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<https://reachmd.com/programs/cme/igg4-rd-case-conversations-igg4-related-autoimmune-pancreatitis-and-cholangitis/24306/>

Released: 06/26/2024

Valid until: 06/26/2025

Time needed to complete: 15 minutes

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### IgG4-RD Case Conversations: IgG4-related Autoimmune Pancreatitis and Cholangitis

#### Dr. Culver:

Hello and welcome. I am Emma Culver. I am a consultant gastroenterologist and hepatologist at the John Ratcliffe Hospital in Oxford in the U.K.

#### Dr. Firmin:

And I am Louisa Firmin. I am an upper GI and HPB radiologist based at University College Hospital of London, also based in the U.K.

#### Dr. Culver:

So these are the IgG4 case conversations, and we're going to talk about today, IgG4-related autoimmune pancreatitis and cholangitis. And this educational session has been provided by Evolve Medical Education. So the case description: It's a 74-year-old male who presented in October 2019 with a four-week history of painless obstructive jaundice. He had also lost 5 kilograms of weight, and had had a change in his bowel habit, whereby his stool had become loose, greasy, oily and difficult to flush. He had a past history of prediabetes, which was diet-controlled, and also a history of allergic rhinitis for which he was taking antihistamine. He went to his primary health care physician and they ordered some blood tests, and these included a simple blood panel, a full blood count, kidney function, liver function, and inflammatory markers. And you can see here, he had a predominantly cholestatic picture of liver function with an elevated bilirubin, an elevated alkaline phosphatase and gamma-GT, and a mildly elevated ALT. His synthetic function – his albumin and INR – were entirely normal, and he also had an elevated amylase, only minimally elevated, and also a mildly elevated CRP. So we went on to do some imaging.

#### Dr. Firmin:

So the patient had a CT optimum, which showed a sausage-shaped pancreas, which had lost its normal lobulations. There is no significant pancreatic duct dilatation but there is quite marked condyle duct and dilatation with a very tight stricture in the distal CBD, which is better appreciated on a subsequent MRCP. So this is a static MRCP image of the same patient very shortly after, which again shows a very tight distal CBD stricture, and marked upper common duct and intrahepatic duct dilatation. The axial imaging shows that the patient has quite significant loss of T1 signal. We tend to use the liver as a comparative, and as you can see, the pancreas is lower than the liver rather than – we expect it to be slightly higher signal on the T1 images, which is on the right. The T2 signal is also slightly increased, which is a sign of potential inflammation. Again, these images also show the bile duct dilatation.

#### Dr. Culver:

Thank you, Louisa. So I think on the basis of the images and the clinical history, there's a – there's a possible differential diagnosis, the first of which is pancreatitis, most likely acute because of diffuse swelling or inflammation with this common bile duct stricture. Secondly, and probably the most concerning, would be of a malignancy, but this would need to be a diffuse malignancy, and I guess the thought there would be potential lymphoma. And lastly and importantly, we've got to consider the possibility, as we are aware, of autoimmune pancreatitis. And that can either be a type 1 autoimmune pancreatitis, which we know is associated with IgG4 systemic disease, or a type 2 autoimmune pancreatitis, which usually occurs in younger individuals and is associated with inflammatory bowel disease.

So the patient went on to have an endoscopic ultrasound, in order, actually, to look both at the pancreas and also to take some biopsies.

And here, you can see a very diffuse enlargement of the pancreas, with a hypoechoic, patchy, diffuse attenuation. And actually, when we look to the common bile duct, there was a thickening along the common bile duct wall. Fine needle biopsy was possible using a 22-gauge needle, and this revealed a dense, lymphoplasmacytic infiltrate with some cy – with some fibrosis. And also, staining for IgG4-positive cells revealed greater than 10 per high-power field were IgG4-positive over IgG. The patient was referred to a specialist, who went on to do further blood tests, and these included a serum IgG4 level, which was elevated greater than two times the upper limit of normal, a serum IgE level, which was elevated between three and four times the upper limit of normal, complement levels which were low, and C4 specifically with less than the upper limit of normal. And also, the patient had some other markers excluded to look for cancer. Of noted, the CA99 is elevated, but that occurs in many cases of obstructive jaundice and is not specific to cancer. And the amylase, as before, was elevated but again is not specific for acute pancreatitis and can occur in other pancreatic conditions. So this made the diagnosis of IgG4-related autoimmune pancreatitis and cholangitis most likely.

The patient went also on to have some functional assessments of the pancreas, and that was predominantly due to the abdominal bloating, with oily, greasy stools and weight loss. And as you can see here, the HbA1c, which is a marker of diabetes, was elevated. The fecal elastase, which is a marker of exocrine pancreatic insufficiency, was low, and the fat-soluble vitamin, vitamin D, which is also important to bone health, was also low. So this suggested the patient had pancreatic exocrine and endocrine insufficiency, related to their inflammation. The first day it was important to induce disease remission, and the way of doing that – the patient was given prednisolone, and the patient received 40 mg of prednisolone for two weeks, and then 30 mg of prednisolone for two weeks, and at the week 4 time point was assessed: firstly, clinically, to make sure that the jaundice is improved; secondly, in terms of biochemically, to make sure their liver function test, which has now massively improved, and also their inflammatory markers were lower; and to look at their serological level of IgG4, which at this point had normalized. Of note, it does not normalize in all patients. These steroids were then tapered over the next three months, and then repeat imaging was performed in order to actually assess an imaging response to treatment.

**Dr. Firmin:**

So, this is an RCP image at three months. This, as you can see, shows a reduction in the structuring of the lower CBD, and a decrease in the amount of intrahepatic duct dilatation. As you can see, there is also a little bit of irregularity but it's a relatively smooth stricture. There's no definite indication of any cholangiopathy. The axial imaging shows that there's actually been a fairly significant loss of volume of the pancreas, and the T1 signal has improved, suggesting that the degree of inflammation has decreased.

**Dr. Culver:**

So given the thought that there was treatment response, this was a good thing. However, we realize that this patient had high risk factors for relapse. Firstly, there was some degree of active inflammation that was still present on the scan. But secondly, as you can see in this doughnut chart here, there were predictors for relapse. And our patient, which is a male gender, has an elevated IgG4 greater than two times the upper limit of normal at presentation, had a high IgE, and also had biliary involvement even though there was no proximal cholangiopathy. And this puts him in a higher category for risk of relapse, and he was therefore had mycophenolate, 1 gram, twice daily added onto his regime in order to reduce that risk.

He also required treatment of his damaged pancreas in the form of enzyme replacement and multi-vitamin replacement for his exocrine insufficiency. He was put initially on metformin, but then subsequently insulin for his endocrine insufficiency, and for his bone health he received a DXA bone scan which confirmed thinning of the bones in the situation of cholestasis, and he had his vitamin D replaced and also started a bisphosphonate for bone health.

The patient continued to be followed up in the clinic on a 6-monthly interval, and three years later in 2021, he re-presented. And at this time point, he had some anti-gastric discomfort, which was very nonspecific, and his liver function tests were entirely normal, and so was his CRP, but his serum IgG4 had gradually crept up and was once again greater than two times the upper limit. So he went on to have some further imaging.

**Dr. Firmin:**

So, for this patient, because the LFTs were normal, we went on to do a PET-CT, in part to look and see if there were any other organs that were now involved. The PET-CT, however, only showed that there is again diffuse pancreatic disease, with increased activity throughout the pancreas, and no other sites of active disease.

**Dr. Culver:**

So, the patient was seen in clinic. We could see that there was active inflammation, as Louisa said, on the PET-CT scan. We checked to make sure he was taking his drugs, and indeed he was. And therefore, as a result of that, he had discontinuation of his mycophenolate, and we switched drugs to B-cell depletion, and this was to treat active IgG4-related pancreatic disease. And he received a gram on day 1, and a gram on day 14. And over time we monitored his blood tests – his serum IgG4 normalized at month 3,

and then also at the month 6 timepoint, and he started to receive repeat B-cell depletion therapy at 12-monthly intervals, and remained in disease remission.

So, IgG4-related pancreatic biliary disease. This is part of a systemic, multi-system, condition, that is characterized by masses and swellings and strictures throughout the body. We know that there are elevated IgG4 levels, both within the blood and also in the tissue of involved organs. And the pancreatic-biliary phenotype is one of four main phenotypes of disease. And as you can see here, it predominately affects males, most often the sixth decade of life, and it has usually an elevated IgG4 and IgE, in around about 80% of patients. You can see the characteristic findings that Louisa described before, with this kind of sausage-shaped pancreas with a pseudo-capsule on the outside, and often irregularity of the pancreatic duct. On MRCP scan, you can see the common bile duct stricture, but we can also see strictures into hepatic cholangiopathy, which is associated with a higher risk of relapse. On an endoscopic ultrasound, we often see a diffuse or sometimes focal hypoechoic mass, and often a thickened common bile duct. And ERCP is not used diagnostically, but can be used in order to be able to brush strictures to exclude cancer, and also for temporary stent insertion.

Histologically, the characteristic findings are that of a lymphoplasmacytic infiltrate, which is both CD4 T cells and also B-cells and plasma cell rich, and obliterative phlebitis which is the squashing of the vessels by the inflammatory cells, and a storiform or swirling or cartwheel pattern of fibrosis. And as you can see on the right-hand side here, the predominant plasma cell infiltrate is IgG4, and it makes up greater than 40% of the overall infiltrate.

In terms of managing IgG4 pancreatic biliary disease, there is an adjunct to corticosteroid management, and that is endoscopic. So in those people, particularly if you present with jaundice, and particularly if you are uncertain of the diagnosis, then actually a short-term stent can be inserted in order to allow for biliary flow. And this can be a fully covered metal stent, a plastic stent, or more recently biodegradable stent. What we shouldn't be placing is an uncovered stent because that has placed malignancy and is very difficult to remove.

In terms of medical management, the most frequently used drug is still corticosteroids, despite its toxicity, and that is usually high-dose, at 30-40 mg for the first four weeks, and after confirming disease response, tapering over the next 3-6 months. A combination of immunosuppressive therapy reduces the risk of relapse, and there are different immunotherapies that can be used, and they are listed here. B-cell depletion has been used both in induction and also for rescue therapy, and can be used either in single dosing or as a maintenance infusion. And I think at all time points, we have to balance medication toxicity versus efficacy. And particularly in the case of corticosteroids, we know that 30-50 percent of these patients are diabetic, and importantly, adverse effects have been described in between 50 and 70 percent of patients. And you can see some of those side effects listed here.

So I think it's really important to confirm radiological response to treatment in patients who have pancreatic biliary disease, particularly because we get concerned about patients who may have a pancreatic or even biliary cancer, and also because we want to make sure that they have actually gone into disease remission because it helps us define how long we are going to consider treatment. And so this isn't actually the same patient as we discussed during our case, but I think it shows some really lovely examples. And Louisa, would you talk us through these, please.

**Dr. Firmin:**

And so this is a CT scan of a patient, before and after treatment, and it shows that there has been a significant reduction in the volume of the pancreas, with less swelling, improved enhancement of the pancreas, and now you're starting to see a little bit more of the normal shape of the pancreas as well. So, we actually use MRCP quite a lot in disease response, mostly because it doesn't have any radiation, but also it gives us very nice information on the bile ducts, which can be much more difficult to see on CT. So this is a really beautiful example of an MRCP. The pretreatment scan shows that there's an upper bile duct stricture, as well as a lower bile duct stricture, and these have significantly improved post-treatment. And you can see that the degree of intrahepatic duct dilatation is significantly improved, and the bile duct has almost normal appearance, which is, you know, exactly what we want to see.

**Dr. Culver:**

So, key lessons in this session: I think pattern recognition is really important in the diagnosis and also management of patients with IgG4 pancreatic biliary disease. Typical clinical features may be absent, and particularly in those patients who have a focal pancreatic enlargement or a specific biliary stricture, it's really important to exclude cancer. And I think it's also important, as we did in PET-CT scan, to assess the evidence of other organ involvement in the disease, particularly if the serum IgG4 remains elevated. Current treatment strategies are very much aimed at symptom control and halting active inflammation. And whilst we know that corticosteroids are highly effective, they have significant side effects in this population, and so we need to consider disease-modifying immunosuppressive drugs in those with high risk of relapse, or the alternative being more targeted therapy – and at the moment, B-cell targeted therapy appears safe and effective in both inducing remission and also maintaining remission in the longer term.

I think, lastly, it's important, particularly in those with pancreatic biliary disease, to assess and manage organ function and also damage, because that contributes overall to the symptoms. And with that, I'd like to say thank you very much for joining us today, for this session.

**Dr. Firmin:**

Thank you, Emma.

**Dr. Culver:**

Thank you, Louisa.