A long winded tale of a jaundiced patient

Dr Neliswa Gogela

9th Liver Interest group

Best of EASL: JHB

24.11.2018

THE GASTROENTEROLOGY FOUNDATION OF SOUTH AFRICA

Index case

- 61 years old gentleman
- Medical background history includes

1. Diabetes mellitus
2. Hypertension
3. Gout and osteoarthritis

- Presented with a 2 week history suggestive of obstructive jaundice, no fever and abdominal pain
- ? Intentional weight loss of 20kg

Examination

- Nil acute
- Normal vitals, Apyrexial
- Markedly increased BMI despite weight loss
- Jaundice and no other stigmata of liver disease
- Systemic examination unremarkable

Differential diagnosis

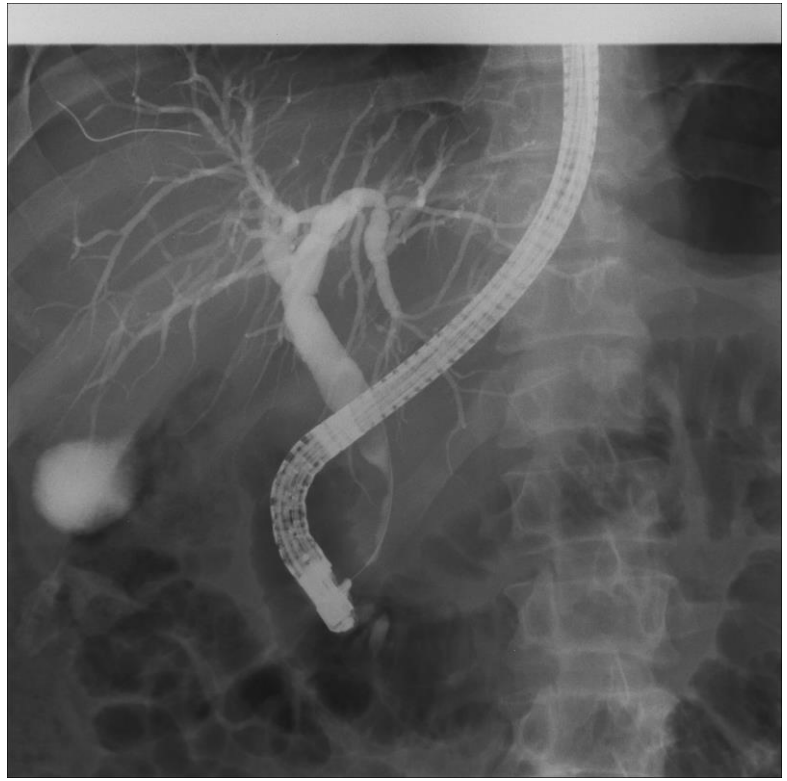
1. CCA vs. HOP tumour
2. Cholangitis related Gallstones
3. Sclerosing cholangitis: Primary vs. secondary
4. Toxins

Investigations

- **Bloods**: Confirm Cholestatic picture
- **Abdominal ultrasound:** ? Pancreatic mass no obvious intra/extra hepatic biliary dilatation
- **CT abdomen:** prominent central intra and extra hepatic ducts, CBD measuring 11mm. Possible enhancement of CBD, no opaque calculus and NO pancreatic mass. ?? PSC vs. CCA
- What are your thoughts? What investigation(s) would you do next?

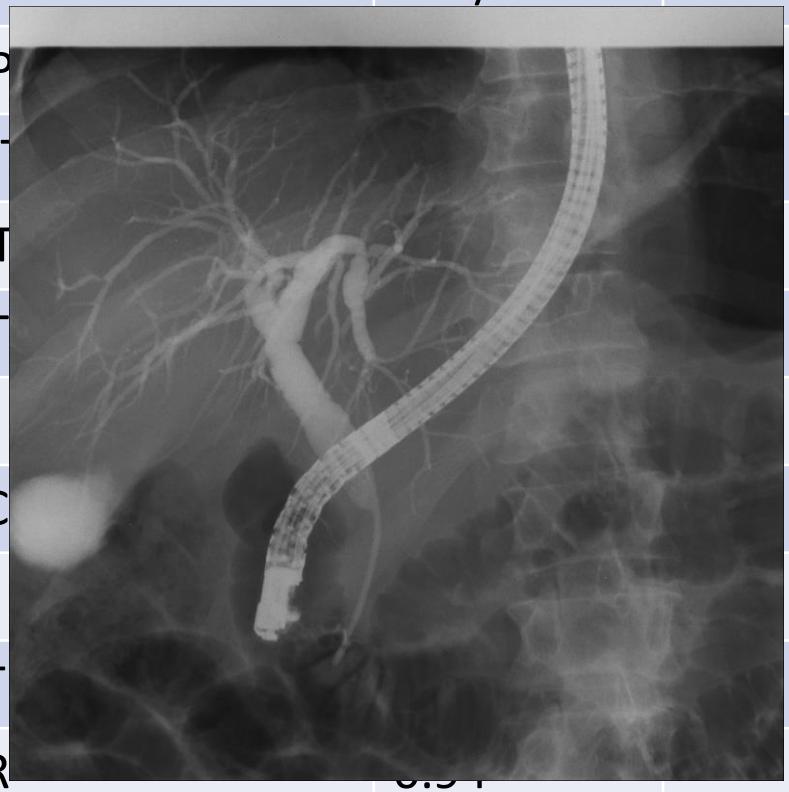
Closer to a Diagnosis

Distal CBD stricture



TEST	11/7/16	20/7/16
TBIL	147/133	85
ALP		
GGT		
AST		
ALT		
CR		
WC		
HB		
PLT		
INR		

Plastic stent across stricture



Results in a span of 2 years

1st Stent + Pred

Stent changed

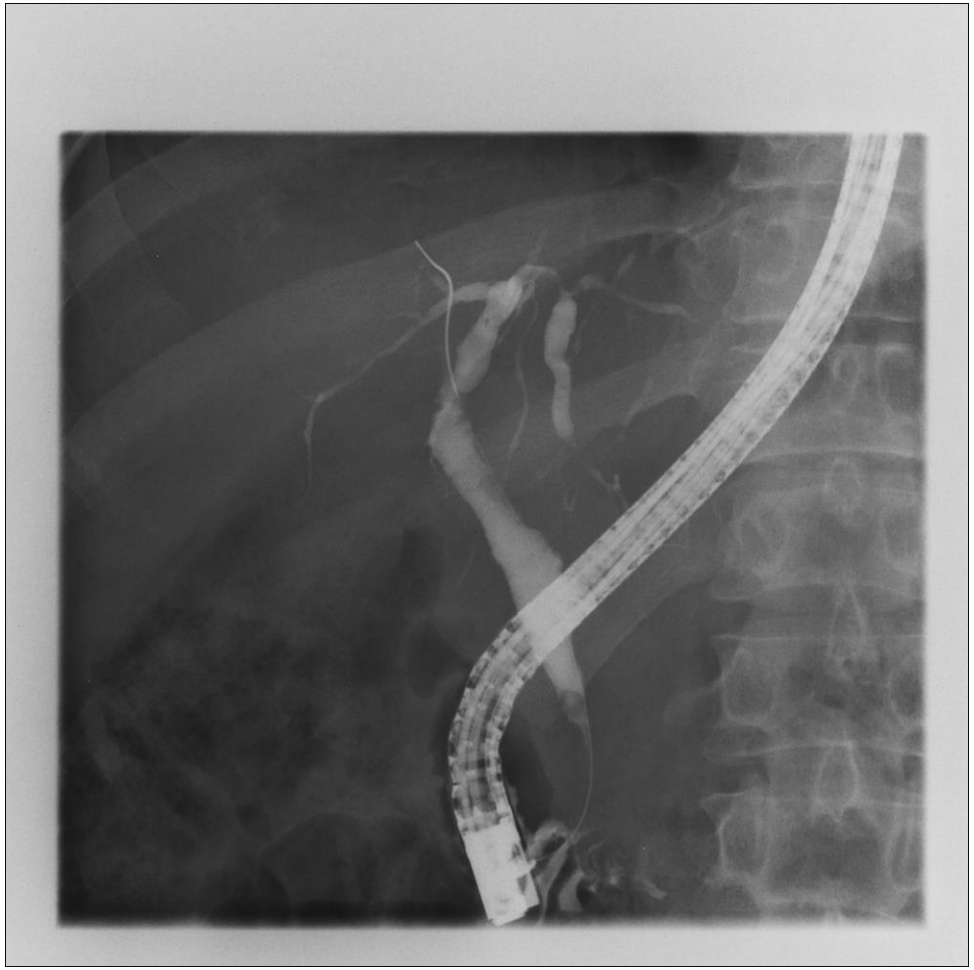
Stent changed

Stent Removed

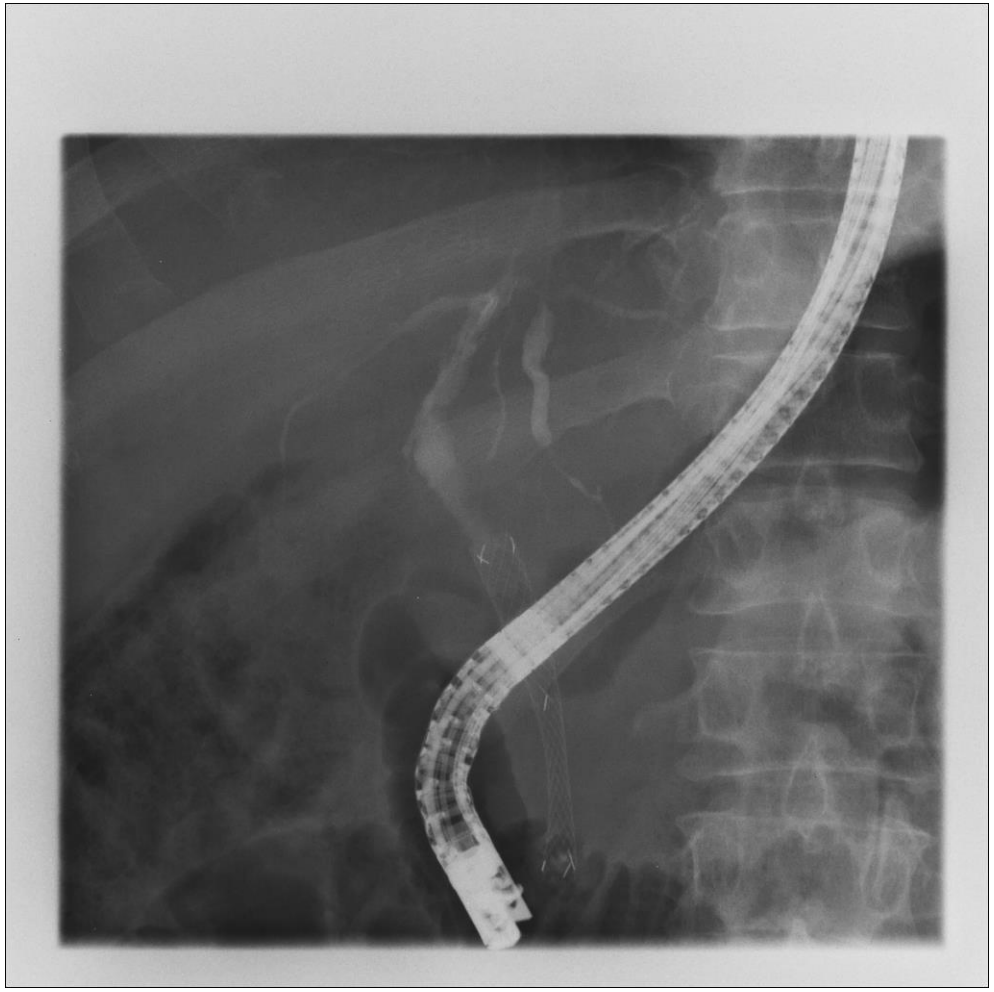
TEST	11/7/16	20/7/16	30/9/16	10/5/17	12/7/17	11/1/18	7/6/18	11/9/18	16/10
TBIL	147/133	85	9/5	4/3	5/2	9/4	6/4	8/3	8/4
ALP	285	262	262	155		152	183	195	248
GGT	314	178	1775	475	111	426	317	219	359
AST	62			45	16	45	34	43	
ALT	40	48	98	65	14	41		26	45
CR	84	99	88	98				130	142
WCC	8.3								
HB	11.9								
PLT	338								
INR	0.94								
IgG4 (0.03-2.0)	13.9		12.7	13.4	10.8	16.7	15.9		18.3

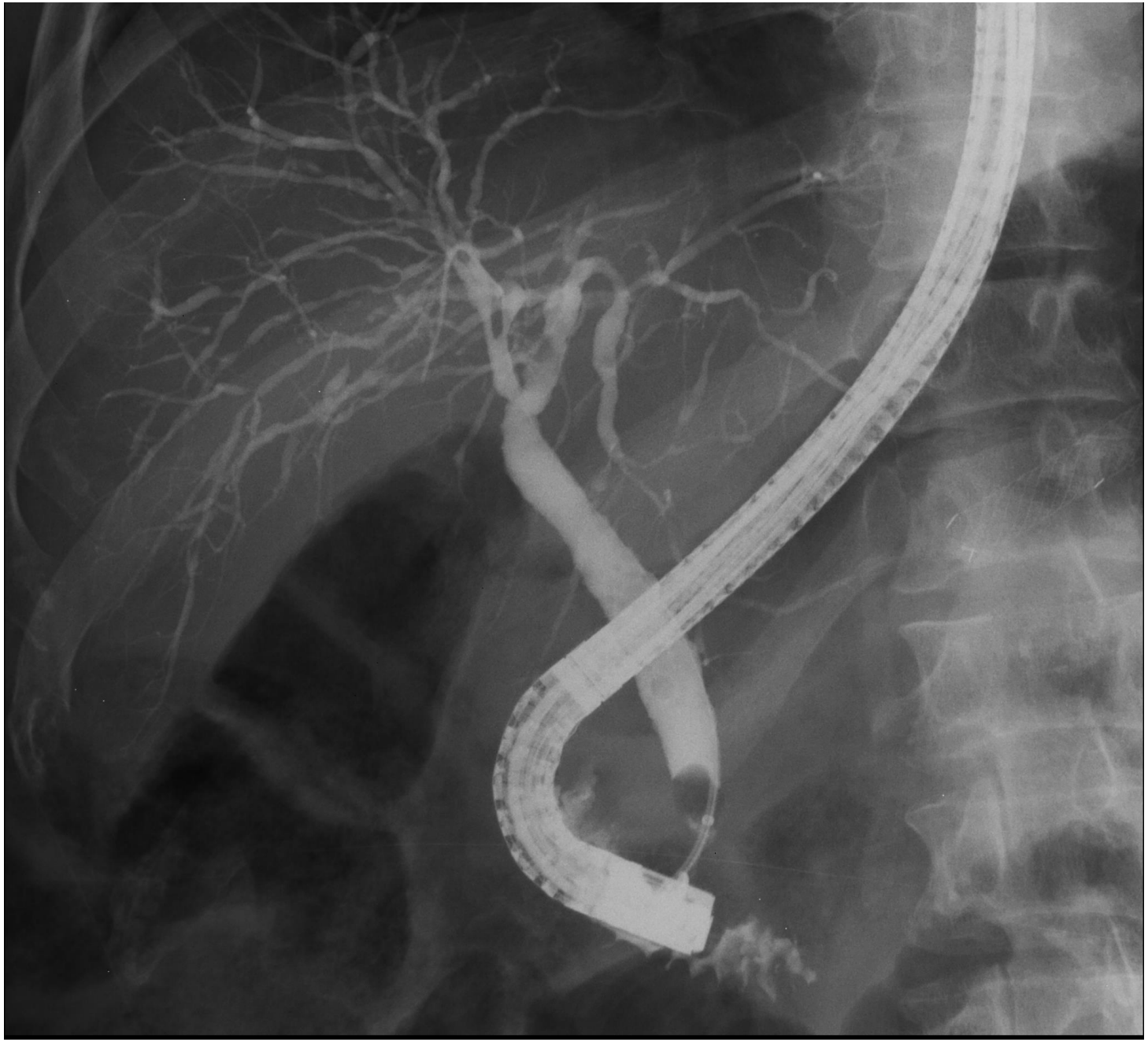
A year later

02/2018 again showing CBD Stricture



Fully covered metal stent





Post stent removal

Diagnosis

IgG4 related sclerosing cholangitis (Type 1)

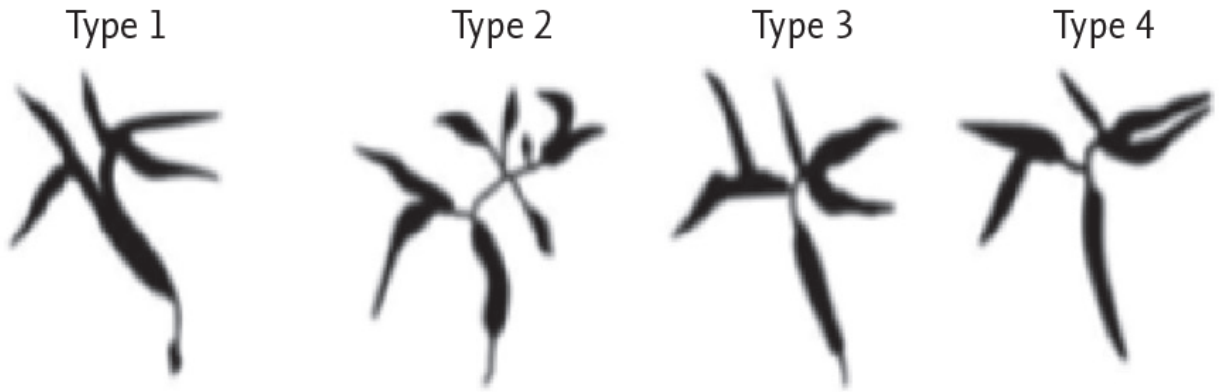
? Other organ involvement

IgG4-related sclerosing cholangitis

- Biliary tract manifestation of IgG4 related diseases, characterized by systemic inflammatory, sclerosing lesions with massive infiltrations of IgG4-positive lymphocytes.
- Most common extra- pancreatic manifestation of IgG4-RD
- Mostly affects older man with variety of presentations, jaundice being the most common presentation followed by pruritis but a few may be asymptomatic
- IgG4 related sclerosing cholangitis may mimic other benign and malignant conditions including PSC and CCA

Great mimic

Cholangiographic classification of IgG4-SC



Common differential diagnoses

Pancreatic cancer	PSC	PSC	PSC
CCA		CCA	CCA
AIP			
Acute/chronic pancreatitis			

https://doi.org/10.3904/kjim.2018.018

Diagnostic criteria

Table 1. HISORt criteria for the diagnosis of IgG4-SC

Histology bile ducts	Lymphoplasmacytic sclerosing cholangitis on resection: LP infiltrate > 10 IgG4+ cells/hpf, storiform fibrosis, phlebitis
Imaging bile ducts	One or more strictures involving intra- or extra-hepatic bile ducts Fleeting/migrating biliary strictures
Serology	IgG4 > 2 × ULN
Other sites	Pancreas: classic features of AIP on imaging or histology Retroperitoneal fibrosis Renal: parenchymal low-attenuation lesions Salivary/lacrimal gland enlargement
Rt response to treatment	Normalisation of LFTs or resolution of biliary stricture

https://doi.org/10.3904/kjim.2018.018

IgG4-SC vs. PSC

Table 2. Comparison of PSC and IgG4-SC

	PSC	IgG4-SC
Sex, male:female	1.5:1	7:1
Age of onset	Young (< 40)	Older (> 50)
Presentation	Cholestatic liver biochemistry	Obstructive jaundice
Biliary abnormalities	Beading, short band-like strictures, peripheral pruning	Long smooth strictures, low CBD stricture, prestenotic dilatation
Raised serum IgG4 levels	< 20%	> 70%
Pancreatic involvement	< 5%	> 80%
Multiorgan involvement	No	Yes
Association with IBD	80%	< 10%
Histology	'Onion-skin' fibrosis	Lymphoplasmacytic infiltrate, obliterative phlebitis
Response to steroids	Rare	Yes

https://doi.org/10.3904/kjim.2018.018

Treatment

- Corticosteroids are the mainstay of treatment
- Induction dose is given at 30-40 mg/ day for 4 weeks followed by taper of 2.5mg every 2 weeks over a period of 3-4 months
- Response is usually seen within 4-6 weeks, improvement of clinical symptoms, reduction in serum IgG4 levels and radiological symptoms
- Maintenance therapy: for relapse or multi organ involvement
- Suggested prednisone dose is 5mg/day with or without other immunomodulators (AZA @1.5mg/kg or MMF

Sandanayake et al Clin GH 2009

Treatment outcomes

- RCT conducted in Japan:

1. Fewer relapse rates reported in patients placed on maintenance therapy for 3 years compared to those who stopped pred at 26 weeks.
2. Relapse free survival was longer in maintenance arm.
3. No serious corticostreiod related therapy. (Dose 5-7.5mg/day)

- Another small study in UK concluded that relapse/failure were common especially amongst patients with biliary disease (IAC)

Masamune et al Gut 2017; Sandanayake et al Clin GH 2009

Primary sclerosing cholangitis

- Affects mostly younger males; median age of 40
- Maybe difficult to distinguish from IgG4- SC, similar symptom profile unless history of IBD
- IgG4-SC cholangiographic features revealed by ERCP are associated high specificity (88%) but low sensitivity (45%)
- In PSC strictures tend to be shorter and biliary tree appears beaded whereas in IgG4 strictures are longer and are both intra and extra hepatic with low bile duct strictures
- Other features that seem to favor IgG4 to PSC include, circular symmetrical thickening of bile duct wall, smooth outer /inner wall margins and homogenous internal echoing in all imaging modalities

Tanaka et al Clin GH 2017

Table 2. Established Subtypes of Primary Sclerosing Cholangitis.*

Subtype	Diagnostic Approach and Criteria	Cholangiographic Features	Histopathological Features	Management	Other Features
Classic	MRCP or ERCP with typical cholangiographic features; elevation of alkaline phosphatase level (more than doubled) for >6 mo; exclusion of causes of secondary sclerosing cholangitis	Affects small and large bile ducts	Mixed inflammatory-cell infiltrate, usually more intense around bile ducts; often nonspecific and nondiagnostic	Evaluate and treat coexisting conditions; endoscopic management of dominant stricture; liver transplantation for advanced disease	70–80% of patients have inflammatory bowel disease; increased risk of colon and gallbladder cancer, cholangiocarcinoma, and hepatocellular carcinoma
Small-duct	Liver biopsy; elevation of alkaline phosphatase level (more than doubled) for >6 mo; exclusion of causes of secondary sclerosing cholangitis	Affects only small bile ducts	Mixed inflammatory-cell infiltrate, usually more intense around bile ducts; often nonspecific and nondiagnostic	Evaluate and treat coexisting conditions; liver transplantation for advanced disease	May progress to classic subtype; associated with longer survival and less risk of cholangiocarcinoma than classic subtype
Associated with autoimmune hepatitis	Laboratory evidence of autoimmune hepatitis plus MRCP or ERCP findings of primary sclerosing cholangitis; exclusion of causes of secondary sclerosing cholangitis	Affects small and large bile ducts	Lymphoplasmacytic infiltrate, interface hepatitis	Same as for classic subtype (see above); treatment for autoimmune hepatitis	Better prognosis than with classic subtype but worse prognosis than with autoimmune hepatitis alone

NEJM 2016, 375:1161-70

Cholangiocarcinoma

- Indistinguishable from type 1 disease (distal CBD stenosis) and type 3 and type 4 disease may mimic hilar CCA
- A review of 185 patients who underwent resection for presumed hilar CCA found that 17% had no malignancy and 50% had IgG4-SC

- Presence or association with AIP supports IgG4-SC to CCA
- Diagnosis can be challenging, ERCP guided cytology yield is low for diagnosis of CCA

- Per-oral cholangioscopy with visually targeted biopsies has greater diagnostic accuracy compared to ERCP (sensitivity and specifity 85% and 100% respectively)
- Neither CA 19.9 or IgG4 Levels accurately distinguishes the two

Erdogan et al Br J Surg 2008; Navaneethan et al Gastro endo 2016

Our patient

- 2 years after his diagnosis - Liver clinic
- Stent free for a month and enzymes/serology slowly going up but remains asymptomatic
- ? Can we biopsy and consider for steroids
- He has long standing diabetes, CKD unexplained and mentions he has a hernia op booked soon

What to do?

- Will a biopsy help or change Management?
- Will you consider giving steroids ? What dose
- For how long ?

- **MRCP**: diffuse tapering of CBD and hepatic ducts with tapered narrowing of the distal CBD. Interval deterioration with progressive narrowing of central ducts and slight upstream dilatation. ?? Suspected tubulointerstitial nephritis related to IgG 4

- Progressive disease with possibilty of kidney involvement

- He needs steroids

Conclussion

- Diagnosis of IgG4 related disease is still a challenge
- Often diagnosis is made during/after patient has undergone surgery
- Should always be considered as a differential when a patient presents with unexplained obstructive jaundice
- Satisfying condition to manage, steroid responsive
- Relapse are common and low dose maintenance steroids is advised