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Case Study

The Challenge of Distinguishing Between Cholangiocarcinoma and IgG4-related Sclerosing Cholangitis

Emer Chang[1], Emma Culver[2]

[1]*Medical Sciences Division, Univerity of Oxford, UK.*
[2]*Oxford University Hospitals NHS Foundation Trust.*

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Key Learning Points
Dr Emma Culver

1. Distinguishing IgG4-related disease (IgG4-RD) from malignancy can be challenging.
2. Elevated serum IgG4 concentrations are not diagnostic of IgG4-RD and can be seen in other malignant, infective, and inflammatory and autoimmune conditions.
3. IgG4-related sclerosing cholangitis (IgG4-SC) type 3 and 4 often mimics. cholangiocarcinoma (CCA), whilst IgG4-SC type 2 mimics primary and secondary sclerosing cholangitis.
4. IgG4-SC is an indolent condition where jaundice and liver tests can improve spontaneously, whereas CCA is usually aggressive and progressive without treatment.
5. Obtaining tissue via biliary biopsies can help to secure the diagnosis. However, samples are often small and may be non-diagnostic. Cellular atypia is suggestive of malignancy.
6. The absence of corticosteroid response is an exclusion criterion in the EULAR/ACR classification criteria for IgG4-RD and would suggest an alternative diagnosis.
7. Shared decision making via specialist multi-disciplinary team meetings is essential for optimal diagnosis and management decisions in rare and complex diseases.
8. Good open communication with patients to manage diagnostic uncertainty and conduct therapeutic trials are important to manage expectations and reduce unnecessary anxiety.

Summary

This case report summarises Mr X's clinical history examination and focuses on the diagnosis of his cholangiocarcinoma. Here, we discuss the extent to which we can distinguish cholangiocarcinoma from a similarly presenting but distinct condition: IgG4-related sclerosing cholangitis. Highlighting advances in diagnosis of each disease and providing suggestions for how this may be applied to better distinguish between the two diseases, whilst also considering the patient's lived experience of uncertainty surrounding their diagnosis.

1. Introduction

1.1 Cholangiocarcinoma

Cholangiocarcinoma is a rare aggressive biliary tract malignancy with poor prognosis. It comprises 3% of GI malignancies[1]. Chronic inflammation and/or cholestasis are involved in pathogenesis[2]. Cholangiocarcinoma can be classified based on location of tumour in biliary tree. Localised intrahepatic cholangiocarcinoma has a lower 5-year survival rate in comparison to localised extrahepatic cholangiocarcinoma (15% vs 30%)[1]. The high mortality rate can be attributed to the often asymptomatic and thus delayed clinical presentation as well as highly aggressive growth and chemotherapy-refractory nature of cholangiocarcinoma. Surgical resection is potentially curative providing a median overall survival of 51.1 months, but relapse rate following resection is 60%[1,2].

Crucially, most patients (~70%) are not fit for surgical resection, because of late presentation meaning tumour is too large (median size 6cm) and/or has invaded surrounding structures making resection unsafe[3]. The most frequent presenting complaint is jaundice due to biliary tract obstruction caused by tumour growing towards hepatic hilum. Several imaging modalities are used to aid diagnosis, staging, follow-up and assessment of treatment response, including abdominal ultrasound, CT and MRI. However, these fail to pick up the early stages of disease. Timely diagnosis of cholangiocarcinoma is further complicated by its similarity to the clinical, biochemical and radiological presentation of IgG4-related sclerosing cholangitis.

1.2 IgG4-related sclerosing cholangitis

IgG4-related disease (IgG4-RD) is a rare chronic fibro-inflammatory condition that can affect multiple organs. IgG4-related sclerosing cholangitis (IgG4-SC) is a manifestation of IgG4-RD affecting the biliary tree. It is characterised by increased serum levels of IgG4 and histological features including infiltration of IgG4-positive

plasma cells, storiform fibrosis, obliterative phlebitis and eosinophilia[2] . IgG4-SC affects men in their 60s[4]. Chronic exposure to environmental and occupational antigens are risk factors that can lead to immune dysregulation in genetically susceptible individuals by triggering expansion of pre-existing IgG4-switched B cells promoting unregulated inflammation and T-regulatory cell mediated release of pro-fibrotic cytokines. Type 4 IgG4-SC involving hilar bile duct strictures presents most similarly to cholangiocarcinoma with painless jaundice. There is no single diagnostic test for IgG4-SC. Instead, HISORt(histology, imaging, serology, other organ involvement, response to treatment) criteria[5] and Japan Biliary Association IgG4-SC diagnostic criteria[6] are used, stating the following as IgG4-SC features: thickened bile duct wall,biliary strictures,raised serum IgG4 levels,multiple organ involvement and histology. IgG4-SC diagnosis is also confirmed by response to corticosteroid therapy.

1.3 A complex diagnostic challenge

Cholangiocarcinoma and IgG4-SC can both present with painless jaundice and weight loss. Moreover, both IgG4-SC and cholangiocarcinoma can be diagnosed on imaging based on presence of bile duct masses, strictures and/or lymphadenopathy. This may be further complicated by IgG4-SC increasing risk of developing cholangiocarcinoma[2].

This has led to misdiagnosis which is concerning as it leads to unnecessary surgical resection of presumed cancer[7], inappropriate treatment delay and furthers patients' anxiety and confusion regarding their disease diagnosis and prognosis.

Effective methods for clearly distinguishing between cholangiocarcinoma and IgG4-SC are lacking. This knowledge would greatly optimise patient outcomes through: 1) timely treatment,2) clarifying patient prognosis, 3) identify patients likely to respond to targeted therapies and 4) would help to minimise patient anxiety about these difficult diagnoses.

2 Case presentation

Mr X is a 69-year-old retired project manager that presented to GP with burning chest pain, indigestion, abdominal bloating and fullness, nausea and abnormal metallic taste in mouth. His past medical history includes prostate adenocarcinoma (November 2019, T2cN0M0 maximum Gleason score 3+4=7), gout (September 2004, last acute flare >10 years ago), sarcoidosis (1982, in remission). Mr X has a family history of skin, breast and prostate cancer, has never smoked tobacco and drinks 18units alcohol per week. Current medications include LHRH analogue/ bicalutamide for prostate cancer and febuxostat for gout. He has no allergies.

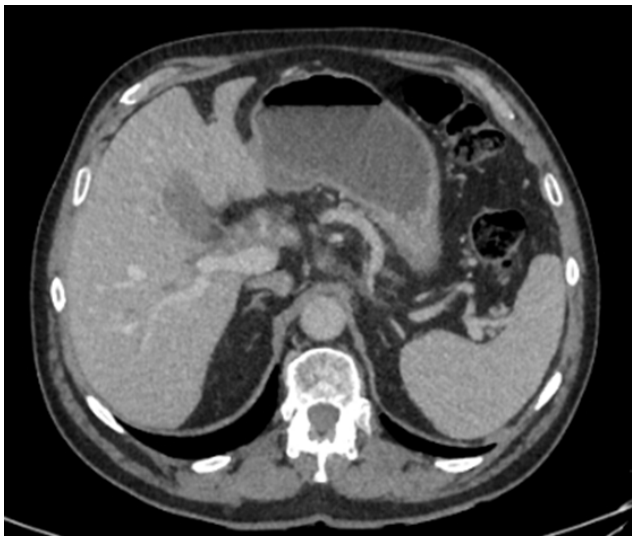

Figure 1: CT abdomen of Mr X in October 2020 showing ill-defined soft tissue at hepatic hilum encasing hepatic artery and abutting anterior aspect of portal vein, highly suspicious for cholangiocarcinoma.

A 2-week course of omeprazole failed to ameliorate reflux symptoms and the following month Mr X re-presented to GP with 1-week history of dark urine, pale stools, pruritis, appetite suppression and weight loss. Mr X reported no abdominal pain/fevers/vomiting. On examination, mild scleral jaundice, airway patent, clear chest, heart sounds I+II+0 , prominent bowel sound, peripheral oedema of left foot and ankle (usual for patient), warm peripheries, capillary refill time < 2s. GCS15/15 alert and interactive. Calves were soft and non-tender (SNT).

Abnormal liver function tests and raised C-reactive protein level (5.3mg/L) were also identified, as shown below:

Total bilirubin level, plasma	70 umol/L
Alanine aminotransferase level, plasma	593 Int Unit/L
Alkaline phosphatase level, blood	621 Int Unit/L

This was suggestive of obstructive aetiology.

Abdominal ultrasound showed no significant abnormality. However, abdominal CT-scan found abnormalities highly suggesting cholangiocarcinoma: intrahepatic biliary dilatation with abrupt tapering of common bile duct (CBD) just beyond cystic duct due to abnormal hepatic hilar soft tissue, which also encased hepatic artery (figure 1) . There was also inflammatory change around the superior mesenteric artery and enlarged adjacent nodes (11mm).

At this point bicalutamide was stopped due to cautioned usage in hepatic failure. Mr X underwent an urgent Endoscopic Retrograde Cholangio-Pancreatography (ERCP) to further identify cause of deranged LFTs. Biopsies were not obtained due to fluid/food retained in stomach causing gastroscope to not pass beyond D1. Bloods showed IgG4 was marginally elevated at 1.08 and carbohydrate antigen 19-9 (CA19-9) was undetectable <2 leading to consideration of possible underlying IgG4-SC. There were also some radiological signs of IgG4-SC on CT but still indeterminate and much more likely to be locally advanced cholangiocarcinoma.

Mr X underwent MRCP with contrast (gadolinium) to further determine whether mass in biliary tree was cholangiocarcinoma or IgG4-SC. This demonstrated significant dilation of proximal intrahepatic ducts, stricture of mid CBD with concentric soft tissue thickening with increased enhancement involving wall of CBD on delayed imaging in keeping with intrahepatic carcinoma (figure 2).

Late November 2020, Mr X reported worsening pruritis and 4 kg unintentional weight loss over 6 months. However, no cough/fever/night sweats/haemoptysis/ vomiting. On examination there was visible jaundice but otherwise unremarkable.

Mr X was further investigated and managed using percutaneous transhepatic cholangiography (PTC) where biopsies were taken at distal CBD and hepatic hilum. Distal CBD obstruction was stented and internal-external biliary drain inserted.

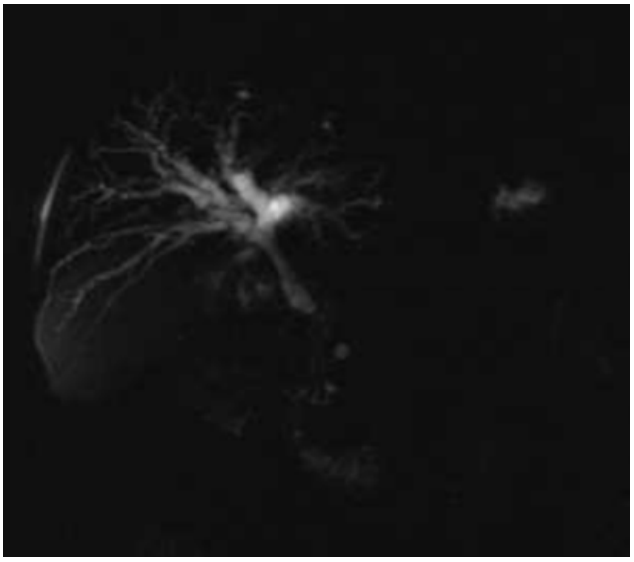

Figure 2: MRCP of Mr X in November 2020 showing stricture in mid-CBD with concentric soft tissue thickening and localised enhancement and significantly dilated proximal intrahepatic ducts indicating intrahepatic cholangiocarcinoma.

3 days post PTC the external biliary drain was removed and fluoroscopy showed free drainage of contrast through patent biliary stent into duodenum. The biopsy showed some atypical cells that could not be more precisely determined. This evidence further supported a malignancy diagnosis. Although a repeat biopsy was not feasible, given the clinical, radiological findings and suspicious biopsy, Mr X was treated for unresectable cholangiocarcinoma and offered palliative chemotherapy.

This cholangiocarcinoma diagnosis took Mr X by surprise as he understood the suspicion of cancer but thought it was unlikely. He was shocked to learn that cancer was inoperable due to involvement of key vessels and chemotherapy would be with palliative intent. Mr X was concerned about how this would impact his prostate cancer treatment. It was explained to Mr X that treatment of cholangiocarcinoma would take priority over his hormone therapy and radiotherapy for prostate cancer, as cholangiocarcinoma progresses faster.

Further investigation of IgG4-SC was paused, because serum IgG4 was only marginally elevated and Mr X should be treated for cancer due to possible duodenal involvement, which likely caused his reflux symptoms.

In December 2020, Mr X started gemcitabine and cisplatin chemotherapy for cholangiocarcinoma. CT scans from January and February 2021 (see figure 3) were taken to gauge chemotherapy response.

Despite his initial suspected diagnosis of cholangiocarcinoma, IgG4-SC was reconsidered given he was not deteriorating as rapidly as expected for cholangiocarcinoma, as evidenced by minimal disease progression on recent CT scans (figure 3) and his improved appetite and activity. Therefore, chemotherapy for cholangiocarcinoma was paused whilst he commenced a trial of high dose oral prednisolone (4 weeks at 40mg and then reduce to 30mg daily for 2 weeks).

In May 2020, on admission to surgical emergency unit he presented with epigastric pain (severity 4/10) that did not radiate but was made worse on palpation. He was also vomiting, feeling faint, distended abdomen and jaundiced. No change in bowel habit/fever/diarrhoea. On examination tender epigastrium with no guarding, but irregular heart rate.

- Observations: HR 92, irregular, BP 139/98, SpO2 97% RA, RR 20, Temp 36.6
- Bloods: raised LFTs, normal inflammatory markers and normal bilirubin
- VBG: raised lactate (3.9mmol/L) and raised blood glucose (19.7 mmol/L), not known diabetic
- Ketones were within normal range (0.4mmol/L)
- ECG confirmed atrial fibrillation.

The most likely diagnosis was biliary obstruction secondary to cholangiocarcinoma/ IgG4-RD. However, it was also important to rule out ischaemic bowel disease due to raised lactate and consider pleural effusion, bowel perforation and gastritis as other differential diagnoses due to epigastric pain.

Chest x-ray showed lungs and pleural spaces were clear. CT angiogram aorta showed that in comparison to previous CT scan stomach distended with fluid with a transition point adjacent to distal biliary stent where there was ill defined soft tissue. No small or large bowel obstruction. Mildly atherosclerotic abdominal aorta that was patent with no stenosis or thrombus, key to rule out as IgG4-related disease due to its association with thrombotic events[8]. CT scan also confirmed the ill-defined soft tissue surrounding CBD suggestive of cholangiocarcinoma remained unchanged. However, there was increased pancreatic duct dilation. Overall, this CT scan indicated gastric outlet obstruction caused by cholangiocarcinoma. Gastroscopy also showed a near obstructing D1/D2 polypoid mass and 6 biopsies were taken (results not yet reported).

Hence Mr X was given a nasogastric tube for decompression and IV fluids and IV hydrocortisone (instead of oral prednisolone). On this admission, IgG4-SC diagnosis was reconsidered. IgG4-SC was unlikely, given the lack of convincing reduction in soft tissue mass shown on CT with steroids. Therefore, steroid trial was stopped and Mr X restarted his chemotherapy for cholangiocarcinoma.

3 days post admission, Mr X felt much better. Nasogastric tube was removed and he was tolerating fluids, ensures and soft diet well. On this admission, he had persistently high blood glucose up to 27mmol/L with HbA1c over 10%. This is likely steroid induced hyperglycaemia which was managed by corrective Actrapid 4 hourly. He was discharged 5 days post admission and as an outpatient to be reviewed by several teams: 1) Oncology; 2) Diabetes: started him on 40mg OD gliclazide; 3) Gastroenterology: to see if duodenal stent needed; and 4) Cardiology: to review new diagnosis of atrial fibrillation during admission. Mr X felt "fed up" and wanted to "regain lost ground". He was anxious because he was overwhelmed by being managed by several teams and his diagnosis changing several times.

3 Discussion

3.1 Factors that can help differentiate cholangiocarcinoma from IgG4-SC

3.1.1 Laboratory measurements

Patients with IgG4-SC can have elevated serum IgG4 (sIgG4) levels[6]. The sensitivity and specificity of sIgG4 levels is limited, as sIgG4 levels can be raised in other diseases including cholangiocarcinoma, vasculitis and primary sclerosing cholangitis (PSC) as well as in health. However, Ohara et al demonstrated sIgG4 levels greater than 2.1 g/l gave a 100% specificity when distinguishing

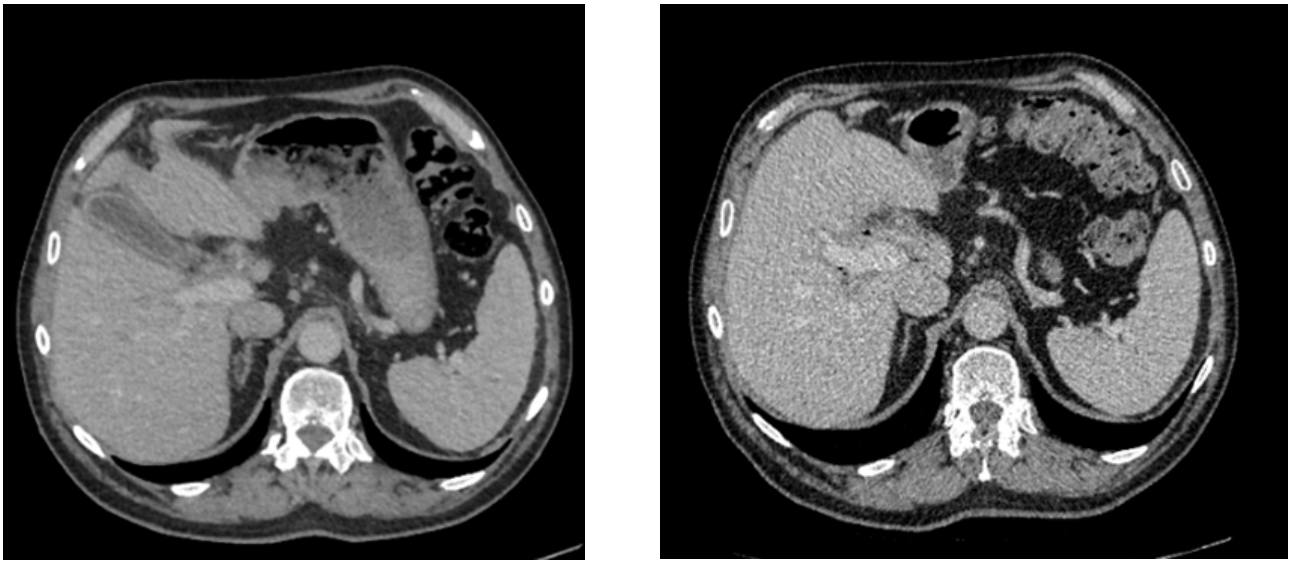

Figure 3: (left) CT scan from January 2021 and (right) CT scan from February 2021. CT scans show minimal disease progression and may be suggestive of IgG4-SC.

type 4 IgG4-SC from cholangiocarcinoma[9].

Comparing levels of blood IgG4 to IgG RNA as measured by quantitative PCR test could overcome the issue of raised sIgG4 levels in both IgG4-SC and cholangiocarcinoma. The rationale being the presence of dominant IgG4+ B cell receptor (BCR) clones in the blood of IgG4-SC patients[10].This has been further supported by a study of 135 patients where blood IgG4:IgG RNA ratio accurately delineated IgG4-SC from cholangiocarcinoma with better sensitivity (94% vs. 86%) and specificity (99% vs. 73%) than sIgG4 alone[11].This qPCR test could also improve early diagnosis.

CA19-9 alone is not diagnostic. CA19-9 levels are expected to be greater in cholangiocarcinoma, but they may also be raised in IgG4-SC, as CA19-9 levels greater than 37U/ml were found in 63% of IgG4-SC and 77% Cholangiocarcinoma patients[2].

3.1.2 Imaging

IgG4-SC has similar findings to extrahepatic cholangiocarcinoma including narrowing of long segments of the biliary system and contrast enhancement of the biliary wall in regions affected by strictures. In terms of differences, some studies suggest that lesions involving the intrapancreatic bile ducts and concentric wall thickening are significantly more common in IgG4-SC than cholangiocarcinoma[12–14].

Yata et al. study comparing CT findings of 33 patients with IgG4-SC and 39 patients with extrahepatic cholangiocarcinoma found the following features were significantly more common in IgG4-SC than cholangiocarcinoma:(a) wall thickening alone,(b) concentric wall thickening,(c) smooth inner/outer margins,(d) homogeneous attenuation in the arterial phase,(e) a lesion involving the intrapancreatic bile duct,(f) fully visible lumen,(g) funnel-shaped proximal bile duct,(h) skip lesions,(i) abnormal pancreatic findings [14]. In contrast, dual layered attenuation due to delayed enhancement of outer layer of biliary lesion was more common in cholangiocarcinoma, as this reflects cholangiocarcinoma infiltrating surrounding fat tissue[14]. Furthermore, on average there were longer biliary lesions in patients with IgG4-SC than cholangiocarcinoma which may be explained by systemic nature of IgG4-RD. There was also greater biliary dilation in cholangiocarcinoma than IgG4-SC, reflecting greater frequency of biliary obstruction in cholangiocarcinoma[15].

Limitations of this study include selection bias, as the cholangiocarcinoma patient cohort underwent surgical resection, which affects how well these findings can be extrapolated to patients like Mr X with more severe, unresectable cholangiocarcinoma. Interpreting CT scan introduces inter-reader variability, especially as wall thickening/concentricity and homogenous attenuation were reported subjectively. Ideally, future research should aim to quantify the differences in these parameters for more reliable diagnosis.

3.1.3 Histology

As no specific cholangiocarcinoma or IgG4-SC radiology pattern exists, onus falls on histopathological and cytology analysis to confirm diagnosis. Signs of cell atypia and presence of malignant cells confirms cholangiocarcinoma. In contrast, lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and eosinophilia are classic findings for IgG4-SC.

Also given more recent appreciation of IgG4+ plasma cells[10], quantifying the number of IgG4+ plasma cells per high-power field in biopsy specimen may aid delineation. IgG4+:IgG+ plasma cell ratio <40% suggests cholangiocarcinoma whereas ratio >40% indicates IgG4-SC[16].

Whilst histology is highly pertinent to diagnosis, this depends on quality of sample obtained by ERCP. As illustrated in Mr X's case, this can be challenging. ERCP sampling can be improved by (1) using a grasping basket rather than brush, which increases sensitivity for cancer diagnosis by 30%[17] and (2) sampling before inserting stent[18]. Whilst cholangioscopy can be used to improve sensitivity for cancer diagnosis the benefit must be weighed against the greater complication risk relative to ERCP sampling[19].

3.1.4 Treatment trial

Steroids are the gold standard treatment for fibro-inflammatory IgG4-SC. Hence improvement in a patient's condition 4 weeks post-steroids can support IgG4-SC diagnosis. However, a caveat of this approach is that inflammatory areas around strictures seen in

cholangiocarcinoma may also improve with steroids. Furthermore, some patients with IgG4-SC (~1/3) do not respond to steroid regimen after 4 weeks[20]. The use of a steroid trial taken together with the clinical, radiological findings and suspicious biopsy in Mr X's case was informative in reaching a definitive diagnosis.

3.2 Emerging approaches of differentiating between cholangiocarcinoma from IgG4-SC

A definitive diagnosis was reached but at what cost? Mr X whilst now diagnosed with cholangiocarcinoma, developed steroid-induced diabetes following the steroid trial. This further emphasises the need for novel approaches to better distinguish cholangiocarcinoma from IgG4-SC.

Emerging approaches utilise advances in 'Omic' technology. miRNAs are currently being explored as potential diagnostic and prognostic biomarkers, due to their stability and abundance in biofluids. Certain bile miRNAs are shown to increase diagnostic capacity for cholangiocarcinoma when compared to healthy individuals(miR-9)[21] and PSC (miR-1537)[22]. Furthermore when miRNAs were combined with existing CA19-9 values it increased diagnostic accuracy than using CA19-9 values alone[23]. Such studies would be useful to replicate in large, biopsy-determined cholangiocarcinoma and IgG4-SC patient cohorts to see if there is a significant difference in miRNA levels between these groups. Further validation studies will also be necessary to determine optimum diagnostic cut-off levels for bile miRNAs.

3.3 Holistic approach

These emerging approaches are promising, yet will take several years before clinically used. Therefore, in the interim, taking a holistic patient-centred approach is useful when managing cases such as Mr X where there is diagnostic uncertainty that can cause patients understandable concern, anxiety, and confusion. This can be addressed through shared decision making and ensuring diagnostic uncertainty and estimates for likelihood of differential diagnosis are clearly communicated and understood by the patient. Communicating diagnostic uncertainty to patients can be challenging and it is not helped by the current lack of guidelines or tools[24]. However, there is a growing appreciation for this gap in medical training.

4 Conclusion

Mr X's case provides a useful insight into the challenges of diagnosing either cholangiocarcinoma or IgG4-SC and provides a platform to discuss current and emerging approaches to better distinguish between cholangiocarcinoma and IgG4-SC. In addition, there is more of an uncertainty in diagnosis than we may acknowledge. This case exemplifies how our management of patients' expectations relating to this can have a significant effect on the patients' wellbeing. Therefore, as healthcare professionals we ought to consider using shared decision making to support patients and ultimately optimise patient care.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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