bile duct within the pancreatic head demonstrated bile duct wall thickening and enhancement.

Now, looking at this constellation of findings, these indicate a process, an inflammative process suggestive of acute and chronic inflammation. Given the diffuse enlargement of the pancreas with loss of lobulations, and involvement of the bile duct, I would like to think of an autoimmune pancreatitis causing both cholangitis and pancreatitis. Now the differential concentration in this is we want to rule out a pancreatic mass. However, the lack of pancreatic ductal elevation, lack of vascular involvement, and concurrent involvement of the

bile duct indicates more of an inflammatory etiology.

Dr. Hernandez-Barco:
Thank you so much. I mean, I agree with everything that you've shared, and if we hadn't had the CT scan images, whenever a patient presents with rapid development of jaundice, especially with the liver function pattern that he had, other considerations are a hepatocellular injury from viral infections, or alcohol or autoimmune disorders. Also, acute pancreatitis with transient obstruction such as from a gallstone. But one very key, important point that you mentioned, especially with the findings in the pancreas is that while IgG4-related disease is in the differential, it's incredibly important to consider cancer. And until that's ruled out, we really can't make a diagnosis of IgG4-related pancreatic and biliary disease. And especially if a patient has painless jaundice, pancreatic cancer must be excluded.

So he underwent additional testing. He had a complete blood cell count, that had a mild normocytic anemia. His eosinophil count was normal. He had normal serum chemistries. His blood glucose was elevated. His serum IgG was 293, with upper limit of normal of that testing 86. And his CA 19-9, which is a tumor marker for pancreas cancer, was normal at 10. His liver function tests were elevated, and at this point, given the lab tests, the imaging findings and his symptoms, the next step that I will usually take in the evaluation for these patients is an endoscopic ultrasound and an ERCP. In his case, we were not able to do the endoscopic ultrasound right when he was in the emergency room, because of his supratherapeutic INR, but he did undergo ERCP.

Dr. Kambadakone-Ramesh:
Thank you, Yasmin, and these are the sequential images from the ERCP procedures. In the left-most image, you can see that there's a high-grade stricture in the distal common bile duct with upstream biliary duct debilitation. Now, whenever you see a high-grade stricture in the common bile duct, you want to differentiate between a benign stricture versus a malignant stricture. An interesting point here is you can see that at this transition between the dilated bile duct and the stenosed bile duct, there's gradual tapering which points to a benign etiology for the stricture. This patient underwent sphincterotomy, and also balloon dilatation of the stricture along with brushing for cytology, and two double pigtail plastic stents were placed.

Now coming the endoscopic ultrasound findings, the endoscopies on US found that the pancreas was lobular with several calcifications within the pancreas, as well as in the pancreatic parenchyma. And also, the pancreas looked diffusely edematous with subtle peripancreatic halo appearance, which is suggestive of a type 1 autoimmune pancreatitis. Biopsies were taken from the head of the pancreas. I would – interesting to see what the biopsy findings and the endoscopic ultrasound showed.

Dr. Hernandez-Barco:
Thank you. And we'll review that in just a side, but an important point – whenever doing an endoscopic ultrasound with a fine needle biopsy, it is important to be sure that you are doing a fine needle biopsy and taking a core of the pancreas. And the reason for that is because you do need architecture to make a diagnosis of IgG4-related disease. It's important to note that the biopsies are not necessarily to confirm the diagnosis of IgG4-related disease, but truly to rule out pancreatic cancer. But an EUS with fine needle aspiration is inadequate for the diagnosis because pancreatic cancer, primary sclerosing cholangitis, cholangiocarcinoma, and even celiac disease can have IgG4-positive cells in the fine needle aspirate, and so it is quite important to do a core biopsy to rule out cancer, and to look at the architecture.

So in this patient, his biopsy results showed an increased IgG4 plasma cells, focal storiform fibrosis, a focus of possible obliterative phlebitis and an atrophic pancreatic parenchyma. So, all of this was consistent with type 1 autoimmune pancreatitis or, in other words, the pancreatic manifestation of IgG4-related disease. On the right hand side – these are not his biopsy samples, but they do show the four classic histopathological findings – and the histopathology in IgG4-related disease is similar across all organs. And there are four major characteristics. The first is a diffuse lymphoplasmacytic infiltrate, which is usually centered around the pancreatic duct and ductile. The second feature is a diffuse fibrosis, which has a very characteristic storiform fibrosis, which has this woven or cartwheel pattern that you don't see in other forms of chronic pancreatitis.

The third feature that we see is obliterative phlebitis, with relative sparing of the arteries. And then, the fourth is IgG4-positive plasma cells. And each organ has a different threshold in order for it to be diagnostic of IgG4-related disorder, and in the pancreas that's greater than 10 IgG4-positive plasma cells per high-powered field.

So what is IgG4-related disease? It's a multiorgan, fibroinflammatory, systemic disease that can impact almost any organ in the body. Type 1 autoimmune pancreatitis is the pancreatic manifestation that we see of this disorder, and IgG4-related sclerosing cholangitis is the biliary manifestation of this disorder. The most common presentation is in older men, typically in the sixth or seventh decade of life, and as with our patient, painless jaundice is what you see most frequently as the initial presentation. It is important to note that because it is a bit of an insidious process, up to 60% of patients will present with irreversible organ damage in the form of diabetes, or exocrine

pancreatic insufficiency. And while it is called IgG4-related disorder, serum IgG4 is only elevated in about 70% of patients, and it's important to note that an elevated IgG4 level does not confirm the diagnosis, and a negative or normal IgG4 level does not rule out the diagnosis. So it can be very challenging to diagnose, but together in a multidisciplinary approach, we can usually get to the diagnosis.

Dr. Kambadakone-Ramesh:
Thank you, Yasmin. As you pointed out, this is a multi-organ system disease, and it's so fascinating that as we have learned more about this disease, we have learned that it involves multiple organs throughout the body, right, from the involving the ovaries, the salivary glands, the lachrymal glands, and in the abdomen involving the pancreas, retroperitoneum, bile ducts, kidneys and the aorta. And as we learn more about this, the imaging manifestations of this disorder are also unique. Coming to the abdomen and the pancreas, as was in this case, there are two major type manifestations of autoimmune pancreatitis. The diffuse form, as we saw in this case, where there is diffuse enlargement of the pancreas along with loss of normal pancreatic lobulations, and a very distinct and characteristic peripancreatic halo of soft tissue density, as you can see on the left-sided image, which very – is very typical of autoimmune pancreatitis. Focal forms can also manifest, with similar appearance where you have a segmental mass-like enlargement with variable enhancement. Typically, it is hypo-enhancing in the early pancreatic phase of imaging, and shows more delayed enhancement. As we discussed, it's a multiorgan disease. You can look at the abdomen – the three areas which are commonly involved are the bile ducts where you have involvement of both the intra and extrahepatic bile ducts with varying degrees of wall thickening enhancement, and intervening areas of stenosis and dilatation.

The kidneys can be involved in interstitial nephritis and on imaging typically we see hypoenhancing areas in bilateral kidneys, which could be rounded or wedge-shaped, extending up to the cortical surface. In the last image, you can see a typical retroperitoneal fibrosis-like manifestation where you have a soft tissue density area in the retroperitoneum encasing the aorta endo. So what is the importance of IgG4 disease, Yasmin?

Dr. Hernandez-Barco:
So, we do see a significant rise in the incidence of IgG4-related disease, and probably this is due to the fact that we are improving our ability to recognize the disorder. And as I mentioned previously, it is very important to recognize this disease early on, because immune dysregulation leads to a very slow destruction of the organs that it involves, and it can lead to irreversible organ damage. And while its incidence is rising, it's important to remember that it does mimic other conditions, including malignancy, pancreatic, biliary, and so if a patient presents with mass-forming pancreatitis – excuse me, with a mass in the pancreas, then we certainly want to rule out cancer before making the diagnosis of IgG4-related disease. The other important point in recognizing IgG4-related disease is that there is treatment, and the treatment is overall effective. And we'll go over that in the next few slides.

The treatment IgG4-related disease really has three major pillars, that are based in our understanding of the pathophysiology of the disease. The pathophysiology includes abnormal antigen presentation from B-cells to cytotoxic T-cells, and these cytotoxic T-cells release a host of factors that lead to a lot of fibrosis and destruction of the organ that's impacted. Steroids are a wonderful choice of medication because it completely decreases the entire immune system, and you get very, very rapid remission. But the problem with steroids essentially is twofold. One, you have very, very high relapse rates once the steroids are discontinued. And steroids, even in a short term, can have a lot of side effects including mood disturbances, bone density issues, diabetes dysregulation. And so, they're fine for the first initial treatment, but there are other options. The second pillar is immunosuppressive therapies. These medications include azathioprine, mycophenolate and others. And these medications have ben used but we don't have robust data on their effectiveness, and they are not predictable in the way that they treat each patient. And so, we've really moved away from these medications to B-cell depleting therapies. And B-cell depleting therapies are quite effective, and they target the B-cells that are really underlying the pathogenesis of this disorder.

So for our patient, who was initiated on steroids – the treatment that you usually use is 40 mg for four weeks, tapering by 5 mg each week, for a total of 12 weeks. But he was treated with three rounds of steroids and developed brittle diabetes during this period of time.

He was transitioned to azathioprine biweekly, but he failed this therapy twice as well.

Dr. Kambadakone-Ramesh:
Thank you, Yasmin. And it's really fascinating, as we go over the imaging, the manifestations in this patient over time. It's – I will show the scans when the patient had recurrent radiographic flare. You can see the CT images from three months and six months later, after initial presentation showing increasing development of pancreatic parenchymal and pancreatic ductile calcifications as well as slightly reduction in the volume of the pancreatic parenchyma. Nine months later, again, you can see has attributed endoscopic interventions with ballooned elevation of the stricture and the stent placement, with increasing the atrophy of the pancreatic parenchyma and increasing the development of ductile and pancreatic parenchymal calcifications. And 15 months later, you can see the pancreatic parenchyma is really strong, with the pancreatic ductile elevation secondary to ductile calcifications. And also, you can see on the first

image documents here that the patient now has a metallic stent with a plastic stent within.

Dr. Hernandez-Barco:
And so, the patient was referred to our care, and we started him on rituximab, and he essentially has been clinically stable without evidence of flare for at least one year. The lessons in this case are, could he have been treated differently earlier on? The answer to that is probably yes. There are factors which are highly predictive of relapse – patients that have multiorgan involvement, elevations of IgG4 greater than four times the upper limit of normal, or proximal biliary involvement. And if a patient fails steroids, or they have a high risk of relapse, B-cell depleting therapy should be considered the first line in these patients. And additionally, it can probably avoid stenting when you have an inflammatory stricture from IgG4-related disease.

So our patient no longer required ERCPs. He did develop exocrine pancreatic insufficiency, which is well-managed on pancreatic enzyme replacement therapy. He has insulin-dependent diabetes, and his MRI shows atrophy and calcifications, but he has not had another flare, as I mentioned, for one year, since receiving B-cell-depleting therapies. And with that, I'd like to thank you, Avinash, for joining me. It's been a pleasure to discuss this disease with you, and really to take care of patients with you over the last few years.

Dr. Kambadakone-Ramesh:
Thank you, Yasmin. The pleasure and honor has been mine to do this with you, and also help take care of patients, which can be often challenging and complex.