## IgG4 related cholangiopathy

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## Introduction

- IgG4 associated cholangitis (IAC) is one manifestation of IgG4 related disease (IgG4 RD)
  - Immune mediated inflammatory disease characterized by inflammatory lesions in the pancreaticobiliary tract with massive infiltration of lymphocytes (typically IgG4 positive plasma B cells) in the bile duct wall, elevation of the serum IgG4 and a good response to corticosteroid treatment
- IAC is associated with type 1 autoimmune pancreatitis (lymphoplasmocytic sclerosing pancreatitis)
- IAC and autoimmune pancreatitis (AIP) may mimic sclerosing cholangitis, cholangiocarcinoma or pancreatic carcinoma
- As IAC and AIP may be difficult to diagnose and mimic malignancy, unnecessary hepatic / pancreatic resections may take place

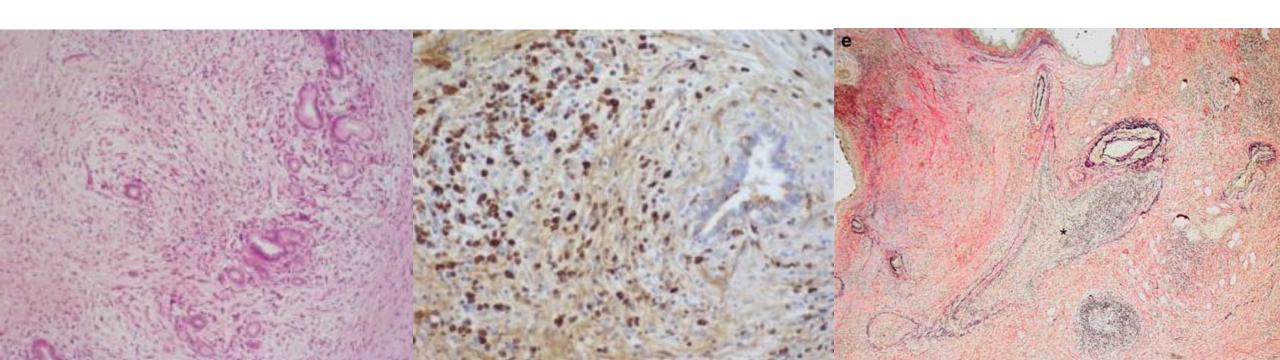
## Pathogenesis

- Poorly understood
- IAC belongs to **spectrum** of **IgG4 related disorders**, which include a number of medical conditions sharing similar histopathological characteristics
  - Multiple organs can be affected simultaneously / consecutively with swelling, loss of function and inflammatory features including lymphocytic infiltration
  - Pancreaticobiliary tract is one of the major localisations; IAC is often accompanied by autoimmune pancreatitis
    - > ½ AIP have hepatobiliary manifestations Kanno 2012
    - Most IAC have involvement of the pancreas Ghazale 2008

Abdominal and pelvic manifestations	Extra-abdominal/extra-pelvic manifestations
Bile ducts (IAC), gallbladder, and liver	Hypophysis
Pancreas (AIP)	Eye, retro-orbital tumor
Stomach, intestine, and ileal pouch	Salivary and lacrimal glands
Retroperitoneum (fibrosis)	Thyroid gland
Kidney	Lung
Pseudotumor	Lymphatic system (especially lung hilus)
Prostate	Vascular system (aortitis)
Testis	Joint

# Pathogenesis

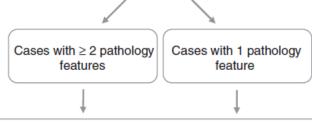
- Histologically IAC / type 1 AIP
  - Dense lymphoplasmacytic infiltrate
  - Abundant IgG4 positive plasma cells
  - Specific pattern of storiform fibrosis
  - Obliterative phlebitis



## Pathogenesis

Characteristic histological features

- 1. Dense lymphoplasmacytic infiltrate
- 2. Fibrosis, usually storiform in character
- 3. Obliterative phlebitis



	Numbers of IgG4+	Ref	
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	6
Pancreas (surgical specimen)	>50	>50	30,32
Pancreas (biopsy)	>10	>10	56,57
Bile duct (surgical specimen)	>50	>50	49
Bile duct (biopsy)	>10	>10	58,59
Liver (surgical specimen)	>50	>50	49
Liver (biopsy)	>10	>10	12,60
Kidney (surgical specimen)	>30	>30	15
Kidney (biopsy)	>10	>10	61
Aorta	>50	>50	16,51,52
Retroperitoneum	>30	>30	8
Skin	>200	>200	62,63

IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD

Orange boxes = Probable histological features of IgG4-RD

## Clinical picture

- Older males
  - Generally >60 yrs

Male / female 8:1

Ghazale 2008

Tanaka 2014

Association with IBD is controversial

Shimosegawa 2011

Possible role for environmental factors (solvents, gases)

de Buy Wenniger 2014

- Mild to moderate abdominal pain, weight loss, obstructive jaundice and pruritus
- New onset DM, steatorrhea

## Imaging

- Mass forming lesions vs biliary strictures/ sclerosing lesions
  - May be difficult to distinguish from malignancy, sclerosing cholangiopathies (PSC)
- Cholangiography variable with corresponding differential
  - Hilar stenosis klatskin
  - Distal CBD stenosis chronic pancreatitis, pancreatic cancer, cholangiocarcinoma
  - Diffuse structuring in intra- & extra-hepatic systems PSC

### Biochemical

- Elevated serum bilirubin, ALP, GGT, Ca 19-9, IgG4 Fluctation!
  - IgG4 <4x ULN non-diagnostic (can be elevated in ca, PSC)
  - 20-25% of IAC / AIP can have normal IgG4
  - Ca 19-9 frequently elevated
- Rheumatoid factor, ANA may be positive but lack specificity, sensitivity

## Diagnosis

 No accurate diagnostic test for IAC / IgG4 RD – leads to diagnostic delay

 Serum IgG4 only diagnostic when raised > 4x the upper limit of normal

- Diagnostic criteria
  - Organ manifestation patterns
  - Imaging findings
  - Serum tests
  - Histological features
  - Response to immunosuppressive therapy

#### Diagnosing pancreaticobiliary manifestations of IgG4-RD Autoimmune pancreatitis (type I) IgG4-associated cholangitis Stricture(s) of intra-hepatic, proximal extra-hepatic Clinical suspicion of pancreatic disease or intra-pancreatic ducts, with: Classical imaging for AIP + Previous pancreatic/ Absence of classical imaging biliary resection or core Classical imaging for AIP + one of the following: for AIP biopsy of pancreas elevated serum IgG4 elevated serum IgG4 showing diagnostic features of AIP/IAC other organ involvement Negative workcompatible FNA up for cancer histology Two or more of the following: elevated serum IgG4 Definite Definite suggestive pancreatic imaging findings diagnosis of diagnosis of One of the following: other organ involvement AIP IAC serum IgG4 > 2 x ULN bile duct biopsy with > 10 (histologically) proven IgG4 positive cells / hpf other IgG4-RD spectrum Response to 2 weeks of Combined with following organ involvement adequate steroid findings after 4 weeks of adequate steroid treatment: treatment: Two of the following: In all cases of non-· significant decrease in markedly improved biliary response to adequate · elevated serum IgG4 serum IgG4 strictures allowing stent steroid treatment: removal clinical / radiological markedly improved evidence for other organ morphology as withdraw steroids! liver enzymes < 2 x ULN objectivated by imaging involvement reconsider presence of significant decrease in serum (CT, ultrasound, MRCP) malignant disease · compatible FNA histology IgG4 and CA19.9

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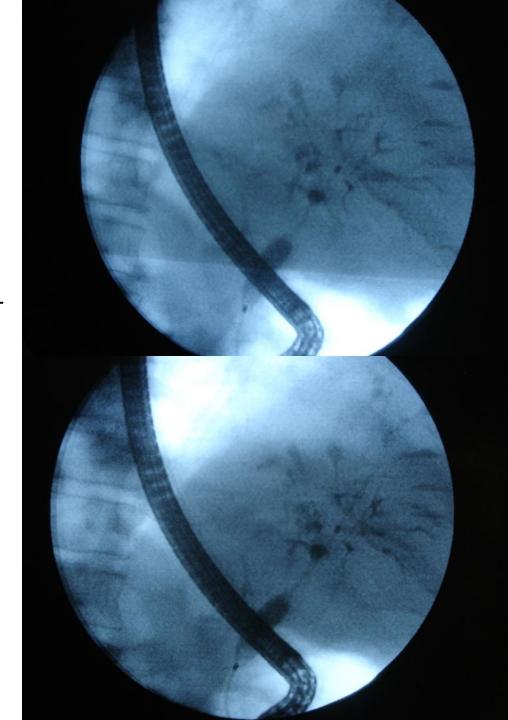
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#### Case 1 – Mr NM

- 64 yr old man, African extraction
- BG: DM, Hpt, blind L eye, PS1
- 1<sup>st</sup> seen 2010
  - Obs jaundice, 10kg LOW
  - Bili 198/121, ALP 448, GGT 1651, AST 127, ALT 89, Ca 19-9 200,8
  - CT distal obstruction, no mass
  - ERCP stricturing of hilum, intrahepatic ducts stent placed
  - Brushings benign cells, lymphocytes
  - IgG 33,52 (7-16)
  - Thought to be malignant
- 2012 no pain, jaundice, loss of PS, LOW bili 24/15, ALP 651, GGT 2300, Ca 19-9 57
  - IgG4 elevated
  - Positive liver biopsy



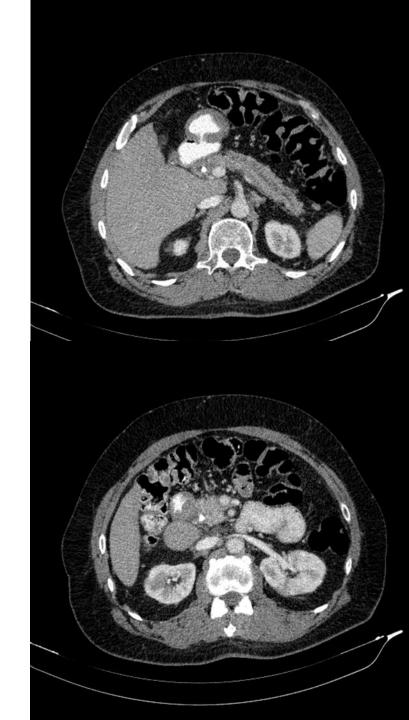
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- BG: DM
- 1<sup>st</sup> presented April 2009
  - Abdominal pain, LOW
  - Bili 17/6, ALP 313, GGT 763, ALT 180, AST 116, Ca 19-9 245
  - CT: enlarged, sausage shaped pancreas
  - Subsequently Bili 36/19
  - ERCP: CBD stricture, diffuse intra-hepatic strictures
  - Serum IgG4 6 (0.084 0.888)



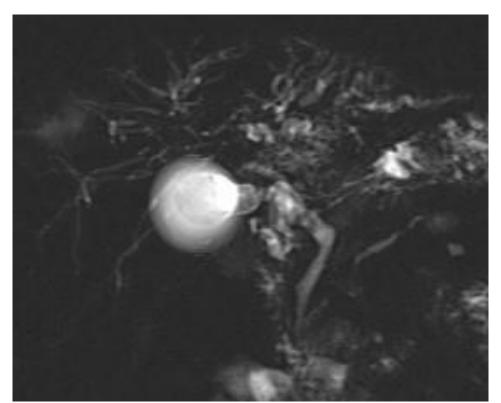
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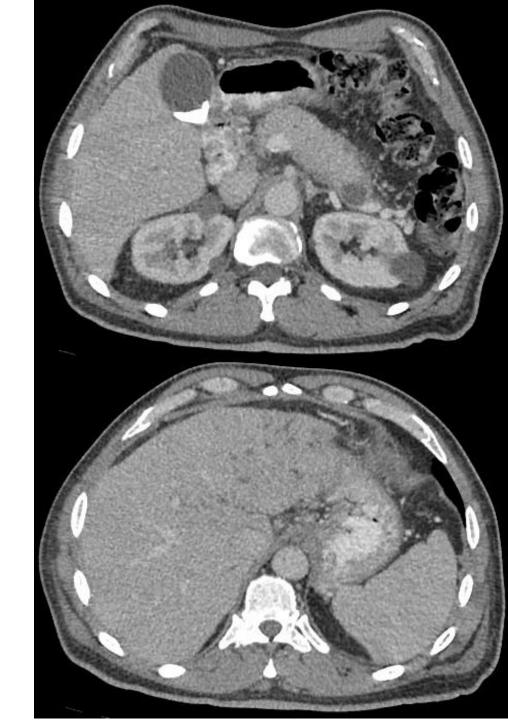


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  - Rxed with oral prednisone
  - CT 5/12 post end of Rx



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- Returned 2014
  - Obstructive jaundice





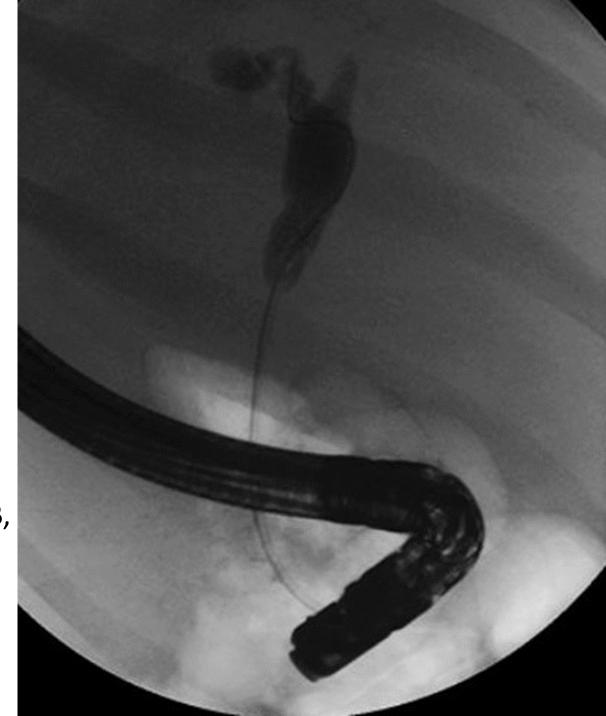
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- 49 year old woman, African extraction
- BG: nil
- Presented May 2012
  - Fluctuating clinical jaundice, progressive pruritus, mild LOW
  - Bili 74/43, ALP 211, GGT 86, ALT 34, AST 41, alb 28, Ca 19-9 normal
  - CT: HOP mass
  - MRI/MRCP: multifocal caliber variation of intra- & extra-hepatic biliary tree, dilated GB, dilated CHD, stenosed CBD
  - ERCP: long distal CBD stricture
  - Surgical resection: Histo: IgG4 RD AIP.



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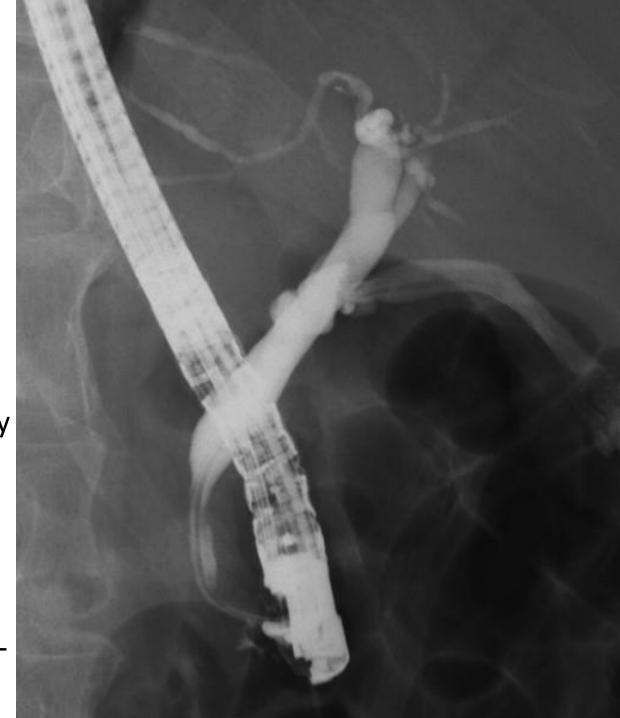
#### Case 4 – Mr BD

- 64 year old man; compatriot of Solly Marks; of mixed extraction
- BG: hpt, hyperchol, IHD, good baseline
- Presented Jan 2013
  - Obstructive jaundice, LOW
  - Bili 181/102, GGT 150, AST 48, ALT 61
  - Ca 19-9 5.7
  - CT: dilated CBD tapers abruptly within bulky HOP
  - ERCP: distal benign CBD stricture
  - IgG4 21.6 (0.84-0.888)
  - EUS: ill defined mass
- Good response to steroids; relapse on completion. Subsequent response on reinitiation



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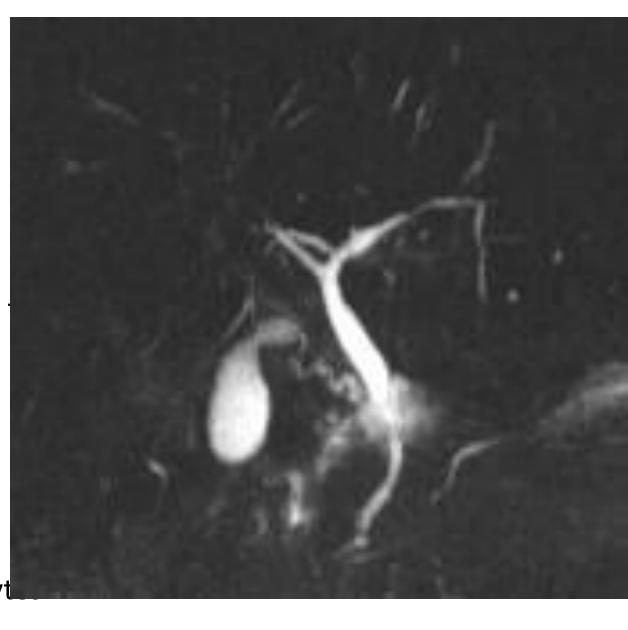
#### Case 5 – Mr YH

- 58 year old man, mixed ancestry
- BG: DM; dxed chronic sclerosing sialadenitis (on histolology) prev year
- Presented Jan 2014
  - LOW, Obstructive jaundice / pruritus
  - Bili 40/34; ALP 313, ALP 405, GGT 292, ALT 77, AST 64, Ca 19-9 1721
  - U/S: thickened GB wall, hepatomegaly
  - CT: thickened GB / CBD walls
  - MRCP: sclerosed intra-hepatic ducts
  - IgG4: 37.1 (0.03 2.01)
  - Liver bx: proliferating bile ductules, absent normal caliber interlobular duct, lymphocytes
     >10 IgG4-positive plasma cells / HPF



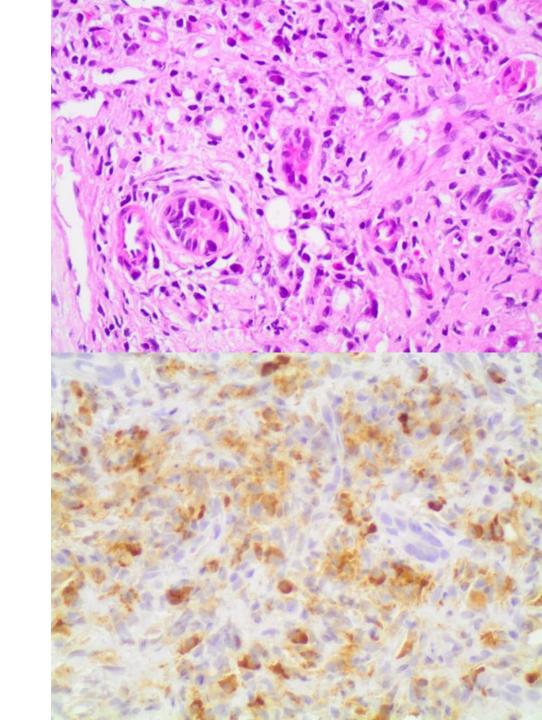
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	Bilirubin	ALP	GGT	ALT	AST	Ca 19-9	IgG4
Case 1	198	590	1886	127	157	200	33.5 (IgG 7-16) <b>2x</b>
Case 2	17	313	763	180	116	247	6 (0.084-0.888) <b>7x</b>
Case 3	74	211	86	34	41	N	0.71
Case 4	286	276	42	91	94	5.7	21.6 (0.084-0.888) 24x
Case 5	42	405	292	77	64	1721	37.1 (0.02-2.01) <b>19x</b>

## Conclusion

- IgG4 cholangiopathy is uncommon
- The clinical and radiological picture is varied
- Diabetes is a prominent clinical feature
- Early diagnosis requires a high index of suspicion
- Histology remains the gold standard
- Important clues include
  - a prolonged clinical course
  - fluctuating clinical / biochemical picture
  - clinical / radiological features not in keeping with malignancy
  - multifocal / benign appearance on cholangiography
- Of particular note:
  - Ca 19-9 may be elevated
  - Elevation of the serum IgG4 is variable
- Therapeutic trial of steroids only once malignancy has been excluded