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

Hubers 2015

Pathogenesis

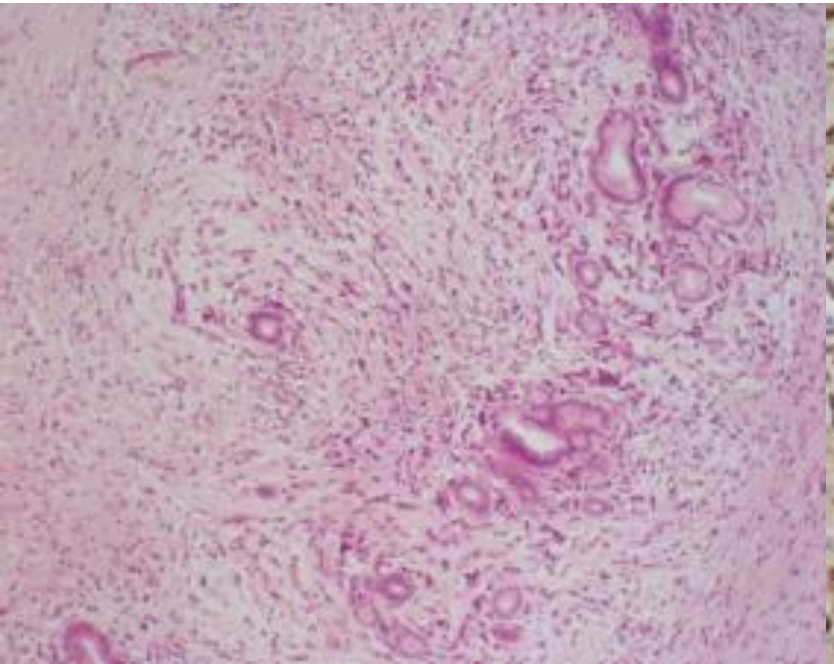
- Poorly understood
- IAC belongs to **spectrum** of **IgG4 related disorders**, which include a number of medical conditions sharing similar histopathological characteristics
  - **Multiple organs** can be affected simultaneously / consecutively with swelling, loss of function and inflammatory features 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

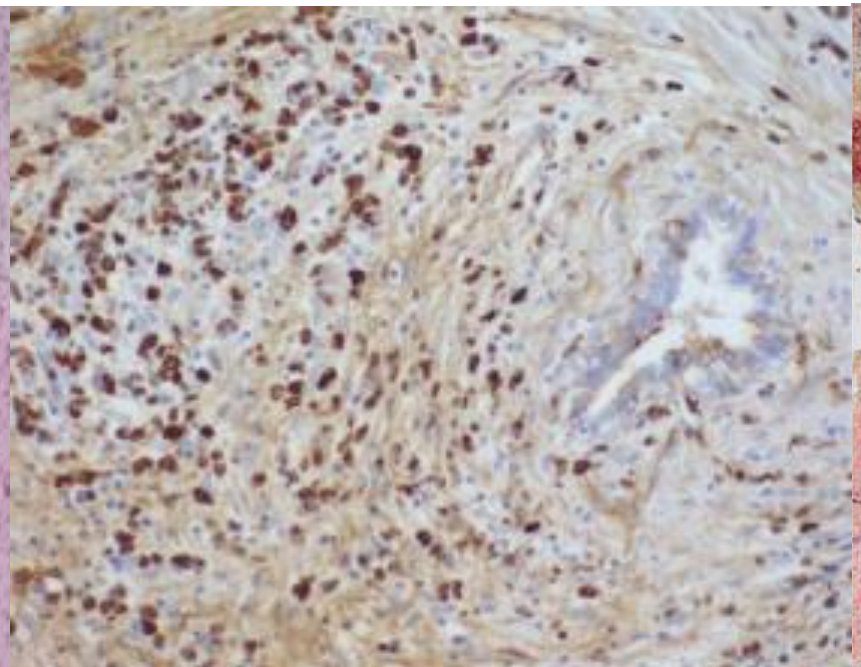
Abdominal and pelvic manifestations	Extra-abdominal/extra-pelvic manifestations
Bile ducts (IAC), gallbladder, and liver	Hypophysis
Pancreas (AIP)	Eye, retro-orbital tumor
Stomach, intestine, and ileal pouch	Salivary and lacrimal glands
Retroperitoneum (fibrosis)	Thyroid gland
Kidney	Lung
Pseudotumor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

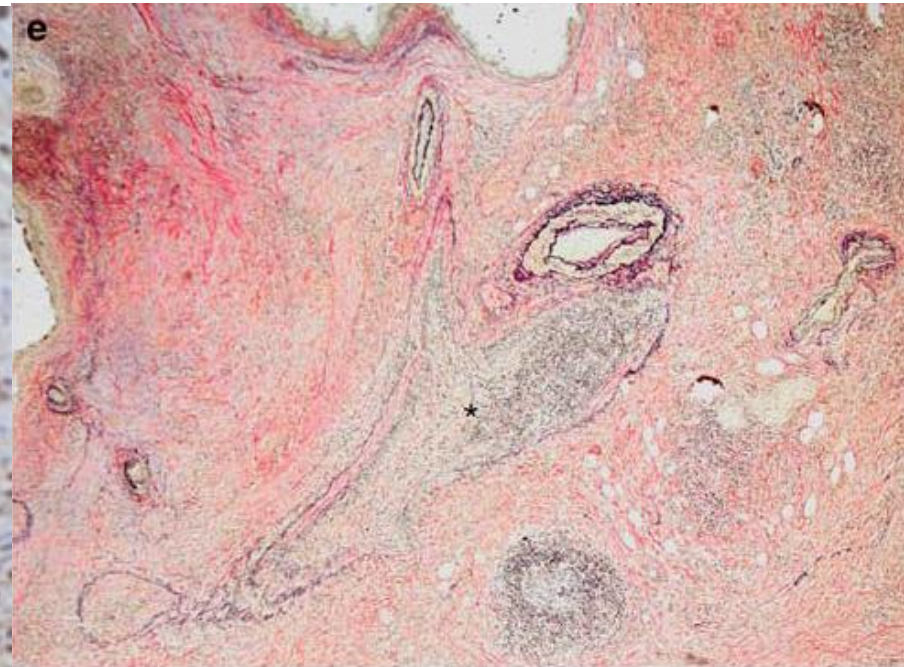
Hubers 2015

Pathogenesis

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







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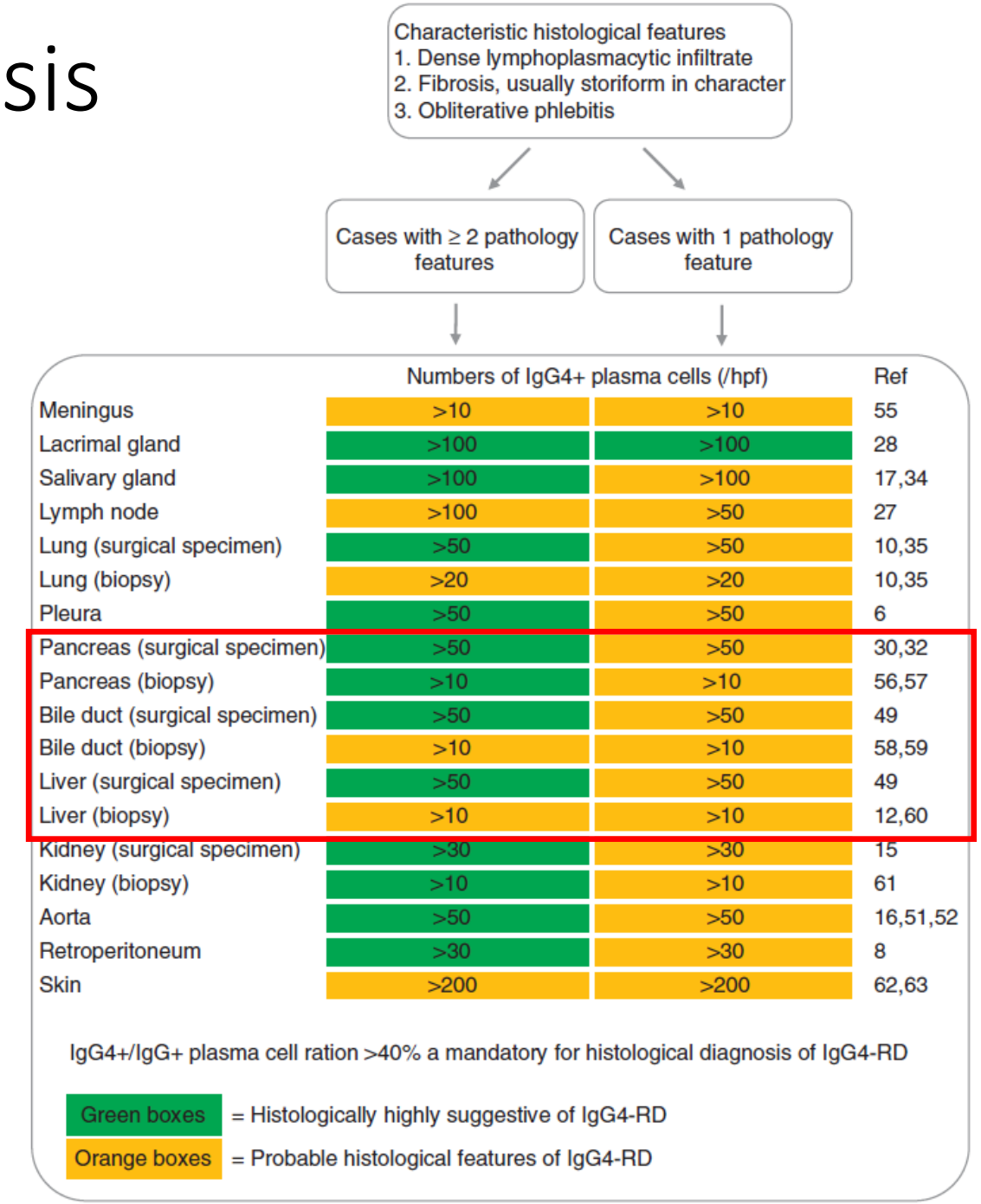


Deshpande 2012

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

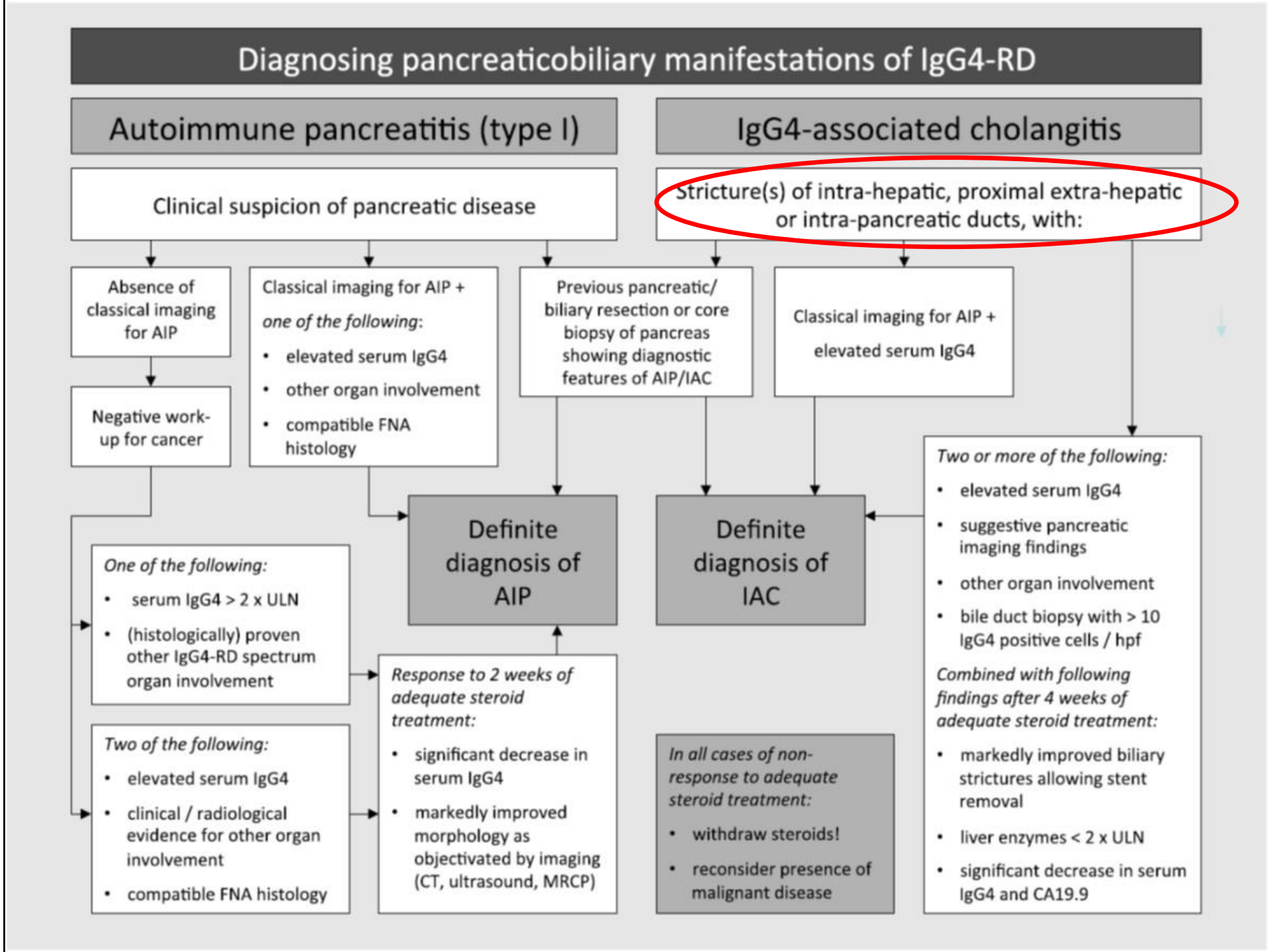
- Elevated serum bilirubin, ALP, GGT, Ca 19-9, IgG4 - Fluctation!
  - IgG4 <4x ULN non-diagnostic (can be elevated in ca, PSC)
  - 20-25% of IAC / AIP can have normal IgG4
  - Ca 19-9 frequently elevated
- Rheumatoid factor, ANA may be positive but lack specificity, sensitivity

Diagnosis

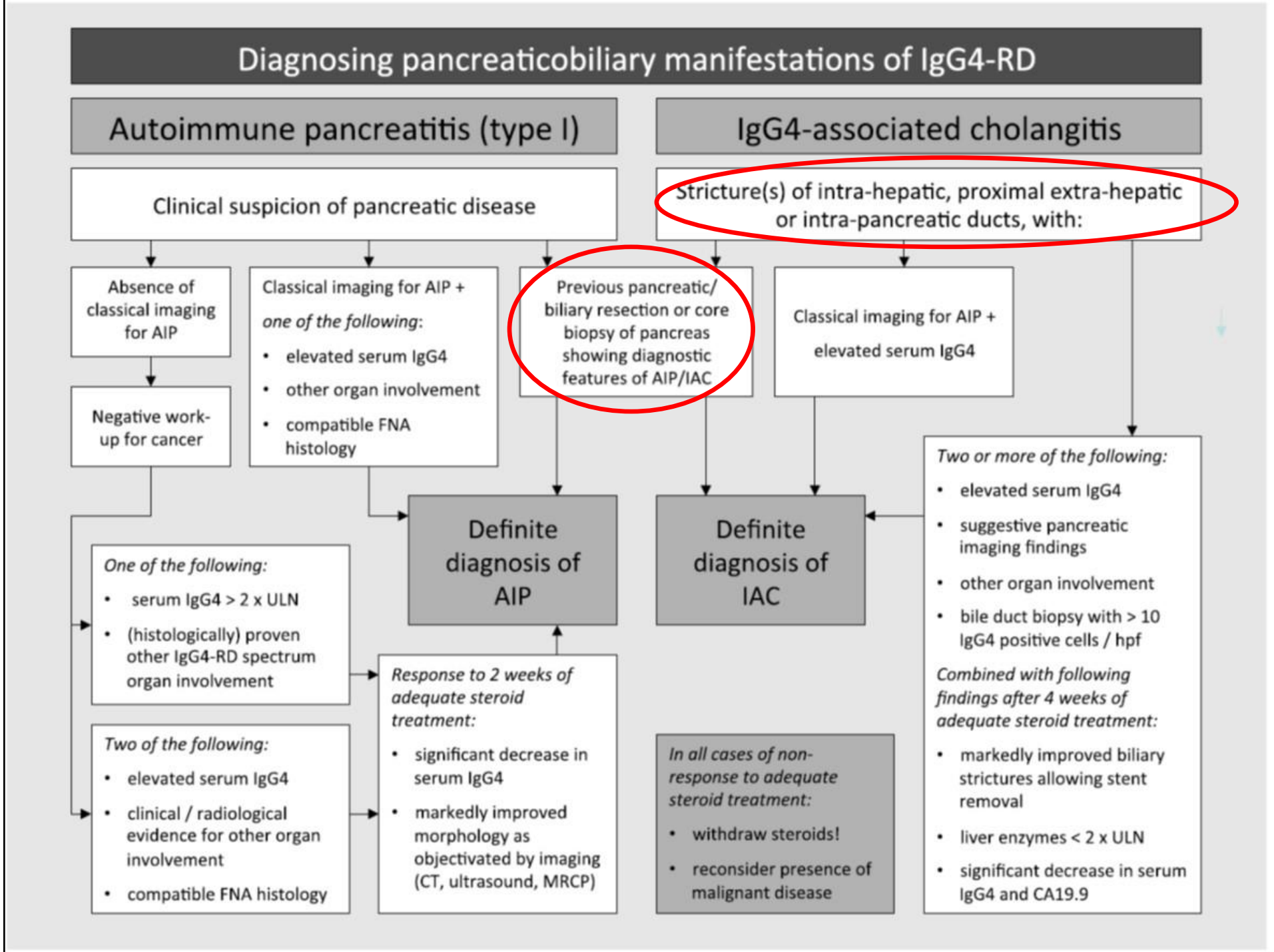
- No accurate diagnostic test for IAC / IgG4 RD – leads to diagnostic delay

- 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



Chari 2009
Hubers 2015



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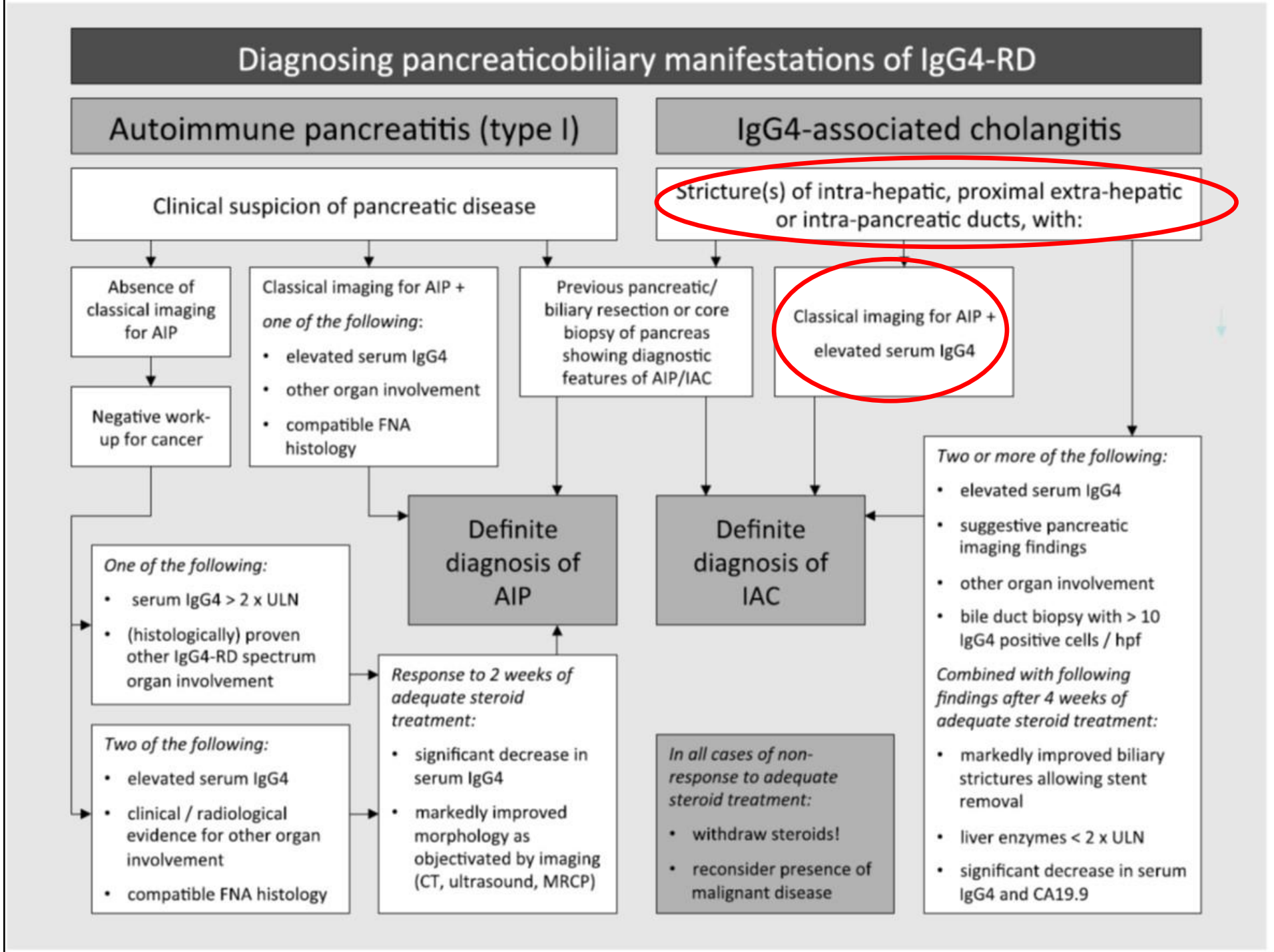

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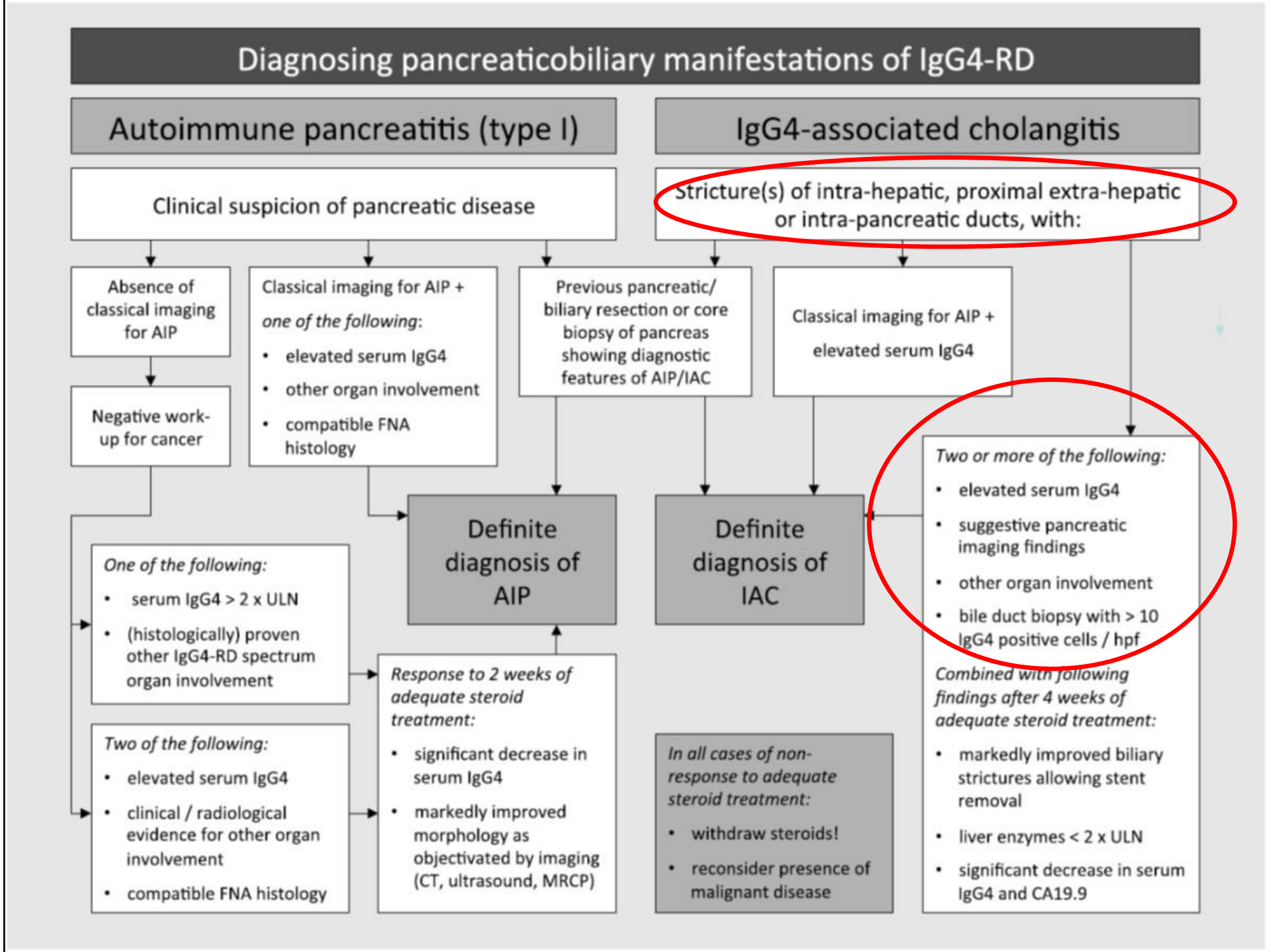

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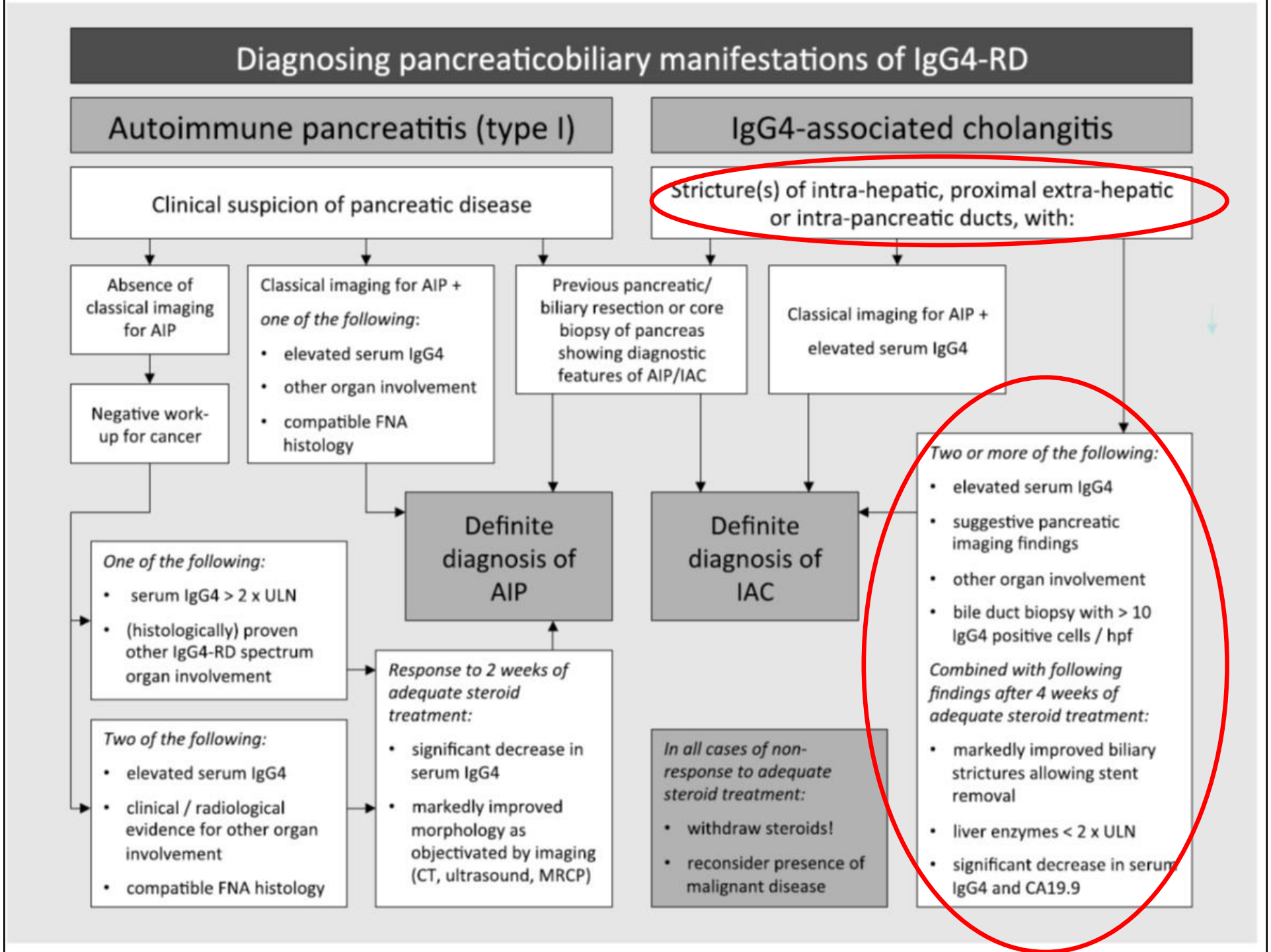

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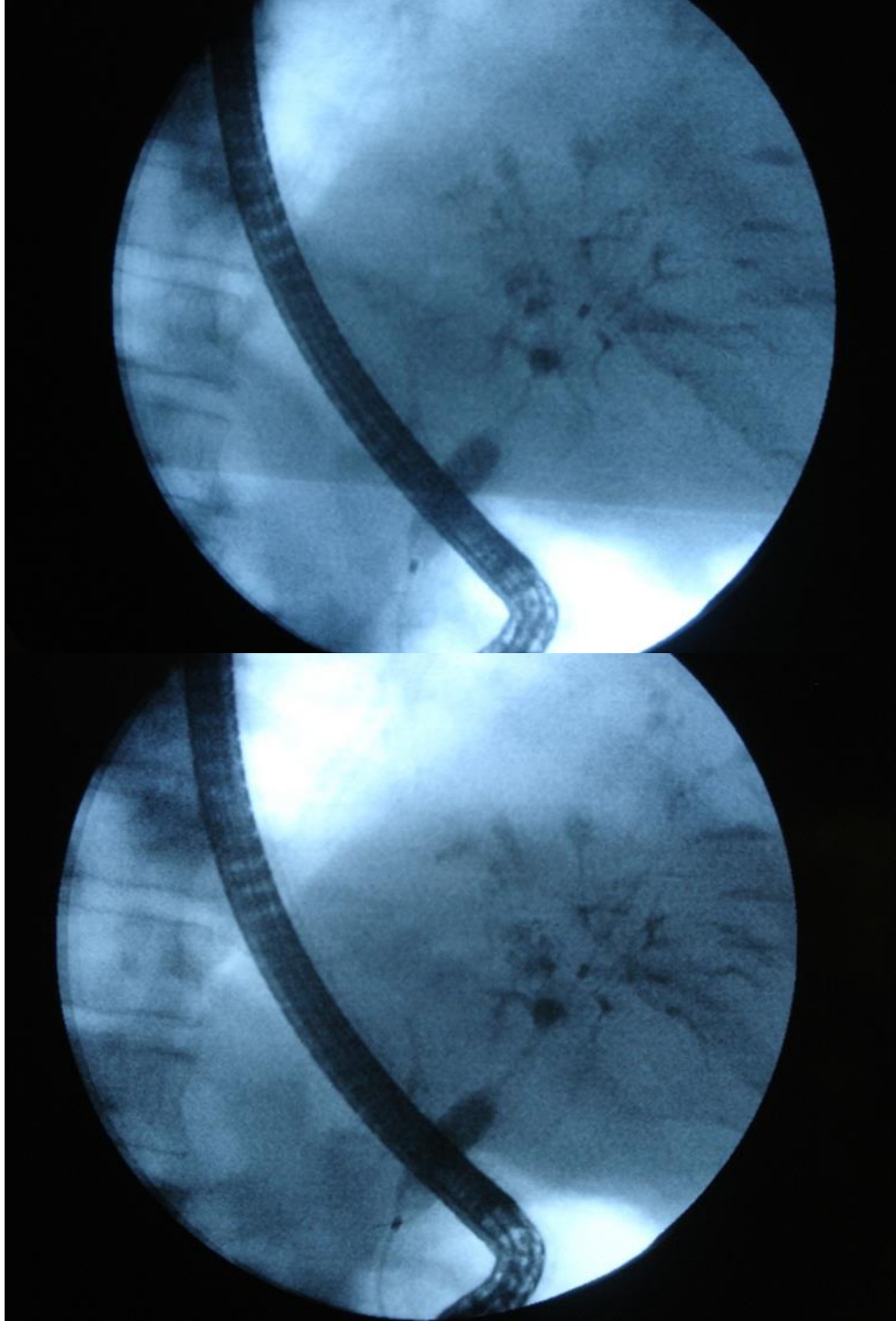
Case 1 – Mr NM

- 64 yr old man, African extraction
- BG: DM, Hpt, blind L eye, PS1
- 1st 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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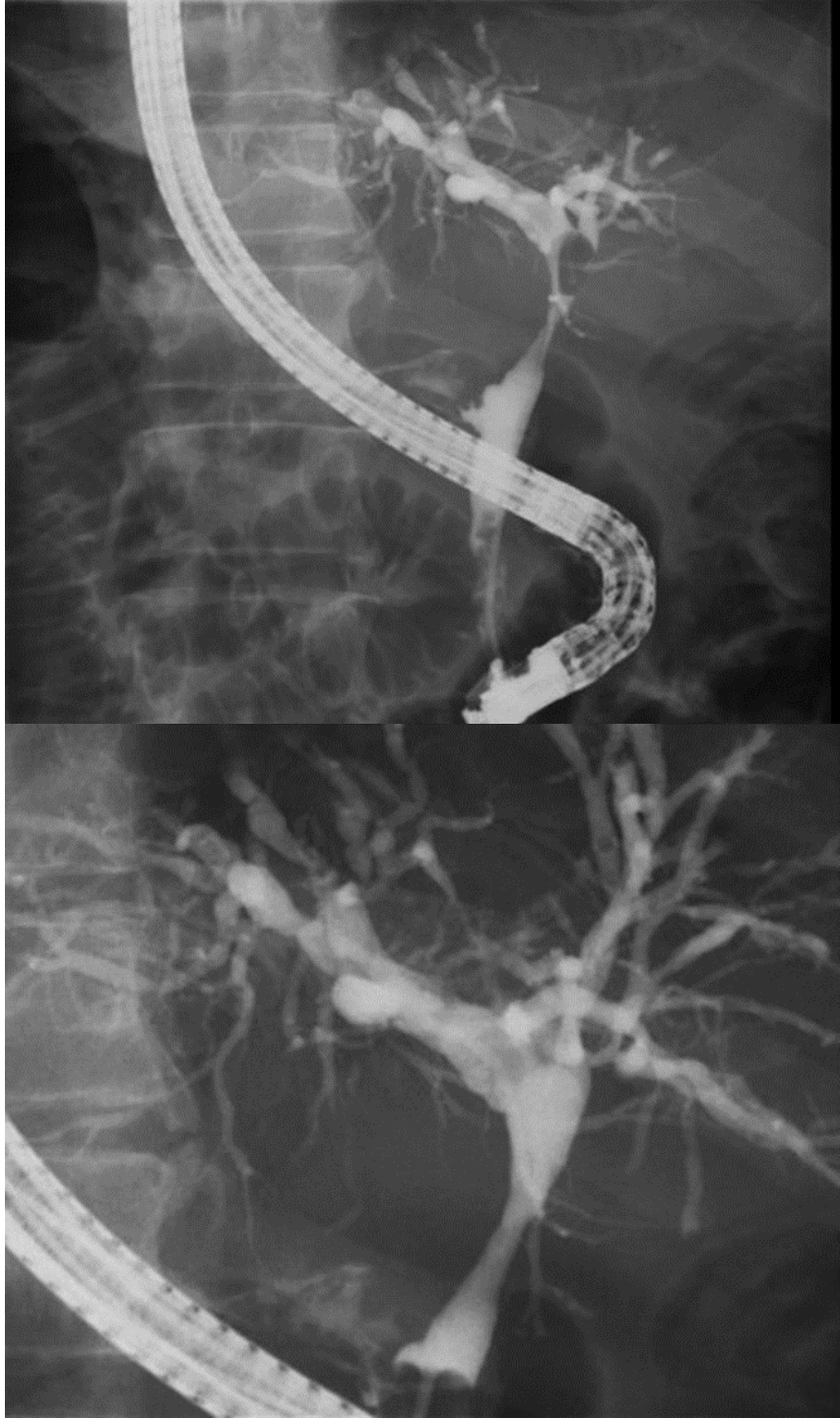

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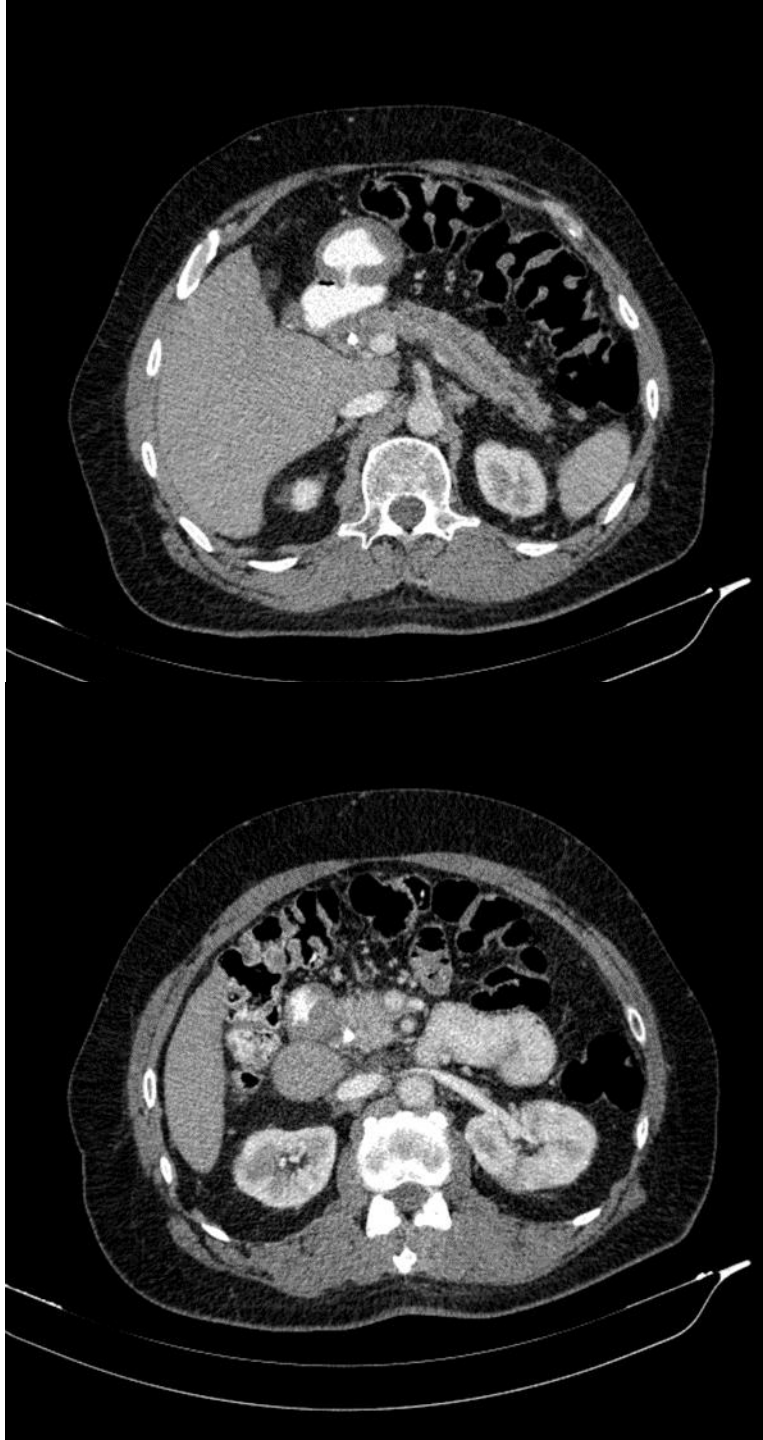
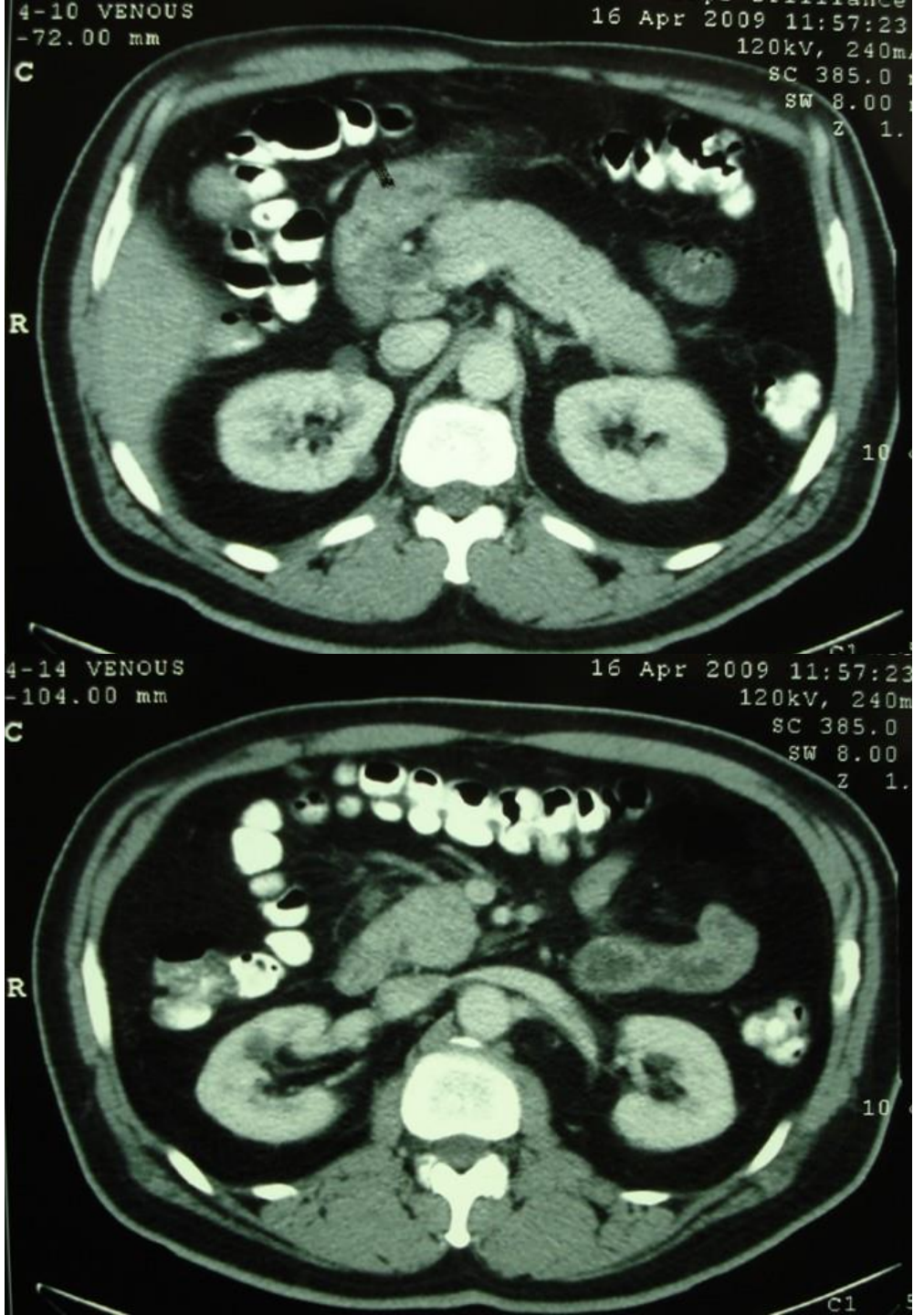


Case 2 – Mr LB

- 54 year old man, mixed extraction
- BG: DM
- 1st 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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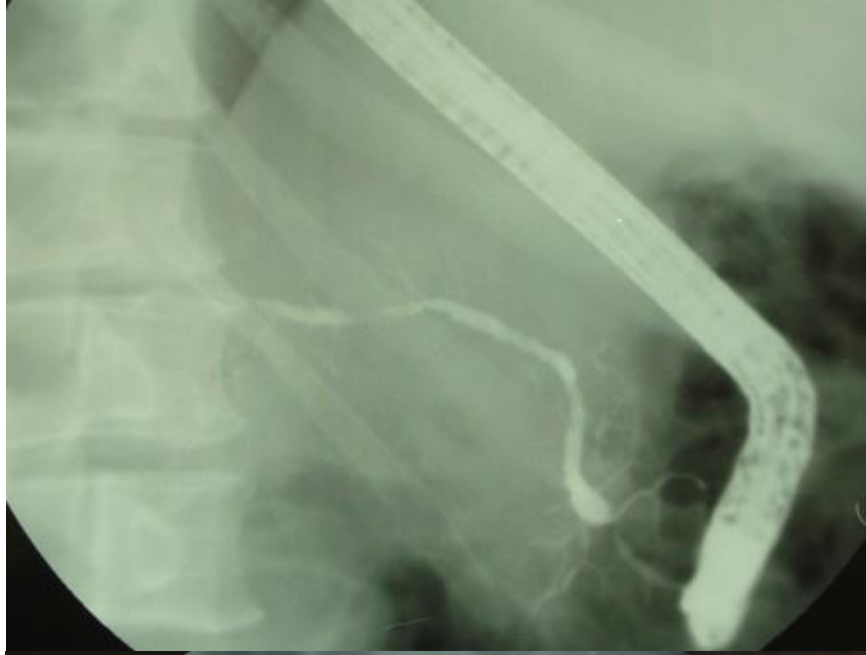

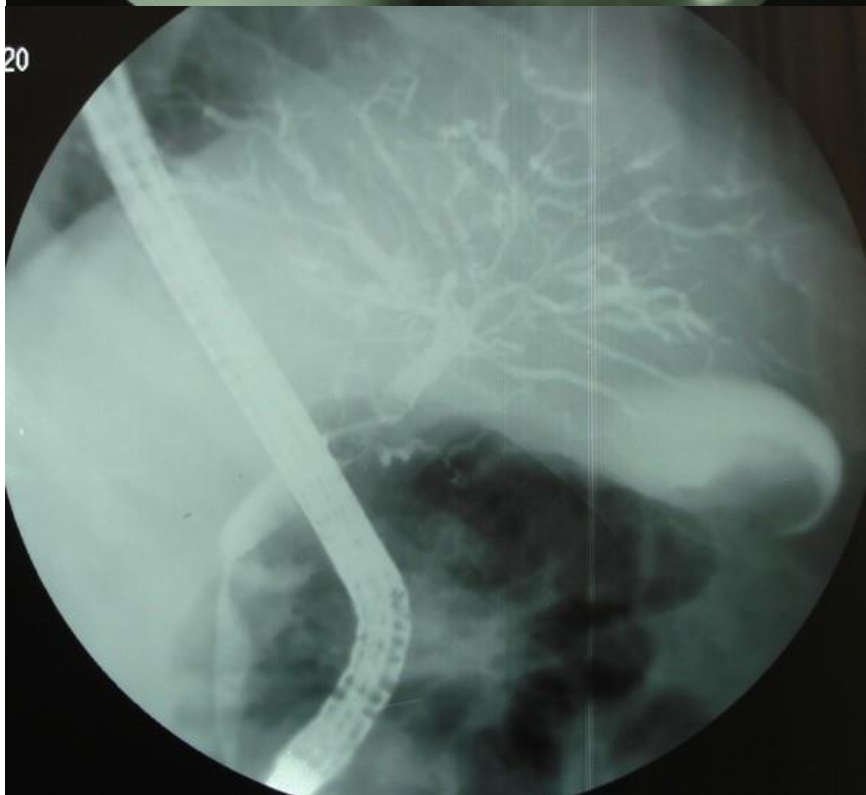

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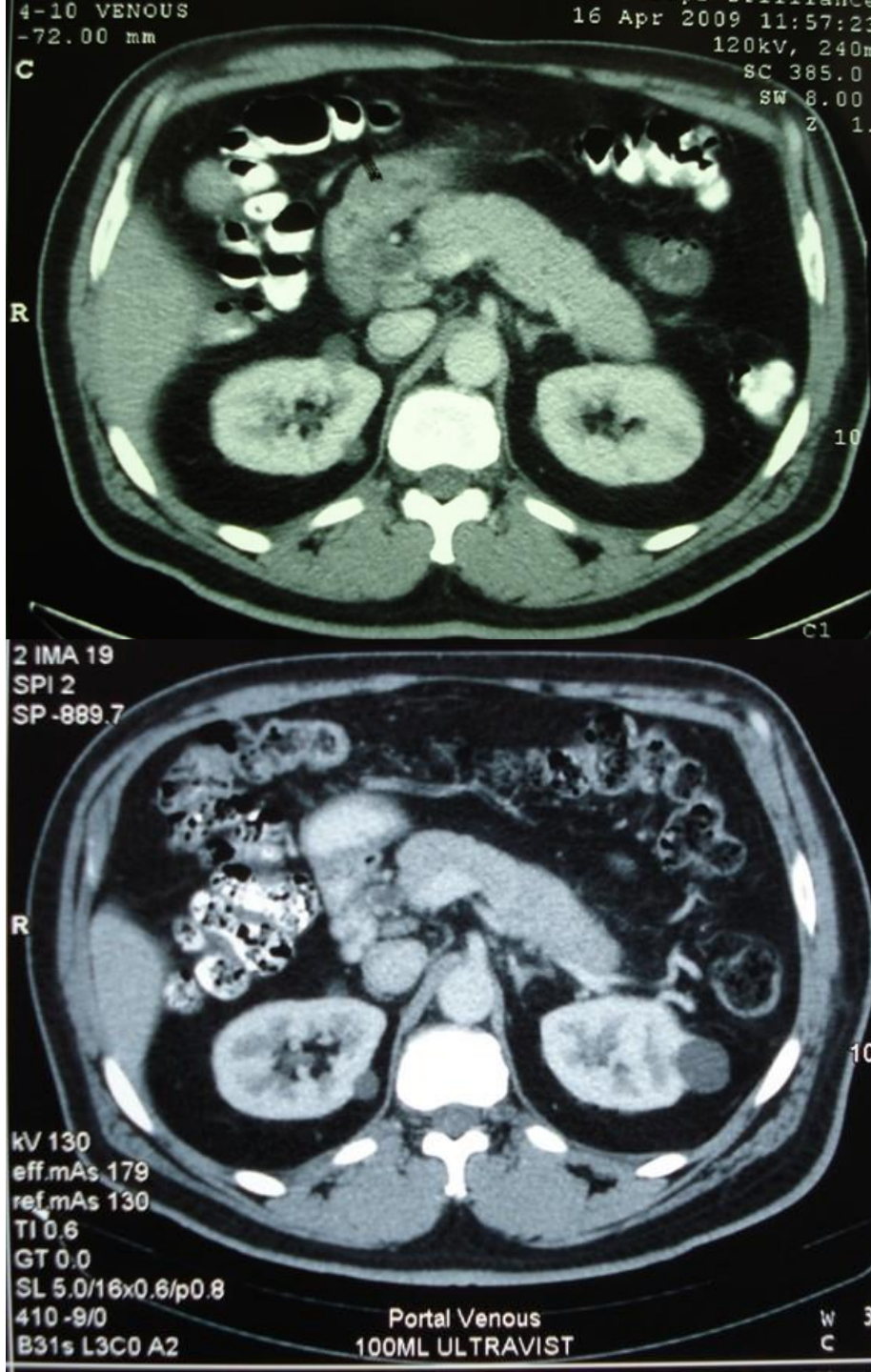
  - Rxed with oral prednisone
  - CT 5/12 post end of Rx



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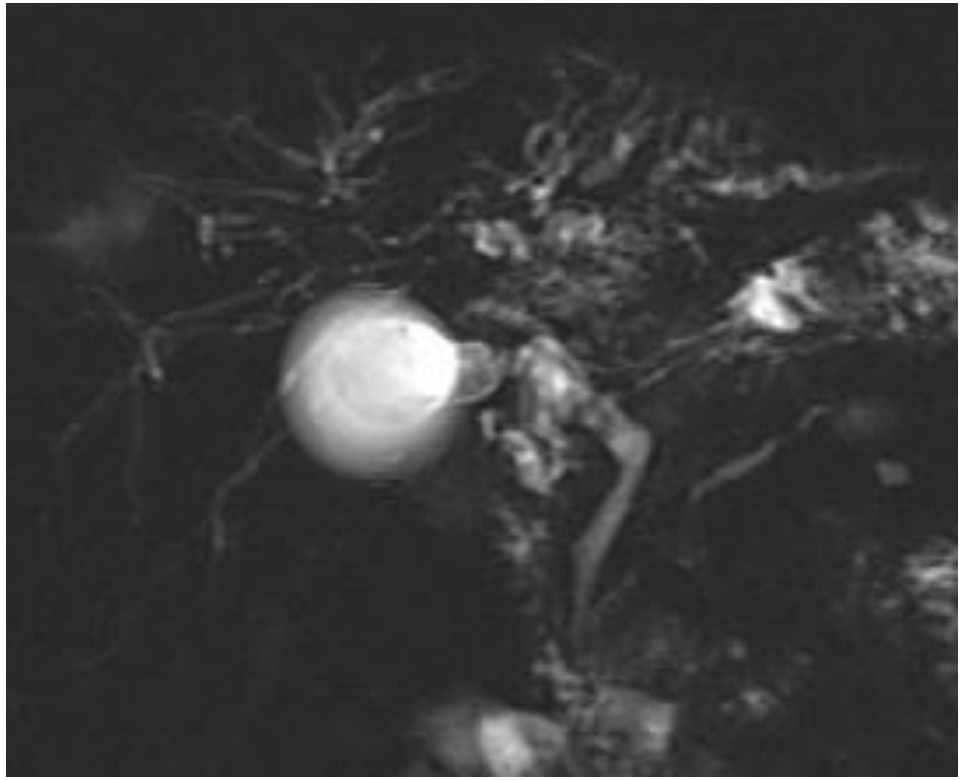
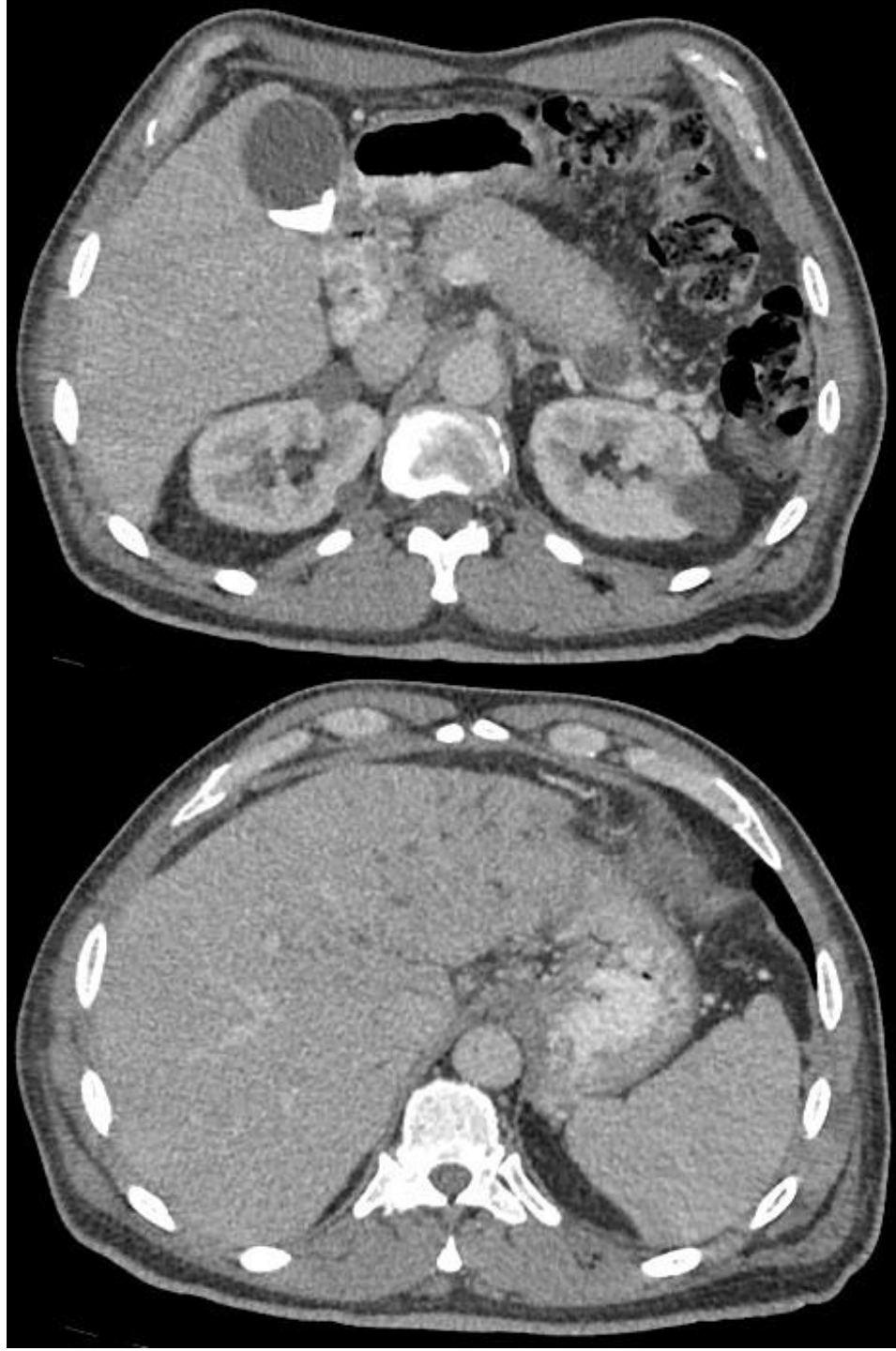
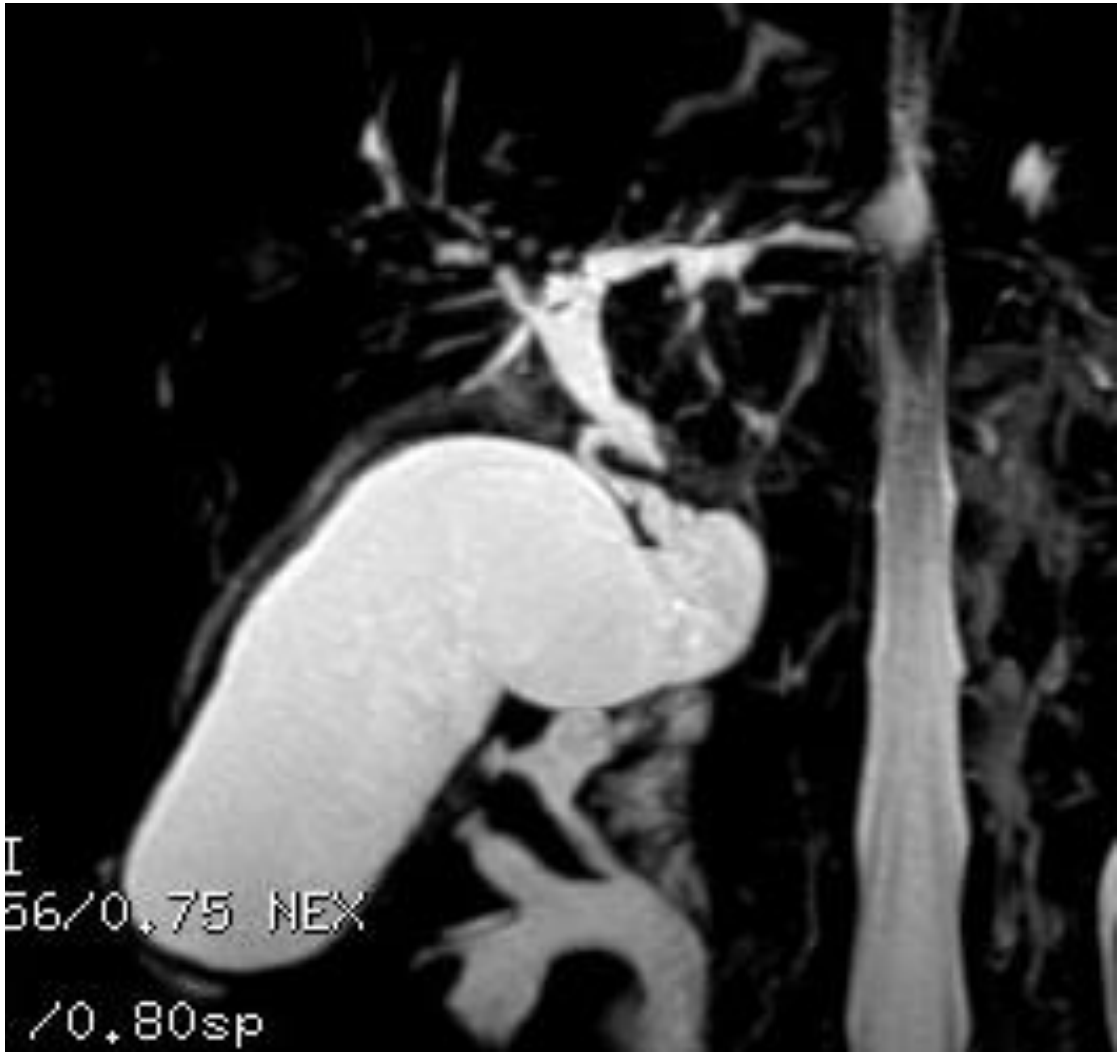
- BG: DM
- Returned 2014
  - Obstructive jaundice





Case 3 – Mrs NT

- 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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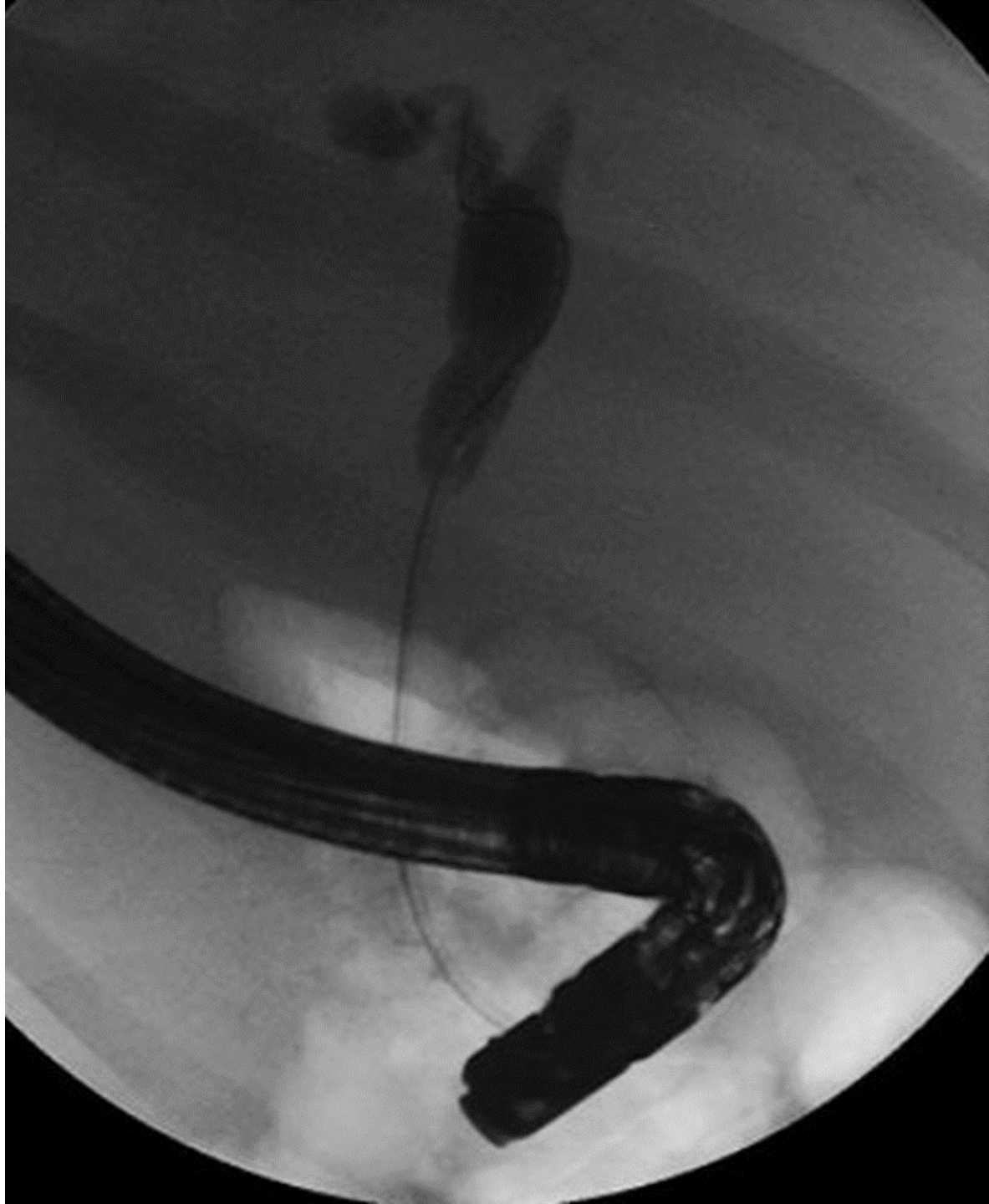
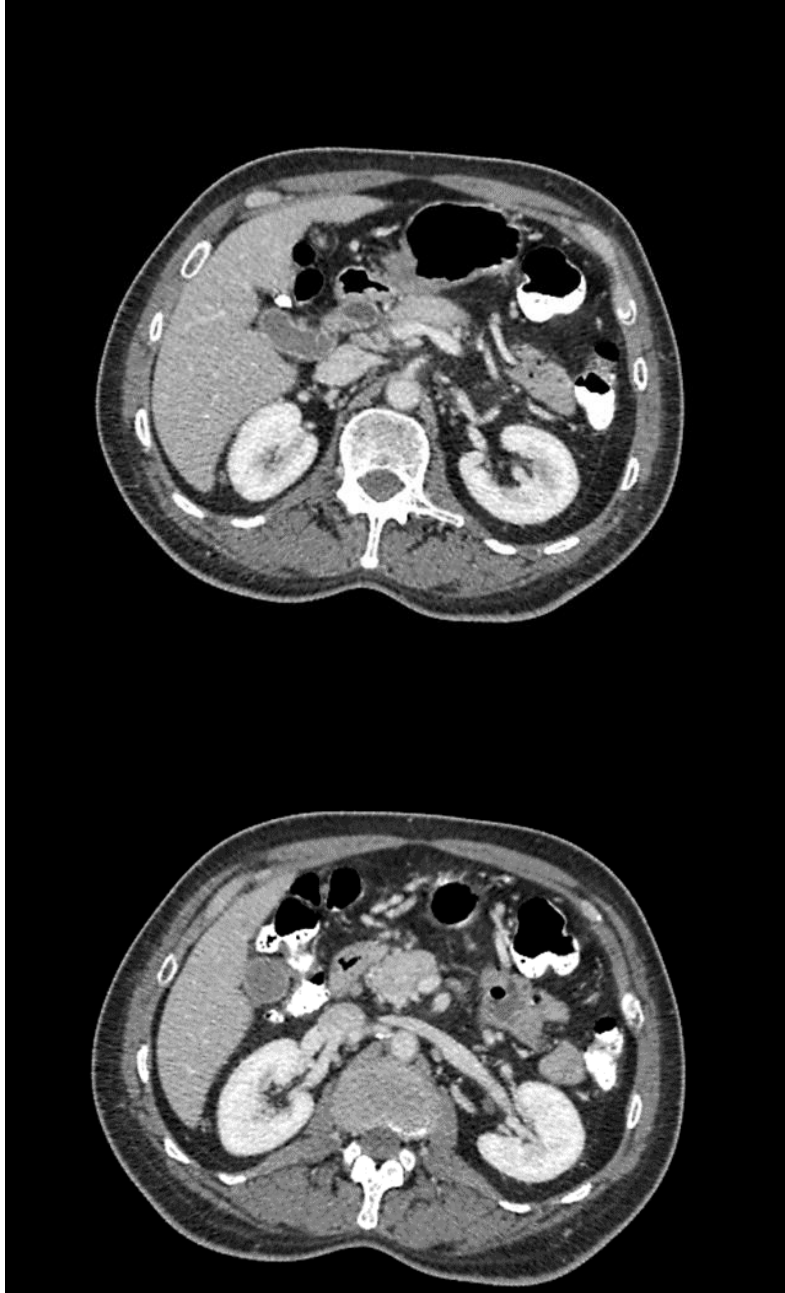


Case 4 – Mr BD

- 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 re-initiation



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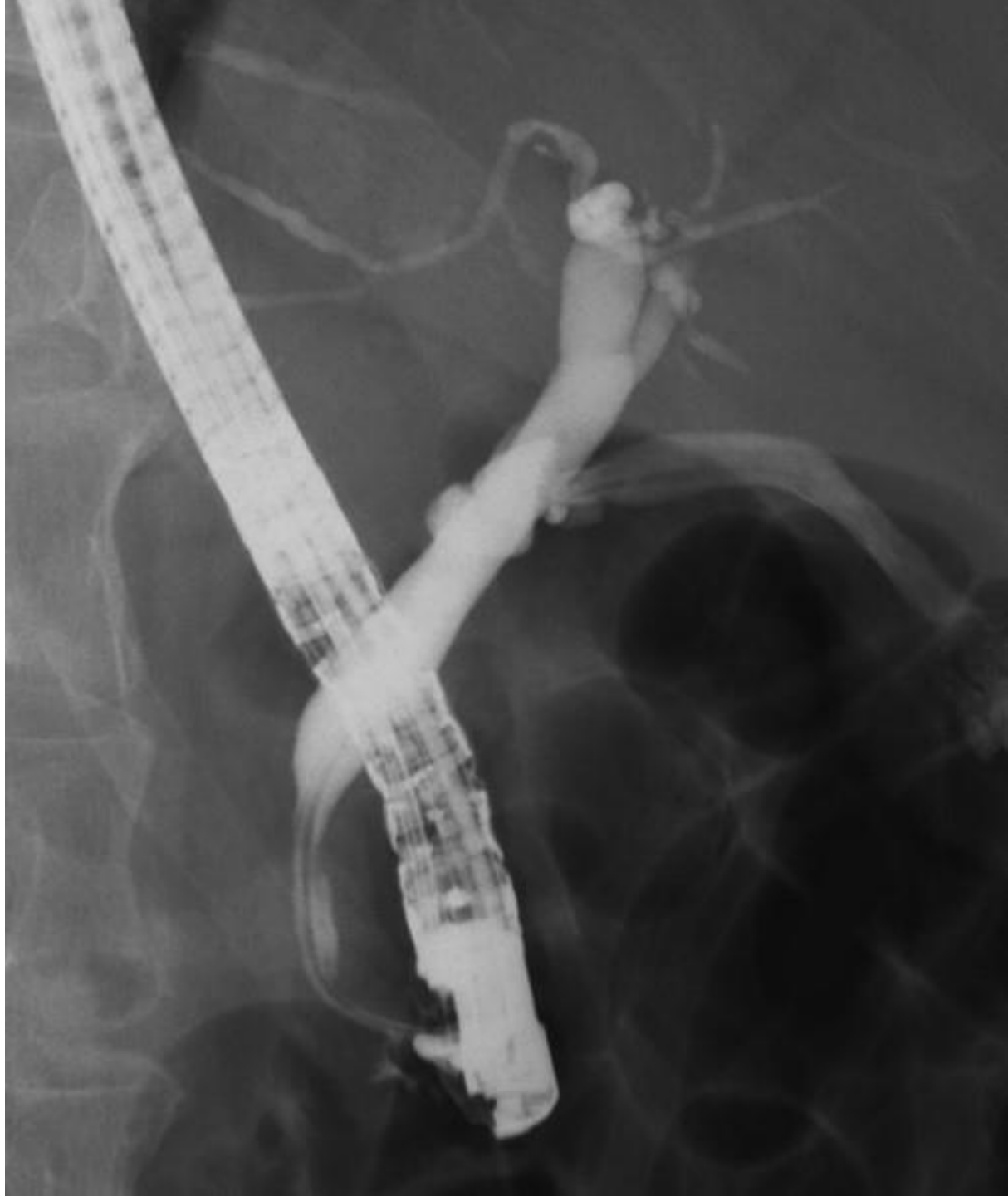

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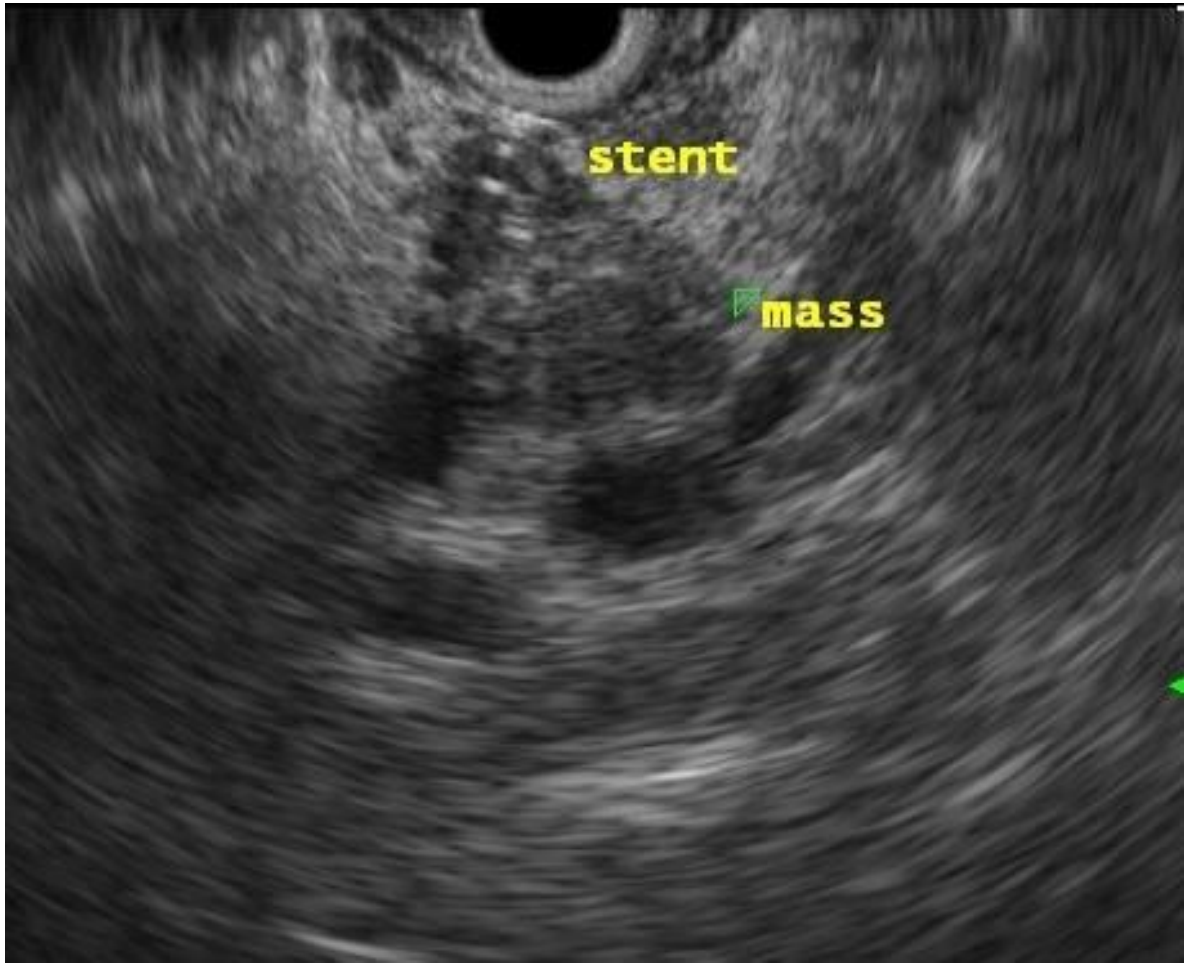
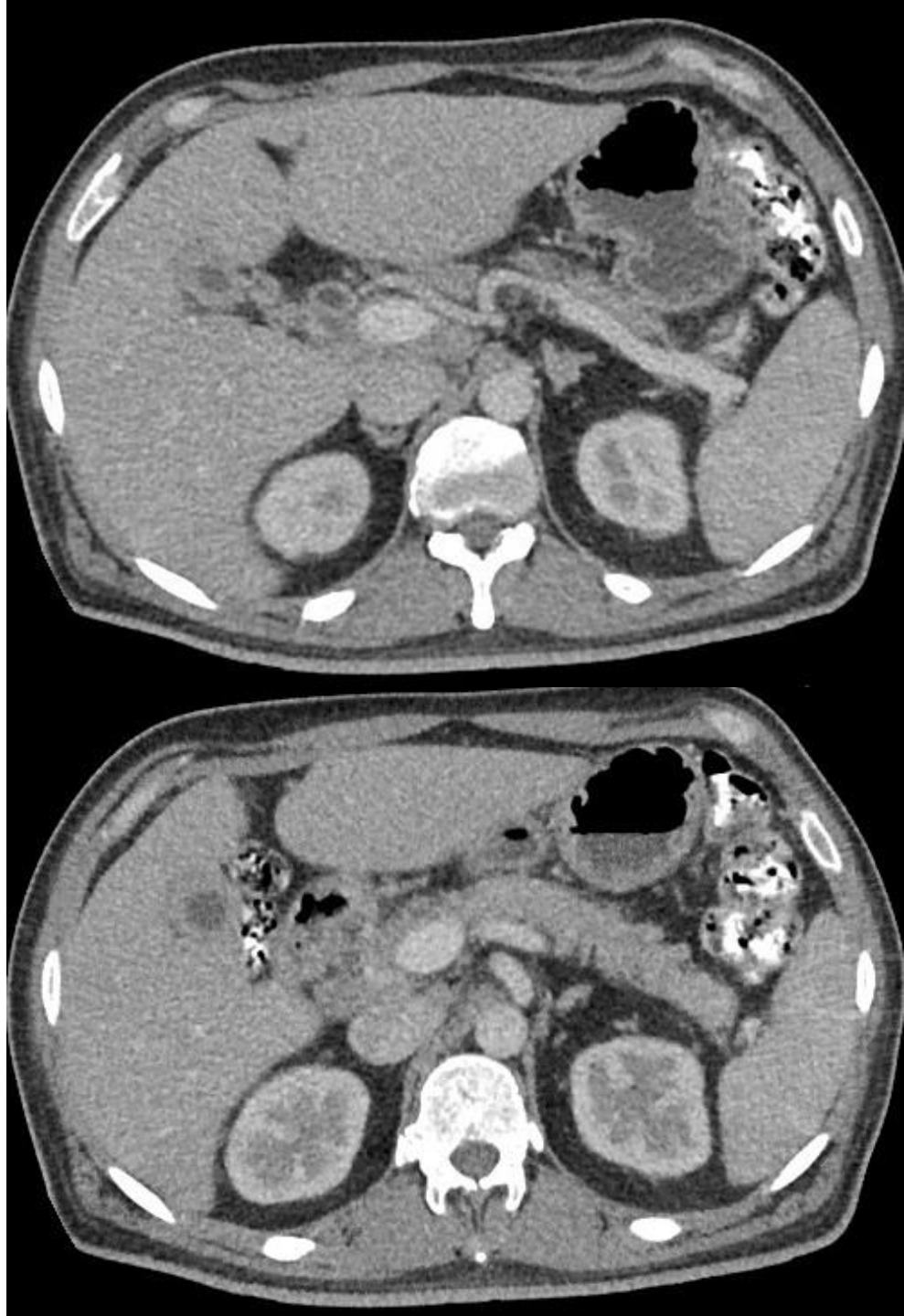


Case 5 – Mr YH

- 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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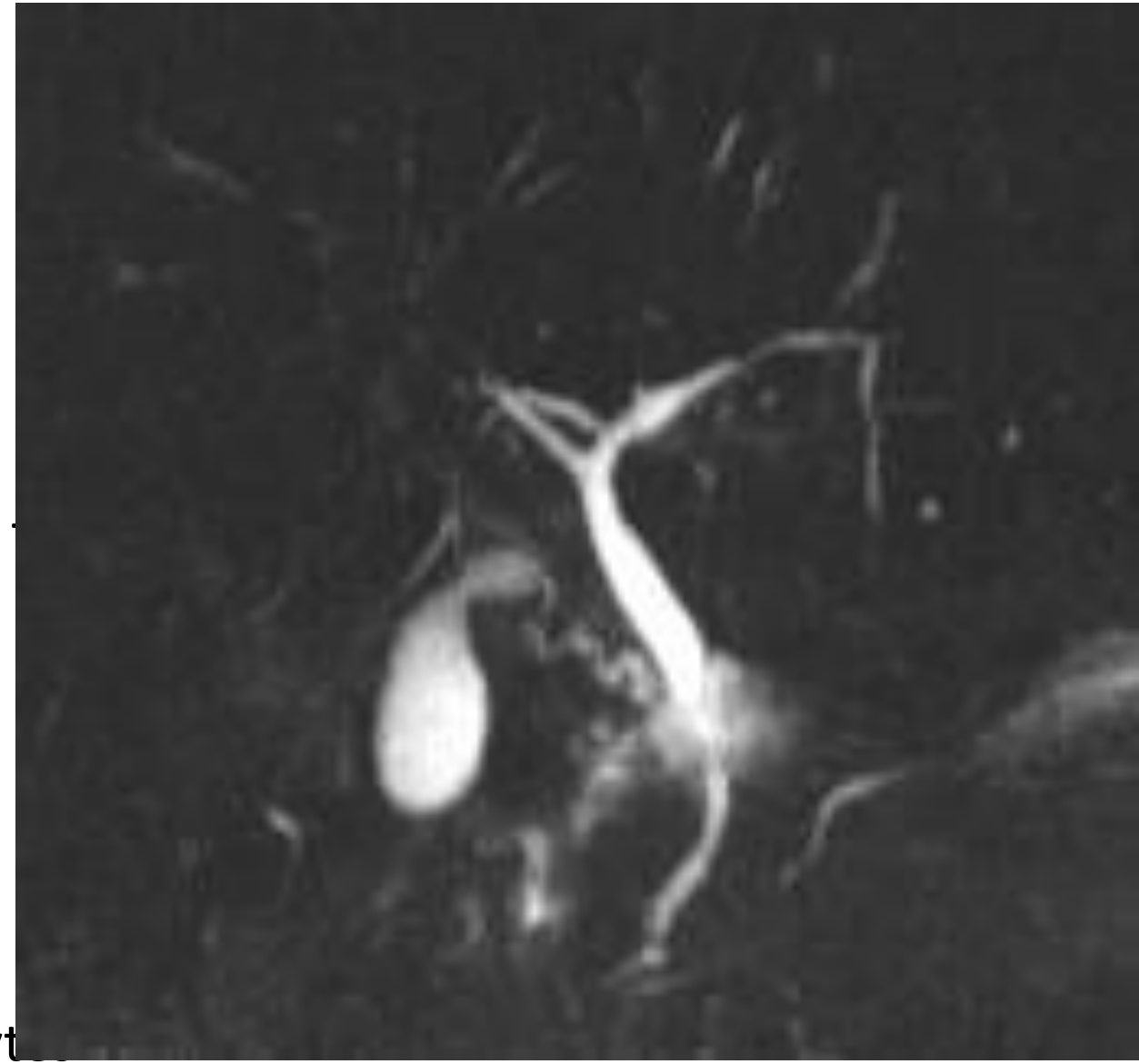

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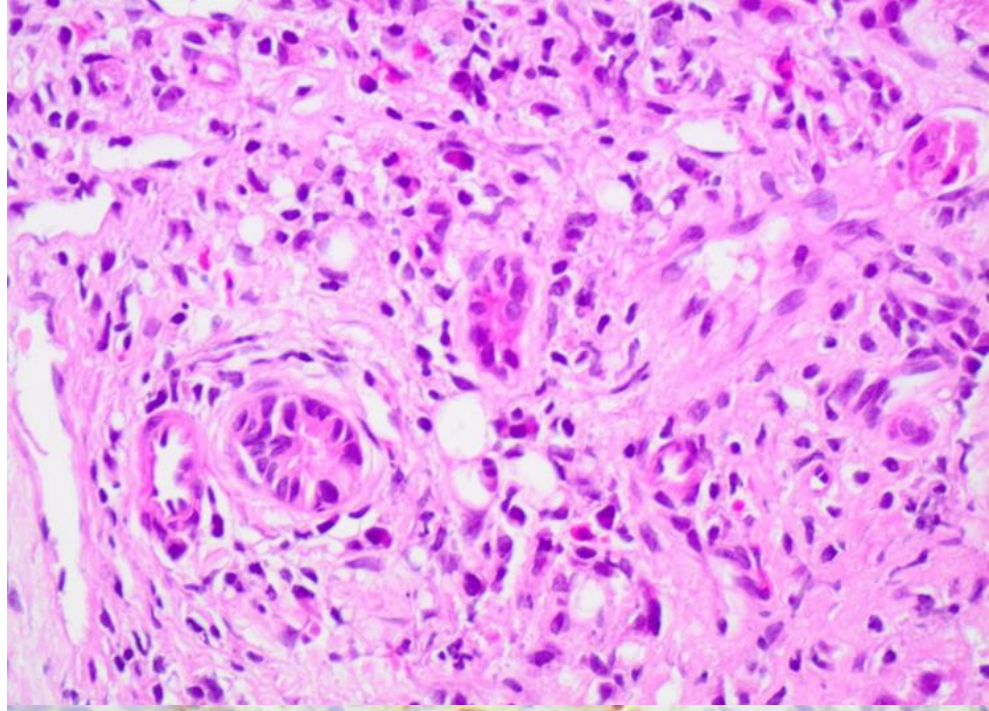

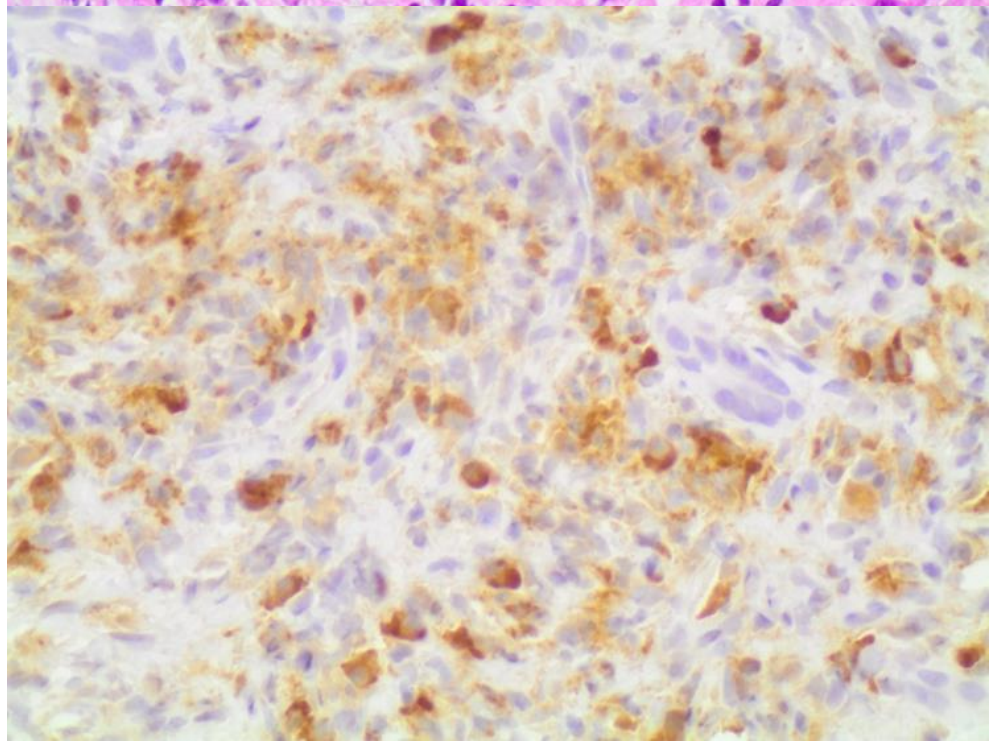

	Bilirubin	ALP	GGT	ALT	AST	Ca 19-9	IgG4
Case 1	198	590	1886	127	157	200	33.5 (IgG 7-16) **2x**
Case 2	17	313	763	180	116	247	6 (0.084-0.888) **7x**
Case 3	74	211	86	34	41	N	0.71
Case 4	286	276	42	91	94	5.7	21.6 (0.084-0.888) **24x**
Case 5	42	405	292	77	64	1721	37.1 (0.02-2.01) **19x**

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