Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/digesting-igg4-rd-an-interactive-multidisciplinary-case-conference/24307/

Released: 10/30/2024
Valid until: 10/30/2025
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Digesting IgG4-RD: An Interactive, Multidisciplinary Case Conference

Announcer:
Welcome to CME on ReachMD. This replay of a live broadcast titled Digesting IgG4-RD: An Interactive Multidisciplinary Case Conference is provided by Evolve Medical Education and is supported by an independent medical education grant from Amgen.

Dr. Stone:
Hello, welcome to digesting IgG4-related disease, a session in which we will discuss two terrifically interesting cases that require multidisciplinary input from gastroenterology, rheumatology, radiology and pathology, and probably additional specialties as well.

I am Dr. John Stone. I'm a Professor of Medicine at Harvard Medical School and the Edward A. Fox Chair in Medicine at the Massachusetts General Hospital. I'm also the Executive Chairman of the IgG Forward Foundation. I will ask now each of my co-panelists to introduce themselves.

Dr. Kambadakone-Ramesh:
Thank you, John. I'm Avinash KR, Chief of Abdominal Imaging at Mass General Hospital and Associate Professor at Harvard Medical School, and I'm delighted to be participating in this interesting Case Conference.

Dr. Stone:
Thank you, Avinash.

Dr. Lohr:
My name is Matthias Lohr. I'm the Professor of Gastroenterology and Hepatology at Karolinska Institute, and a Senior Consultant at the University Hospital.

Dr. Stone:
Thank you, Matthias. And, Yoh?

Dr. Zen:
Hello, I'm Dr. Yoh Zen working at Institute of Liver Studies at Kings College Hospital in London, and Professor of liver histopathology and a Consulting Histopathologist.

Dr. Stone:
Thank you, Yoh.

As you will see, the expertise of each of these consultants is essential to dissecting these interesting cases. We have some preliminaries to go through here. Our disclosures are here. You can read those on your own. We have some additional disclosures here. The activity is supported through an unrestricted educational grant from Amgen.

These are our learning objectives. We have a couple of polls as well. You all have done these before and that will be interesting material for discussion when we get to them. But let's get right into it. The first case, and I thank Professor Lohr for providing both of these cases for our discussion. This one is called Once Upon a Pancreas.

So, the patient presented at a very important time in the world, January 2020, right on the eve of the worldwide COVID pandemic. She was a 68-year-old woman who presented with abdominal pain, and she had weight loss. She lost 11 kilograms over the preceding year. She had frequent, watery stools, fatty oily stools.

Her past medical history was relevant for a significant smoking history. She had a 45-year history of smoking, about 15-pack-years. She rarely drank alcohol. She also had a history of kidney stones, and that's relevant because that was a lot of the initial diagnostic consideration centered around that. The abdominal pain in the emergency room disappeared after treatment with nonsteroidal's and tramadol, but the routine laboratory evaluation that had been performed showed a slight elevation of her liver function tests, her hepatic transaminases.

There was clinical suspicion of kidney stones based on her presentation and indeed, kidney stones were demonstrated on an abdominal CT scan. But there was more seen on the abdominal CT scan in January of 2020. These images are shown here, and I will call on Avinash to enlighten us about the CT scan findings.

Dr. Kambadakone-Ramesh:
Thank you, John. So, what we see here is two images from a contrast-enhanced CT done in January. We see an axial image and a coronal image. As you see, most of the findings are centered around the region of the head of the pancreas, the pancreatic head is edematous. There is also mild thickening of the medial wall of the duodenum, which is shown by the bright arrows. There are two cystic lesions, you see one in the region of the pancreatic or duodenal groove, and you also see some fat stranding of the fat in that region. And there is another cystic lesion in the head of the pancreas.

Additional findings, so you see there's dilatation of the common bile duct and also mild prominence of the pancreatic duct. Now, looking at all these findings, they point to three features, or things which are going on in the head of the pancreas. One, there is inflammatory changes in the region of the pancreatic/duodenal groove, so it's likely there is some element of groove pancreatitis. Secondly, there is a cystic lesion in the head of the pancreas which points to which could be secondary to the inflammation there or it could be a preexisting cyst. And thirdly, the dilatation of the common bile duct and the pancreatic duct up to the region of the head of the pancreas, I would like to get further evaluation to see what's happening in the head of the pancreas. Most of these could be explained by inflammation, but you would want to rule out any neoplasm in the head of the pancreas.

Dr. Stone:
Thank you, Avinash.

So, following this evaluation, the patient underwent an upper endoscopy, and the gastroscopy showed some mild bleeding and edematous mucosa of the descending duodenum and the endoscopist reported that the passage of the tube was somewhat difficult in that part of the duodenum. There was partial insufflation after CO2, partial expansion after CO2 insufflation, but no signs of ulcerations or tumor at that point. It's fair to say that the assessment of the patient at this point was really affected ultimately over the next few weeks by the pandemic.

Biopsies were performed at this time but showed normal mucosa, and the patient was referred in February to surgery. The surgeon started the patient on esomeprazole based on the endoscopy findings, and pancreatic enzyme replacement because of the weight loss and steatorrhea. And a follow-up image of the abdomen was obtained.

Avinash, would you please take us through this image as well?

Dr. Kambadakone-Ramesh:
Oh, absolutely. Thank you, John. So, here again you see a coronal and axial CT image after contrast administration. The findings are similar to what we've seen in January, but there are some changes. For example, the cystic change, what we saw in the pancreatic or duodenal groove has improved. The peripancreatic inflammatory changes are slightly better, but there is persistent duodenal wall thickening. And an interesting finding here is that in addition to dilatation of the CBD, you also see some mild wall thickening of the common bile duct with enhancement, which usually indicates an inflammatory process. The cystic lesion in the head of the pancreas has slightly increased in size. I think it had increased by 5 millimeters.

Now, given that findings, and also this prominence of the pancreatic duct, you would still want to look at the head of the pancreas to make sure there is no mass. And given that the cystic lesion is now more clearly seen, in this patient, we would have typically gotten a 6-month follow-up MRI to make sure that this was a cystic lesion and wouldn't require further follow-up.

Dr. Stone:
So, the surgical consultation follow-up. This is in March, now a month after starting the empiric therapy. There was substantial improvement and the patient had actually gained substantial amount of weight during this period. By this time, of course, the pandemic

was threatening full-throttle and so there was no endoscopy follow-up. That was deferred for a while. So, it was not until October, after the first phase of the pandemic, that a follow-up endoscopy was performed that showed normal mucosa in the duodenum. Repeat duodenal biopsy was normal and endoscopic ultrasound was performed, which showed an atrial thickened slightly inhomogeneous appearance of the pancreas. The width of the main pancreatic duct was 2.2 millimeters. There was a thin-walled cyst assessed to be 2.5 by 1.6 centimeters. No tumor was suspected at this point and no nodular changes were detected.

But then, only 2 months later, in December, 11 months after that initial presentation, the patient presented with frank jaundice and there were laboratory assessments which showed much more elevated liver function tests as well, and a CT scan was performed. Avinash, will you please take us through this?

Dr. Kambadakone-Ramesh:
Thank you, John. Yes, so, interesting CT findings. That is, you again use the axial and coronal CT images with contrast administration. The difference you see compared to the prior scans is the inflammatory changes have resolved, but you see increasing dilatation of the common bile duct and the pancreatic duct which seem to transition in the region of the pancreatic head. And at the site where we earlier saw the cyst, there is a small area of nodular hyperdensity, which raises suspicion for a pancreatic head mass.

Dr. Stone:
OK. Thank you.

Matthias, I think it's time we turn to you. How would you manage the patient at this point?

Dr. Lohr:
Yeah. Well, if we go back to the initial symptoms, clearly this is a patient who certainly has a, you know, problem, quote-unquote, somewhere in the abdomen and most likely with the pancreas which primarily and initially was confirmed by, you know, the findings which were presented to you earlier.

Now, this obviously has a couple of elements which were pointed out. The cyst, the inflammation which became better, the pancreatic exocrine insufficiency which positively responded to the enzyme replacement therapy. So, the initial cause of this patient would have been as expected.

Now, with the latest pictures which we draw to our multidisciplinary team conference, it was obvious that there was more than just inflammation. So, it was decided at the conference that this patient should undergo surgery.

Dr. Stone:
OK, so a surgical referral at this point, a referral back to surgery, and this is the surgical sample.

Yoh, please let us know what you are seeing.

Dr. Zen:
Yeah. So, patient had the Whipple procedure. So, basically pancreatic head, extrahepatic bile duct, and the duodenum was resected and blocked. So, this is the one axial slice of the pancreatic head. We have duodenal mucosa on the lefthand side, and as you can see there are multiple inks on the specimen. So, red color represent the anterior surface of the pancreas and the green color represented superior mesenteric vein groove, and the yellow color is the superior mesenteric artery groove, and the blue area is the posterior retroperitoneal resection margin. So, these colors help us to understand the anatomical location. And the main lesion that is highlighted by A. We have ill-defined mass lesion on the center of the pancreatic head, and it clearly shows direct invasion into the duodenal wall, as indicated by arrow B. So, it's an infiltrative lesion centered on the pancreatic head.

Of the representative sections taken from the infiltrated mass region on histology clearly confirmed invasive ductal adenocarcinoma, moderately differentiated adenocarcinoma. One of the characteristic findings in this case was association with extensive inflammation within the tumor. We have significant lymphocytic infiltrate as well as mucus overproduction as shown by A.

So, this section was taken from the edge of the tumor, and we have two dilated pancreatic ducts, duct A and duct B, and these ductal structures are cystically dilated with intraductal papillary infiltration of the neoplastic epithelium. So, this pathological finding is in keeping with intraductal papillary mucinous neoplasm, so-called IPMN. And in this picture, we also have invasive cancer in the area of C. So, histologically, there is a direct trend [mic cut out] with cancer. So, the most likely explanation is that the pancreatic cancer in this case, derived from pre-existing premalignant IPMN. That is the interpretation of this finding.

So, these are a summary of histopathological findings. So, pancreatic ductal adenocarcinoma, probably arising from IPMN, and adjacent structures such as the duodenal wall and peripancreatic adipose tissue are directly invaded by the cancer, and we found 2 positive regional lymph nodes out of 21, and the tumor was very close to superior mesenteric vein and the mesenteric artery, it grew. So, that

means R1 resection. So, final staging is pT2 N1 L1 V1 which means lymphovascular invasion plus and perineural invasion plus, and R1 resection.

Dr. Stone:
Matthias, do you have any comments about the pathology? And I'm also wondering whether the patient's initial symptoms, which are described rather vaguely, do you think those ultimately were caused by this tumor?

Dr. Lohr:
Honestly, I don't think that you can make this kind of case that it was from the beginning a clear-cut pancreatic cancer. However, if you look at these findings here, this albeit was resectable, is already a T2 tumor, which is, you know, more than 2 centimeters. And then, as explained with positive lymph nodes, lymph vessel invasion, vein invasion, perineural invasion, and ultimately R1 resection status, which puts this patient in a very bad situation for the further cause of the disease, I'm afraid to say.

Dr. Stone:
Thank you. So, there were some –

Dr. Lohr:
There was more.

Dr. Stone:
Yes. There were additional findings in the pathology which raised some very interesting questions that can be also very relevant to other cases as well. So, we want to explore those in some detail.

Yoh, would you please take us through these additional findings?

Dr. Zen:
Yeah. So, this is an axial slice of the superior aspect of the pancreatic head. I think this gross picture is nicely correlated with the CT findings. We have complex partly solid and partly cystic appearance. I think some of the cystic structures we saw on the imaging were due to IPMN, but not all of them. We have a very smoothly aligned 2-centimeter cyst next to the duodenum in this picture, and adjacent pancreas is very fibrotic.

So, this is the corresponding histology section. So, as you can see here, we have unilocular cyst as indicated by A, and multiple arrows, B, shows numerous lymphoid follicles in adjacent stroma. So basically, lymphoid follicular inflammation. And arrow C represent the polypoidal growth of the duodenal mucosa, probably due to Brunner's gland hyperplasia. And arrow D represented extensive hypertrophy of the muscle layer of the duodenal wall. So, these are complex microscopic changes observed just one histology section.

So, this is a high-power view of the cyst wall. So, there was no epithelial lining in that cyst. So, basically internal surface was made by granulation tissue and fibrous connective tissue. So, based on these findings, the cyst was a pseudocyst. And in the cyst wall, we have multiple lymphoid follicles. And then, we also found that a classic storiform-type fibrosis in adjacent pancreas, as you can see here collagenous fibrosis, collagen fibers are arranged in weave pattern in keeping with the storiform-type fibrosis.

Dr. Stone:
And with the word storiform being derived from the Latin word for storea, for woven mat. So, you can see why the pathologists use that term. We'll get to the potential implications of that in a moment.

Dr. Zen:
Yeah. And the other that shows extensive inflammation. This case had a significant inflammation inside the cancer, but also there was extensive inflammation in adjacent pancreatic parenchyma as you can see on the lefthand side. There was a significant lymphoplasmacytic infiltrate. And then, we have on the righthand side duodenal staging of IgG4 and IgG. So, IgG-4-positive cells are stained in red, and the brown cells represent IgG-positive cells. So, basically there are many red-colored plasma cells in this picture, meaning the extensive infiltration by IgG-4-positive cells. And the ratio of IgG-4 to IgG-positive cells is probably greater than 50% in this picture.

Dr. Lohr:
So, that was obviously, rather unexpected, I should say, right? And one could say that the storiform fibrosis which you pointed out, John, is a very typical, not to say enigmatic, finding in IgG-4-related diseases, particularly in autoimmune pancreatitis. And this is underscored by, as pointed out, more than 50% IgG-4-positive cells in this area adjacent to the tumor. That is to say, it's not a peritumoral IgG-4 positivity, which one sees occasionally, but this looks as if here is a genuine, you know, IgG-4 disease also with manifestation in the pancreas itself.

Dr. Stone:
Yoh, could you comment on the absence of obliterative phlebitis? Does the absence of that make IgG-4-related disease less likely?

Dr. Zen:
Yeah. So, if you look at the resected specimen or autoimmune pancreatitis, we normally see obliterative phlebitis, almost 100%. But we couldn't see that finding in this picture. But a caveat is that this case has cancer, so that changes the local anatomical structures, so that may mask preexisting obliterative phlebitis.

Dr. Stone:
OK. And what are the implications of the absence of a GEL lesion? Granulocytic epithelial lesion. What does that imply?

Dr. Zen:
So, the granulocytic epithelial lesion is a microscopic finding of the neutrophil-rich pancreatic duct injury. That is the pathognomonic change of type 2 autoimmune pancreatitis, which is independent of Type 1 IgG-4-related autoimmune pancreatitis. So, if we have a case of suspected autoimmune pancreatitis, we look for IgG-4-positive cell infiltration, storiform fibrosis, obliterative phlebitis for Type 1 autoimmune pancreatitis, and we look for granulocytic epithelial lesion for type 2 autoimmune pancreatitis. In this particular case, we didn't see a granulocytic epithelial lesion.

Dr. Stone:
So, it's a pertinent negative, which makes one think it's not a Type 2 autoimmune pancreatitis. But much of the other peritumoral lesion does indeed suggest type 1 AIP or IgG-4-related disease.

Dr. Zen:
That's right.

Dr. Stone:
So, we have our first polling question. So, I had asked our attendees to chime in on this question. In addition to the very evident ductal adenocarcinoma, with the intraductal IPMN-like lesion, does the patient also have Type 1 AIP, peri-duodenal groove pancreatitis, follicular pancreatitis, or some other pathology that we have not yet considered?

So, while the attendees are musing over this and the results will come up in just a moment, this is a scenario that happens very often, and I personally have been burned with scenarios like this. So, this is a very relevant case with some important take-home lessons. There are also some pathological entities here which will not be particularly familiar to rheumatologists.

Likely more to gastroenterologists, and of course, radiologists and pathologists.

Dr. Lohr:
This is quite true, John. There are some typical elements here which we will kind of talk about in a minute, I suppose. And then others which are not so frequently observed. But I think it's a very showcase that one should not, you know, narrow the diagnostic kind of view on a patient with such a lesion in the pancreas and in this entire area.

Dr. Stone:
Yeah. And you know, the lessons here really are a diagnostic one. This does come up a lot. Of course, in terms of prognosis, that's really going to be defined by the adenocarcinoma, which is very well-confirmed. But there are other diagnostic areas in which this scenario crops up, and this is an important take-home lesson.

We have now the results of the of the poll. Sixty-seven percent of our attendees were convinced by the pathology findings consistent with Type 1 AIP. Others also felt – and of course more than one answer may be correct – that there was evidence of groove pancreatitis. No one was sold on the follicular pancreatitis, and 11% still thought that we might be missing something.

So, let's turn to this. Mathias, maybe you could tell us about your thinking at this point.

Dr. Lohr:
Yes. I mean, we definitely have this pancreatic ductal adenocarcinoma, which was arising from an intraductal that is IPMN-like lesion. As was pointed out nicely by Yoh, there is – once this peritoneal lymphoplasmacytic infiltrate, which is rather typical even for some of the adenocarcinomas, which is not so typical is this parenchymal fibrosis. This is indeed a sign of the type 1 autoimmune pancreatitis. And then, you would, you know, you would expect some elevated IgG-4 in blood, in plasma, which we didn't do beforehand because there was no indication. The fact, as mentioned, that there is no phlebitis which is normally a sign of IgG-4-related diseases in the area of the pancreas, I think we can explain, but the other sign this pathognomonic focal storiform fibrosis pattern is really something which makes you think that this is indeed a type 1 autoimmune pancreatitis. And what other information would be helpful? Well, I almost said it, I think

one would very much like to know what the level of IgG-4 in serum is. And then after the surgery and the histology histopathology came back, we did this, and indeed it was 8.4, which is, as you can see, 7-times the upper limit of normal. So, that indeed confirms that this IgG-4-related disease is the underlying disease in this case. John?

Dr. Stone:
Very interesting. I mean, this is one where I think again the prognosis is not going to be affected by this. This is a scenario that comes up a lot when there is a tumor, and I don't think that we understand it fully. The serum IgG-4 is quite elevated, the pathology is quite consistent with IgG-4-related disease. I think a really relevant question at this point would be, is there an indication of IgG-4-related disease in another relevant organ? Does the patient have major salivary gland disease, orbital disease, lung disease? And at this point, the patient had probably undergone a fairly thorough workup and that had not been detected.

Dr. Lohr:
Right. We looked for that, obviously, in this patient and could not detect any other organ involvement as it is going from the GI or pancreas perspective. So, it was really the only manifestation. Now, I would like to point out that in the initial publication where the IgG-4 serum levels were established as a marker for autoimmune pancreatitis, in the cancer group which served as a control there were, you know, maybe 10 to 15% of the patients had slightly elevated IgG-4 levels in serum. However, I say this one more time, the IgG-4 level in this case is so high that it rectifies the establishment of the diagnosis of an autoimmune pancreatitis/IgG-4-related disease and not only a peritumoral inflammatory response which happens to have some IgG-4 kind of features here.

Dr. Stone:
So, this poses a real diagnostic dilemma, and if you've got a biopsy performed by ERCP or a CT-guided biopsy and you see this, you don't see tumor, you have to wonder what you're missing. And so, this is an area where I've certainly been burned.

Yoh, what do you think about this? Do you see this kind of IgG-4-related disease pathology in a peritumoral location frequently?

Dr. Zen:
Yes. Yeah. So, it can happen, not only pancreatic cancer but also other malignancies such as lung cancer. I would say up to 10% of cases show the IgG-4-rich inflammatory infiltrate in adjacent tumor. But in my experience the ratio of IgG-4 to total IgG-positive cells is usually a bit lower, less than 40%. So, that immunostaining sometimes helps me. So, for instance, if we take a biopsy from a patient with pancreatic mass and it shows autoimmune pancreatitis-like picture, but the IgG-4 ratio is a bit low and the imaging is not suggestible for AIP, I think we need to take a second biopsy just to make sure we don't miss malignancy nearby.

Dr. Stone:
I think that is the critical point. And here, the radiology findings are really, really key and Avinash, you have been kind enough to provide some more classic radiology findings of type 1 AIP. Maybe you could take us quickly through these.

Dr. Kambadakone-Ramesh:
Thank you, John. Yes, this case does represent a diagnostic conundrum because you see several overlapping findings of inflammation and neoplasm. So, I want to quickly go over what we typically see when we have autoimmune pancreatitis presenting in our reading room. So, here in the images, you can see there are two axial images. Typically, when the autoimmune pancreatitis is manifested, it could be either a diffuse form or a focal form. A diffuse form of autoimmune pancreatitis, what we typically see is the pancreas is diffusely enlarged and there is loss of normal lobulations of the pancreas, so it's being described as a sausage-like enlargement because of the loss of normal lobulation. So, you also see a peripancreatic halo of hypoattenuation which could be due to a combination of phlegmon or inflammation or fibrosis. Another feature which is helpful in identifying this entity is the delayed enhancement, which is due to presence of fibrotic tissue within the inflamed pancreas. Main pancreatic duct dilatation can also be seen, but you can also see strictures within the pancreatic duct, which is not commonly seen in patients with pancreatic cancer.

Yeah. So, in this slide, again, shows the diffuse form of autoimmune pancreatitis seen on MRI. And the cardinal findings here are that you see on the image on the left, the pancreas, which is normally hyperintense, that is bright on T1-weighted images, is hypointense, that is it is darker, which indicates the pancreas is inflamed. And if you see it after contrast administration, again you see a sausage-like enlargement of the pancreas with a peripancreatic hypoenhancing tissue. You also see that there is mild irregularity of the pancreatic duct.

Now, this is often a very common finding and a typical finding of autoimmune pancreatitis. But if you move to the next slide, this is where you have a diagnostic conundrum when autoimmune pancreatitis presents as a focal disease. Here, you see that the arrow points to an area of hypoenhancement, hypointensity, on the pre-contrast MR images, which then shows delayed enhancement due to fibrosis. And when we see such sort of a manifestation, oftentimes on imaging, it's hard to differentiate between a neoplasm versus an inflammation. And if you look at our case, the inflammation was centered around the pancreatic head, which is often where mostly a focal form of

autoimmune pancreatitis presents.

And as you discussed, and as Dr. Lohr pointed out, that often patients with autoimmune pancreatitis can have other organ manifestations. So extrapancreatic manifestations, if you look at the radiology literature, can be seen in up to 65% of cases. In this example, you can see that there is involvement of the biliary ducts, which occurs in up to 90% of cases of autoimmune pancreatitis, type 1 autoimmune pancreatitis. And typically, what we see is stricturing or narrowing of the pancreatic portion of the common bile duct with upstream dilatation. You also see bile duct wall thickening and enhancement. The MRCP image here shows it really well where you have stricturing of the distal CBD.

This is an example where you can see coronal CT and axial MR images in a patient which shows renal involvement, which can occur in up to 35% of cases. On imaging, we see them as multiple round hypodense nodules where you can see the arrows point out to, which are scattered throughout the kidneys. We can also see manifestations similar to what we see in the pancreas where the kidneys are enlarged. You see perirenal soft tissue and also urothelial thickening.

Retroperitoneal involvement is another area. Here, you see that there is retroperitoneal fibrosis in a patient with AIP where you see a thick, soft tissue mass encasing the aorta and its branches. There could be involvement of the ureters and on FDG-PET, which is on the right side, you can see there is intense FDG uptake, which indicates there's an inflammatory process.

Dr. Stone:
Yeah. So, looking around for other clues of IgG-4-related disease in other organs of the abdomen, not focusing only on the head of the pancreas, is a critical lesson here.

So, there's several other potential issues. A couple of other ones, anyway, that we should go through quickly. Matthias, could you chat briefly about this groove pancreatitis issue?

Dr. Lohr:
Yeah, this is a particular manifestation of pancreatitis, which is also called degeneration of the duodenal wall because you have pancreatic tissue within the duodenal wall which eventually will be inflamed and build quite typical cysts, and we will have a look at that in just a minute. So, that is another finding in this patient because that's where obviously, the pancreatitis started out. And maybe we can look at the pictures from both the CT and – yes, please.

Dr. Stone
I'm going to show you CT first.

Dr. Lohr:
Oh, yeah, absolutely. So, this is another typical manifestation of groove pancreatitis, where you see enlargement of the head of the pancreas and the inflammation is mostly centered around the pancreatic or duodenal groove. There is peripancreatic fat stranding and also, cystic changes. So, sometimes this has been described in the radiology literature as cystic dystrophy of the duodenum where your pancreatic tissue in the region of the medial wall of the duodenum leading to these findings.

Dr. Zen:
Yeah. So, in the Histology slide on the lefthand side, very pinkish area, there is a diffuse hypertrophy of the muscle layer of the duodenum and that process involves the adjacent pancreatic parenchyma.

Yeah, this is the high-power view. It looks like a neoplastic smooth muscle proliferation, but this process is entirely reactive, and it also involves the adjacent pancreatic parenchyma.

Yeah, just here I put these three needle biopsy cases of groove pancreatitis, and histological changes are really diverse in this condition. The left case was predominantly fibrosis and middle case shows predominantly inflammatory, and the righthand side we have Brunner's gland hypertrophy with adjacent inflammation. So, the microscopic changes are diverse in this condition, therefore it's always difficult to make a diagnosis purely based on histology, and it's always important to correlate with imaging findings and clinical records for the picture.

Dr. Stone:
Thank you, Yoh. We will move past the next one, follicular pancreatitis, since none of our attendees selected that, and we want to move to the learning points very quickly. So, the first is that, let's see –

So, just to let you know how the patient did, first. Unfortunately, she had a very difficult prognosis. From the time she was ultimately diagnosed, she was treated with appropriate chemotherapy but unfortunately, her disease progressed to the development of multiple liver metastases and palliative chemotherapy most recently.

So, her case tells some very important lessons. And the cystic lesions really require a very thorough evaluation. Avinash, would there have been some additional evaluation that you would have done early on that might have been prevented by the pandemic?

Dr. Kambadakone-Ramesh:
Thank you, John. I think this case really highlights the importance of follow-up of cystic pancreatic lesions and at Mass General, and similar to what other places do, we have a multidisciplinary conference which helps manage the patients with pancreatic cysts. We typically follow them up with regular CT or MRI, which depends on the presence of the size of the lesion, as well as presence of other findings. What I would have done differently here, or what we could have done differently, is that getting an endoscopic ultrasound in the initial phase when we saw the abnormalities. But we did see that endoscopic ultrasound was done and the biopsy was negative. So, it seems to me that the due process was followed, but again, these cystic pancreatic lesions, especially IPMNs, are premalignant and can have development of malignancy, not only within the cysts, but also remote from the site of the pancreatic cyst.

Dr. Stone:
Thank you. The other really important lesson here is that IgG-4-related disease-like pathology can occur in a peritumoral lesion, and if the whole of the case, meaning the radiology findings, the clinical findings, the serological findings, don't really add up, you need to wonder whether you might be missing a malignancy. And then finally, even a substantial elevation of serum IgG-4 isn't diagnostic of IgG-4-related disease or Type 1 AIP. One has to consider the entire clinical picture.

So, we'll move on now. That case included a number of lessons that we really needed to dwell on, but case 2 moves beyond the pancreas. So, the patient who presented in July of 2017 was a 65-year-old man who presented to Urgent Care. He had lost 15 kilograms over a 2-month period, and he presented with painless jaundice that became evident two days before presentation. He denied any abdominal pain.

His past medical history was remarkable for a history of smoking and well-controlled hypertension. These were his labs at presentation. A very elevated serum bilirubin, moderate elevation of the hepatic transaminases, and elevations as well of GGT and alkaline phosphatase. He underwent an abdominal CT scan, and let's see, I think we have some images here.

Dr. Kambadakone-Ramesh:
So, the images here show coronal CT images performed with intravenous contrast. What you do see is that there are bright linear structures in the region of the biliary ducts, which are, I think, the biliary stents because the CT seems to have been done after the ERCP. But what we clearly see, where the arrows point to, is a presence of a mass in the region of the hilum of the liver, which is causing obstruction of the bile ducts.

Dr. Stone:
OK. So, timeline of the events here, the patient did have stents placed, as Avinash mentioned, and an MRI and a new ERCP was recommended. The patient did have the ERCP with another stent placed, and then unfortunately presented 4 days later with jaundice and an elevated bilirubin. The new MRI confirmed a 3-centimeter tumor at the hilum of the liver and the decision of the MDT at that point was for urgent, hopefully curative liver surgery. And the patient underwent massive liver surgery with a right-sided hemi-hepatectomy, resection of the caudate lobe, and the extra hepatic bile ducts, lymphadenectomy in the liver hilum, and a left-sided cholangiojejunostomy. So, very, very extensive surgery.

And Yoh, will you please let us know what you're seeing here in the surgical pathology?

Dr. Zen:
So, yeah, this is a resected specimen, as you can see here, that we have ill-defined extensive periductal mass lesion with white creamy solid cut surface. The lesion extends along the large biliary tract.

Yeah. So, the mass was mainly made by fibroinflammatory process. The periductal connective tissue was widely expanded with the massive inflammatory infiltrate. Then as you can see here, the inflammatory process extended along the biliary tree. We have widespread subepithelial inflammatory infiltrate.

And then, despite the extensive inflammation, the lining epithelium was very well preserved without evidence of dysplasia, neoplasia, or malignancy. So, it looks to be active process. Then the peribiliary glands are involved in sclerosing inflammation, and as you can see here, that there are many mature-looking lymphocytes as well as the plasma cells in the inflamed area.

And similar to case number one, we had storiform-type fibrosis on the lefthand side, and we have conclusive obliterative blephitis on the righthand side. And finally, we did double immunostaining for IgG-4 and the MUM-1. MUM-1 is a marker for plasma cells. So, the red-colored plasma cells in this picture are all IgG-4-positive plasma cells, so wide-spread and numerous positive cells in this picture. And the ratio to total plasma cells is again, greater than 50%.

Dr. Stone:
So, at this point this case looks very much like the first case. We have a mass in the liver hilum. It was in the head of the pancreas before. The pathology doesn't obviously show adenocarcinoma here, but it certainly shows very typical IgG-4-related disease pathology.

So, there were some additional labs that were obtained, and in this case the serum IgG-4 concentration was absolutely normal. Note, however, that the total IgG is actually very, very high. So, the pathology we have reviewed here, and these are the serologies. Any comment at this point, Matthias?

Dr. Lohr:
Yeah. This is indeed remarkable, as you pointed out. But even in the first description of IgG-4 used in the diagnosis of particularly, biliary pancreatic manifestation of IgG-4-related diseases, there were cases where, quote-unquote, only the total IgG was elevated. And as you can see in this case, very much elevated. And then, what is also noteworthy, and we actually investigated this, particularly IgG-2 was elevated as well, also double the upper limit of normal, and that is, or can be I should say, indicative of the manifestation of the IgG-4-related diseases in the biliary tract. But there are other explanations.

Dr. Stone:
Indeed, and it was curious that repeat blood work after only a few weeks showed a very, very elevated serum IgG-4 concentration, going from normal to enormously elevated. And this really raises a question of the prozone phenomenon that my group described about 10 years ago. And the prozone phenomenon happens when there is an extreme elevation of serum IgG-4 concentrations, and when the assay for serum IgG-4 is performed by nephelometry. Then in the setting of very, very elevated serum IgG-4, the assay can be terribly wrong and can report a normal value, as was the case in this case. I suspect that the prozone phenomenon was playing a role in that likely spuriously low serum IgG-4 concentration that was reported initially.

So, the patient was referred to rheumatology at this point. And at this point, the patient seemed to be doing better. The patient's pancreatic function had been assessed and was found to be normal. A follow-up MRI had shown no evidence of inflammation in other organs. There was osteopenia, not terribly surprising, as it turns out. But what about treatment at this point?

So, here we have another polling question. So, what would you do, confronted with this case? Is treatment indicated in this patient now? The options are, no therapy needed, B – prednisolone 40 to 60 milligrams a day, C – A combination of a lower dose of Prednisone and azathioprine 150 milligrams a day, or D – B-cell depletion.

So, I'll ask our attendees to consider this scenario.

Dr. Lohr:
Yeah, this will be interesting because, yeah, I'm not going to comment on this now, but in a minute then. But I mean, it was a very unexpected finding, and I must say we are still sometimes tricked by these masses in the liver and in the pancreas, which look like a tumor. And then in the end, turn out to be not a tumor but a manifestation of IgG-4-related diseases either in the biliary tract or in the pancreas. Even these days, as a center of excellence, in those cases where you, as you pointed out, the IgG-4 is then normal, we operate on one or two cases every year, on the pancreas that is, which eventually turn out to be clear-cut out autoimmune pancreatitis type 1.

Dr. Stone:
Indeed, Matthias. In our series of patients from our institution with 120-or-so patients with histories of AIP, 9% of them had undergone modified Whipple procedures.

Dr. Lohr:
And I recall two of my patients who had actually proven autoimmune pancreatitis type 1 and then developed biliary tract lesions which were not only suggestive, but I mean typical, for bismuth 3-4 biliary tract carcinoma, where the brush cytology was negative, but they were underwent, still, to surgery, and then turned out to be IgG-4-related cholangitis.

Dr. Stone:
OK. So, the responses are very interesting here. So, 33% of the attendees felt that no therapy at this point was indicated, and I have to say, the rheumatology consultants at this point agreed and no therapy was administered. Forty-two percent of the patients would have treated the patients with prednisolone alone. Eight percent would have started a lower dose of prednisolone and azathioprine at the same time, and 17% likely convinced of a diagnosis of IgG-4-related disease, would have gone right to B-cell depletion at this point.

So, let's review what happened. So, no treatment was initiated on the basis of the rheumatology recommendation at that time. Some time went by, and the patient developed nasal symptoms, which recalled for him nasal issues that he had had 20 years earlier. The patient was referred to otolaryngology. Polypoid lesion was found, and additional lesions were also found in the nasal tract, and biopsy

was performed.

Yoh, would you please take us through this pathology?

Dr. Zen:
Sure. The stroma of nasal mucosa was expanded with edema and fibrosis. Can I have next one?

So, basically, this specimen shows the almost identical to what we saw in the bile duct. Lymphoplasmacytic infiltrate reaching IgG-4-positive cells in keeping with IgG-4-related disease.

Dr. Stone:
OK, at this point, conservative management was still selected by otolaryngology. Saline rinses and a steroid nasal spray, but no systemic therapy at this point. And then, pulmonary symptoms began. Cough, mucus production. A pulmonologist was engaged, and a CT scan of the chest was performed. And Avinash, please have a go at this chest CT scan.

Dr. Kambadakone-Ramesh:
Thank you, John. So, what we see on this slide are two sets of images from 2017 and 2020. Axial and coronal CT images in lung window. The pertinent abnormality is in the apical segment of the left upper lobe where you see a spiculated lesion, and if you see on the scan from 2020 pointed by the white arrow, this lesion had considerably enlarged in size.

Given this patient's history, while this could be an inflammatory process, we would definitely want to rule out malignancy. So, this patient underwent a PET-CT scan, which showed, you can see the arrow pointing to that abnormality, which we saw in the chest CT. The apical segment lesion shows FDG uptake. Again, that is inconclusive. It could be inflammatory versus neoplastic. So, if you see the image onto your right, a CT-guided biopsy was performed.

Dr. Stone:
So, on CT, the biopsy was actually inconclusive, not atypical or not unusual in that setting. And the FDG scan, Avinash has already gone over. The serum IgG-4 concentration at this point, however, are the highest that they have ever been, almost 15 grams per liter.

So, do we treat or undergo additional diagnostic tests at this point? And the decision at this point was to treat the patient without performing a resection of the pulmonary lesion or anything else. Prednisolone was selected 40 milligrams a day, despite the patient's osteopenia status. Appropriate osteoporosis therapy was undertaken, and fortunately, the CT scan showed substantial improvement with regression of the lesion, and the prednisone was tapered over multiple months to 5 milligrams of prednisolone a day.

But the story wasn't over there. The patient developed testicular symptoms, testicular pain, hematuria, and hematospermia on one occasion, dysuria, a fever of up to 38°, and ultimately, was referred to urology.

So, on physical examination, the patient had a high-riding right testicle while standing. Both testicles had a hard consistency and uneven shapes. The epididymides were tender bilaterally, especially in their caudal portions. But the remainder of the rectal examination and endoscopy were normal. An ultrasound was performed.

Avinash, please take us through these findings.

Dr. Kambadakone-Ramesh:
Thank you, John. So, what you see here is both the testes look mildly atrophic, but the right testes is diffusely hypoechoic with loss, without any appreciable Doppler signal. Even the left testis has some heterogeneous echogenicity. Typically, when we see the sort of picture in the right testis, when it's diffusely hypoechoic, without Doppler signal, we worry about testicular torsion. But clinical context here does not seem to support that diagnosis. The additional finding, which again points to some sort of an inflammatory process, if you see at the right epididymis here, the right epididymis is enlarged, heterogeneous echotexture. And given the constellation of findings of right testicular involvement, with epididymal involvement, which is not common in testicular torsion, this looks like inflammatory involvement from IgG-4 disease, which is not common but can be infrequently seen.

And in the subsequent image here, you can see that there are some, in the region of the vas deferens, there are some hyperechogenic foci which likely indicate calcifications, which could be a nonspecific finding.

Dr. Stone:
OK, so reconsidering treatment at this point, the patient had a full imaging work up again, and the patient was started on B-cell depletion. Remember that this lesion had occurred while the patient was still taking glucocorticoid. So, in May of 2022, the patient received B-cell depletion. Follow-up with urology confirmed clinical improvement of the testicular symptoms. This was confirmed on follow-up imaging studies, and the serum IgG-4 concentration had fallen from nearly 15 grams per liter to 3.4. Dramatic improvement.

Follow-up imaging here, Avinash?

Dr. Kambadakone-Ramesh:
Yeah. Thank you, John. So, the images here are consistent with the clinical picture. The top image shows the epididymis, which is enlarged as we saw before, and the subsequent imaging after treatment shows that the epididymis is now normalized in size, and also, the echogenicity is more normal appearing indicating it was an inflammatory process which responded to treatment.

Dr. Stone:
OK, so reconsidering the treatment, the patient had a wonderful response to rituximab. And following up in the pancreas clinic, the patient has normal fecal elastase measurements and really seems to be under excellent disease control now. You can summarize this complicated course. The patient did actually have IgG-4-related disease causing that mass, precipitating the major surgery that he underwent. It was only after then that his elevated serum IgG-4 concentrations became evident, and the disease evolved to involve other organs over time, including the pancreas, the nose, the lungs, and then ultimately, the testes and epididymis.

So, lessons learned here. IgG-4-related disease often presents as a multiorgan disease not confined to the pancreas or biliary tree. The disease has the peculiar characteristic of appearing to unfold over time. The term that we often use is metachronous disease, becoming evident in one organ after another if effective therapy is not administered. The disease can mimic malignancy, as it did so strikingly in this case. IgG-4-related can occur in just about any anatomical site, but there are 10 to 12 organs that are really viewed as very typical, and these are listed here.

So, I want to conclude with a very exciting therapeutic result. The results of the MITIGATE trial were released only in June. This is the first worldwide randomized double-blind placebo-controlled trial ever conducted in IgG-4-related disease. It evaluated an anti-CD-19 therapy known as inebilizumab in patients with IgG-4-related disease, and the primary endpoint which was disease remission at 1-year, and all three secondary endpoints were achieved with the risk of disease flair reduced in the active treatment group. Reduced by 87% compared to conventional therapy, which was a comparison to glucocorticoids. So, this marks a wonderful new era in the therapy of patients with IgG-4-related disease, and a wonderful high note to end our presentation on.

I'd like to thank all of my co-participants in this and Professor Lohr for the contribution of these two very intriguing bookend cases that teach us much about IgG-4-related disease.

Announcer:
You've been listening to a replay of a live broadcast. This activity titled Digesting IgG-4-RD: An Interactive Multidisciplinary Case Conference 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.