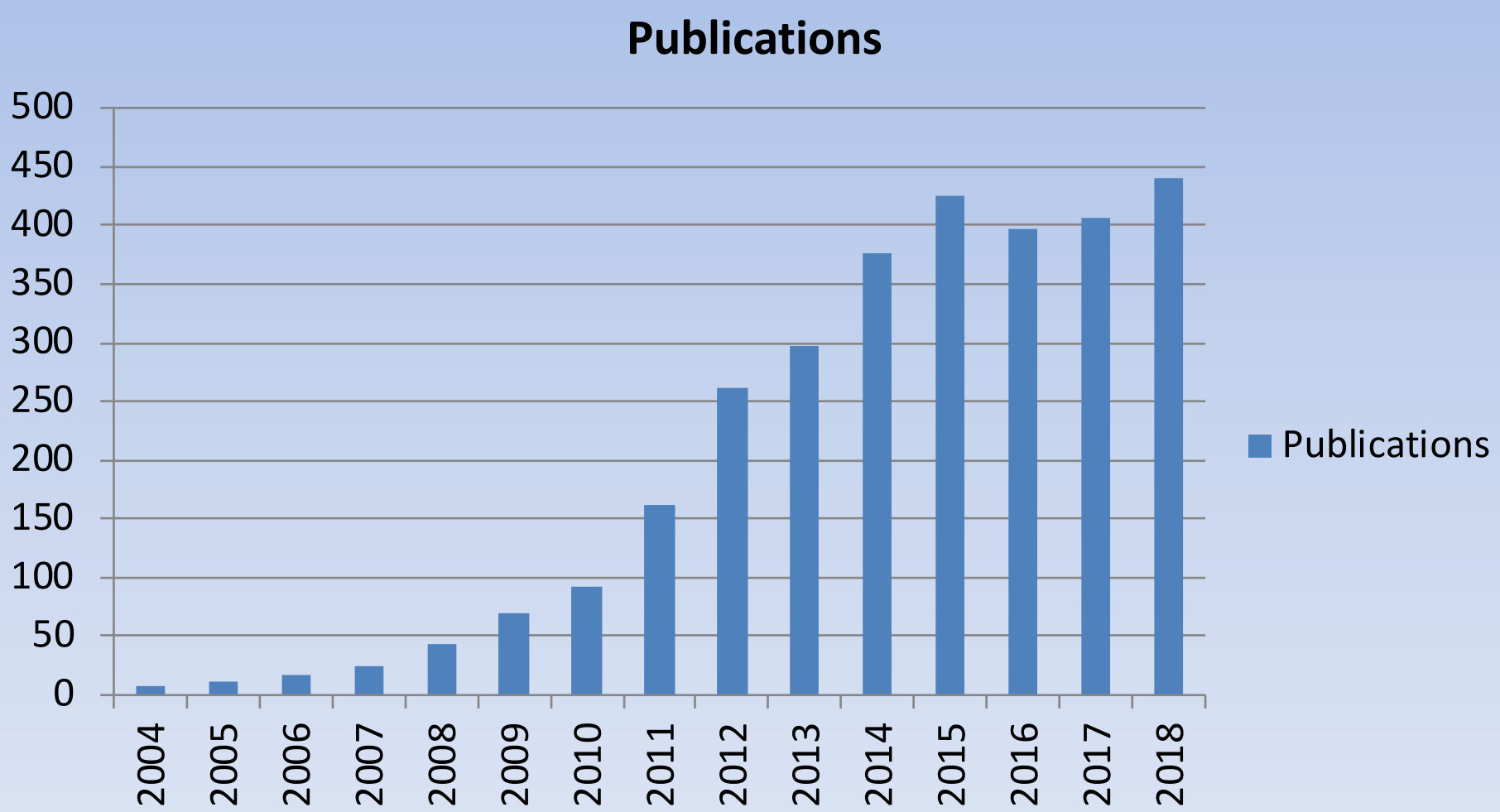
BSG Winter Pathology Update meeting
7.11.19

IgG4-related disease in the hepatobiliary-pancreatic tract – the role of biopsy

Dr Adrian C. Bateman

Southampton

IgG4-related disease (RD)



Plan

- General principles of IgG4-RD
- Diagnostic criteria
- Autoimmune pancreatitis
- Hepatobiliary involvement
- How does histopathology contribute?

General principles

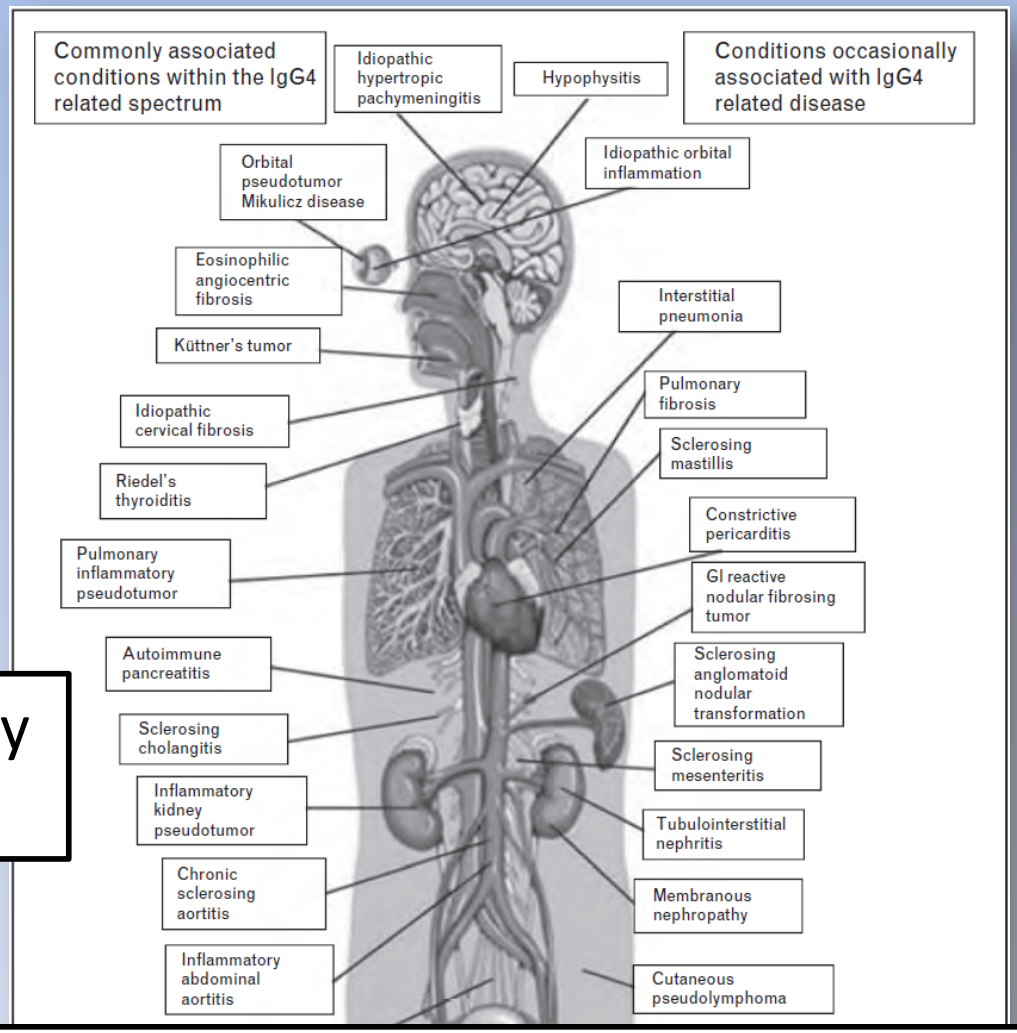
IgG4-RD

- Multisystem involvement
- Patterns of disease distribution may exist
- Tumour-forming or diffuse
- Diagnosis usually requires MDT involvement
- *Usually responsive to immunosuppression*
- Aetiology currently uncertain
- A third of patients have atopy

Spectrum of presentation

Head & neck cluster

Pancreaticobiliary cluster



Typically middle-aged and older men

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Diagnostic criteria

Multidisciplinary

- Mayo criteria
- Comprehensive diagnostic criteria
  - Serum IgG4 concentration raised in 60-80% of cases but may also be raised in 5% of healthy people
  - Serum IgG4
  - Histopathological appearances
  - Response to treatment
- Boston criteria 2012

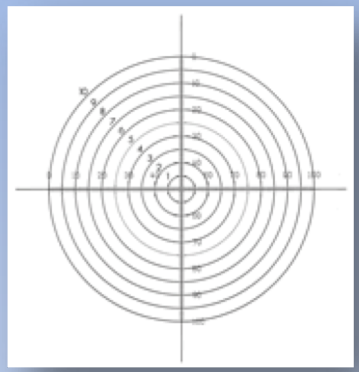
Boston consensus criteria

MODERN PATHOLOGY (2012), 1–12

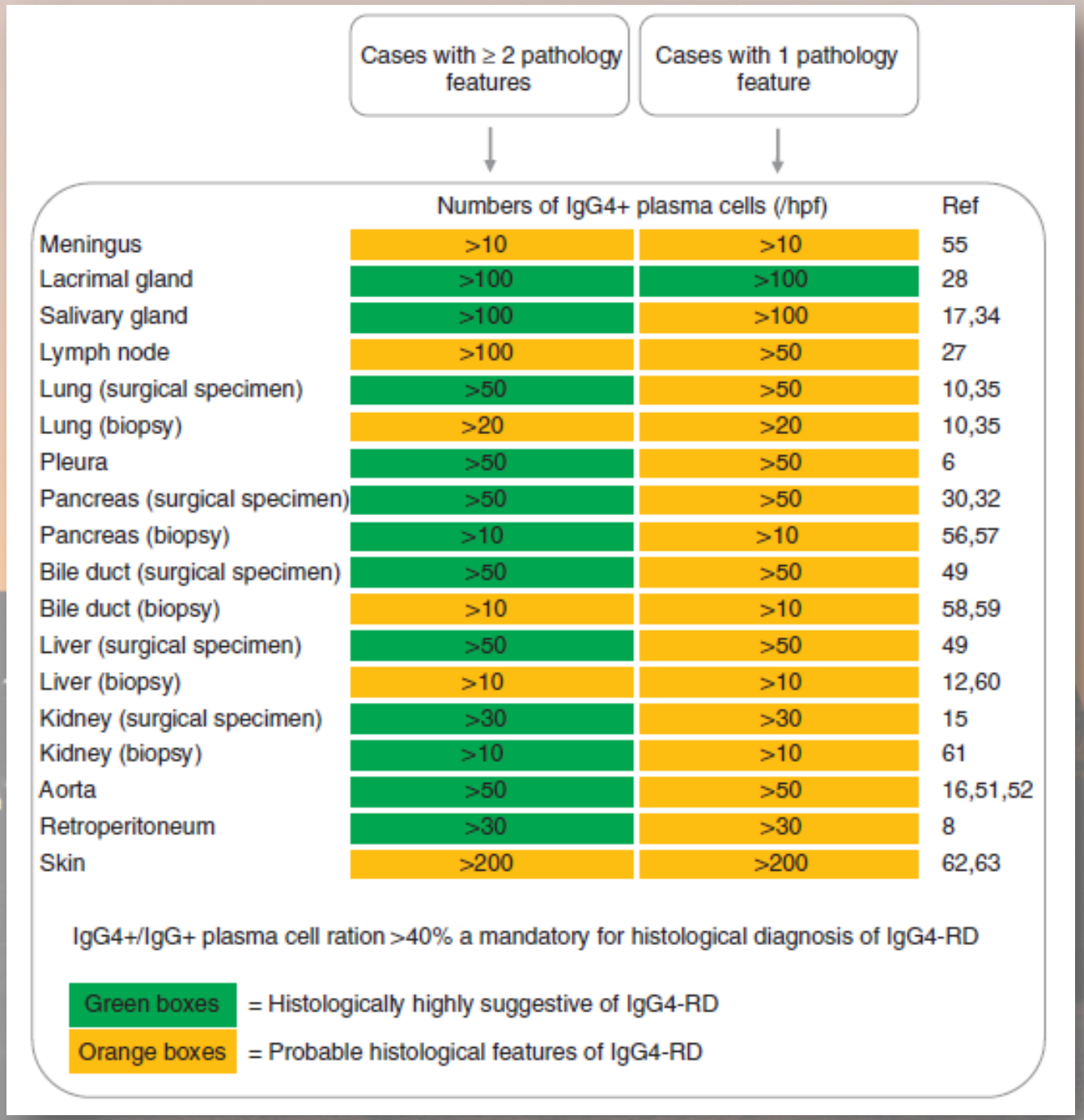
Consensus statement on the pathology of IgG4-related disease

Vikram Deshpande[1,31], Yoh Zen[2,31], John KC Chan[3], Eunhee E Yi[4], Yasuharu Sato[5], Tadashi Yoshino[5], Günter Klöppel[6], J Godfrey Heathcote[7], Arezou Khosroshahi[8], Judith A Ferry[1], Rob C Aalberse[9], Donald B Bloch[8], William R Brugge[10], Adrian C Bateman[11], Mollie N Carruthers[8], Suresh T Chari[12], Wah Cheuk[3], Lynn D Cornell[13], Carlos Fernandez-Del Castillo[14], David G Forcione[10], Daniel L Hamilos[15], Terumi Kamisawa[16], Satomi Kasashima[17], Shigeyuki Kawa[18], Mitsuhiro Kawano[19], Gregory Y Lauwers[1], Yasufumi Masaki[20], Yasuni Nakanuma[21], Kenji Notohara[22], Kazuichi Okazaki[23], Ji Kon Ryu[24], Takako Saeki[25], Dushyant V Sahani[26], Thomas C Smyrk[13], James R Stone[1], Masayuki Takahira[27], George J Webster[28], Motohisa Yamamoto[29], Giuseppe Zamboni[30], Hisanori Umehara[20] and John H Stone[8]

Boston criteria



- Primarily morphological – triad
  - Lymphoplasmacytic inflammation
  - Storiform fibrosis
  - Obliterative venulitis
- Prominent IgG4+ plasma cells
  - Required numbers may vary between tissues
- IgG4+/IgG+ ratio >40%



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Boston criteria

- Histologically highly suggestive of IgG4-RD
- Probable IgG4-RD
- Insufficient histological evidence for IgG4-RD

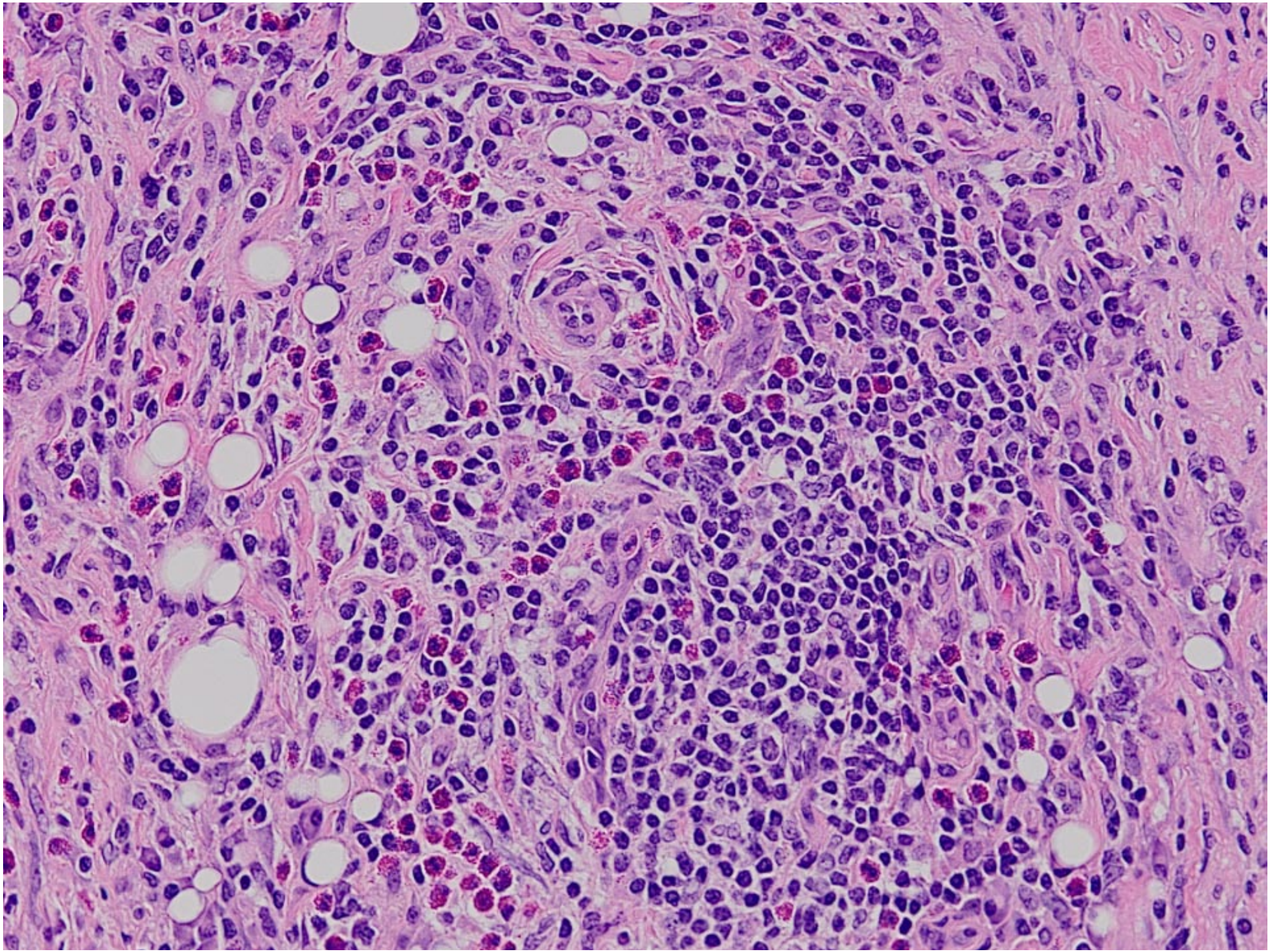
- Prominent IgG4+ plasma cells alone may support IgG4-RD in the appropriate context
- Some conditions can closely mimic IgG4-RD

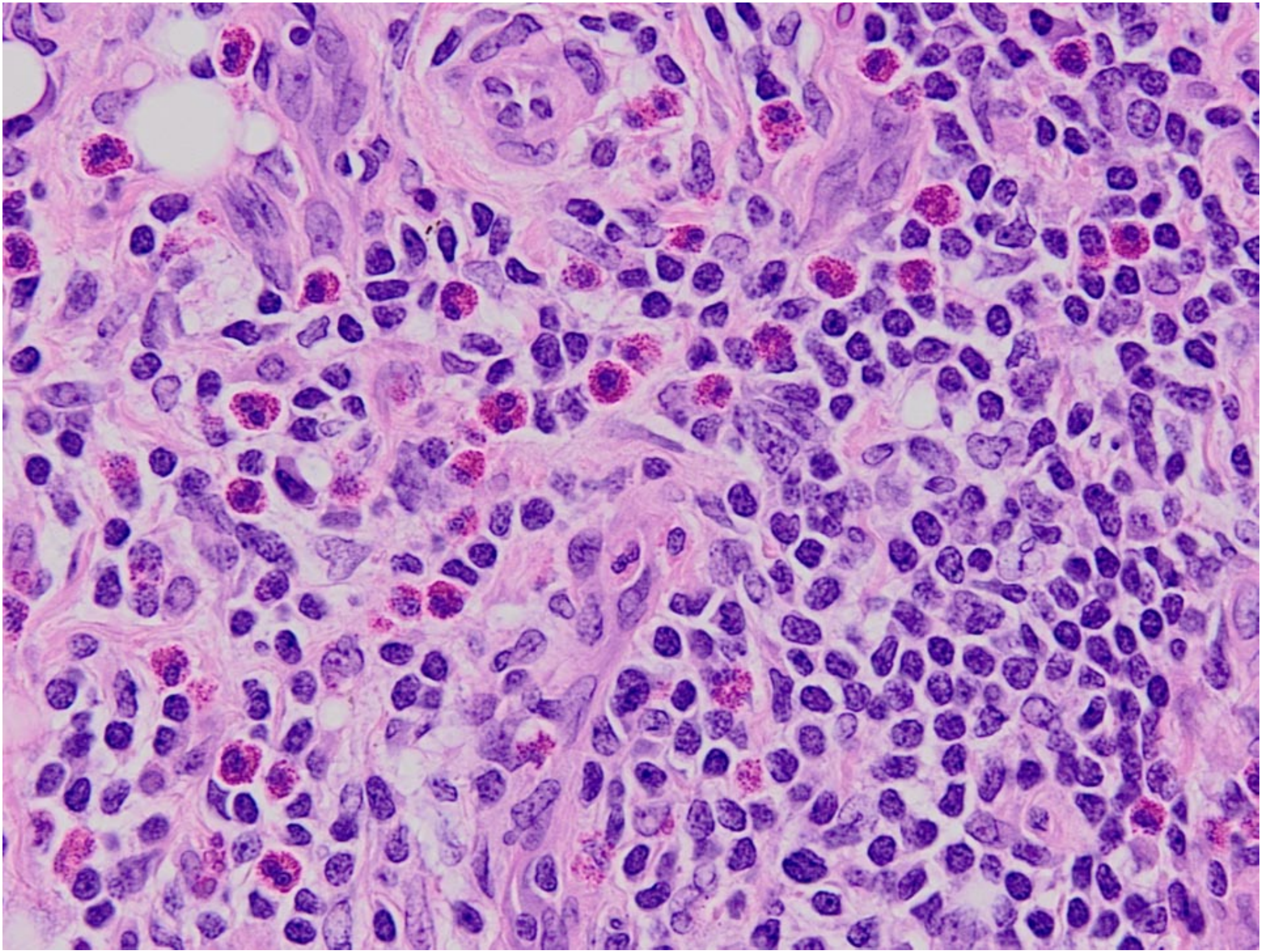
Boston criteria

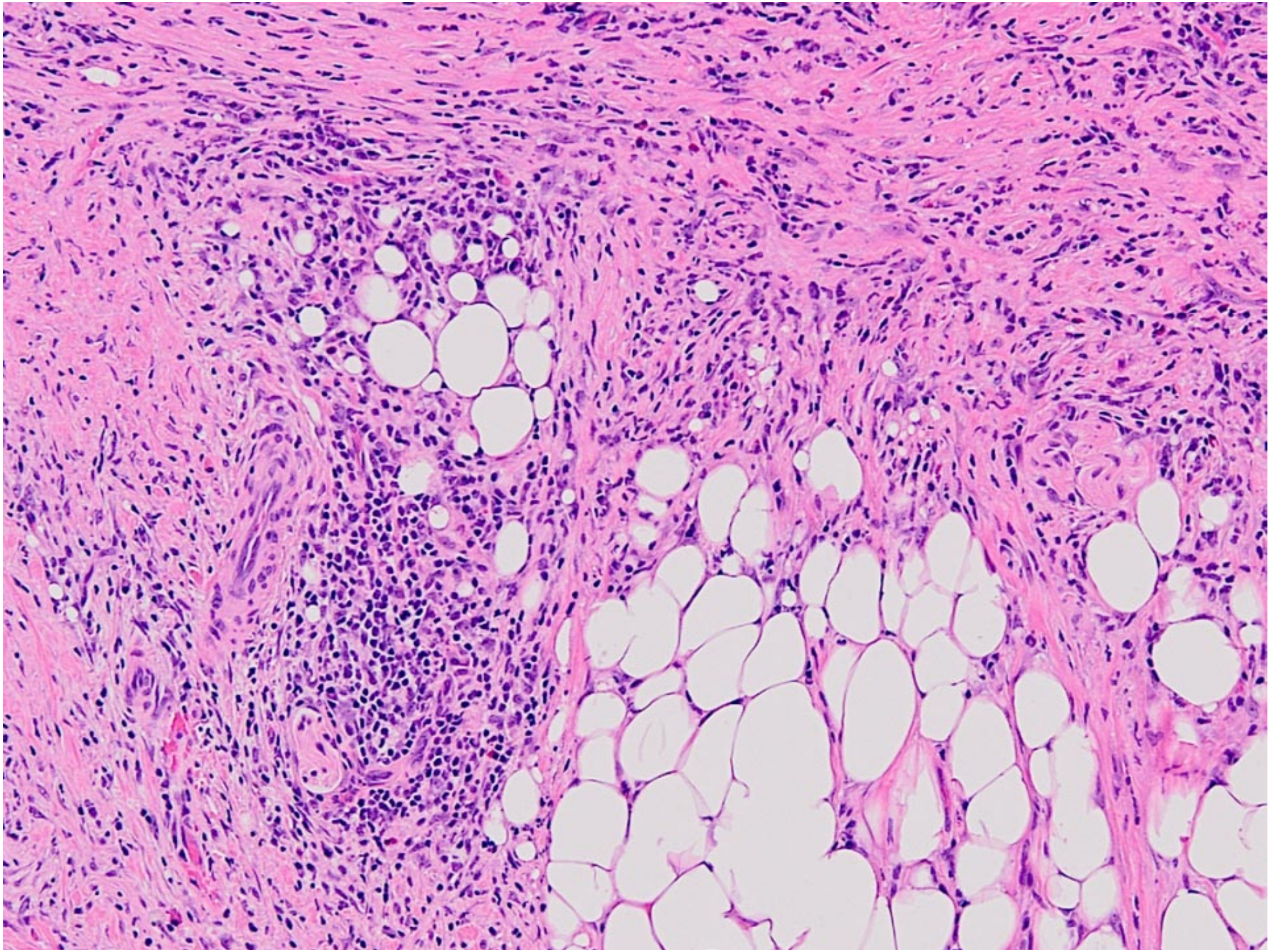
Table 1 Distribution of the IgG4 counts and the IgG4/IgG ratios in the study cohort (n=128 including the seven Küttner tumour cases)

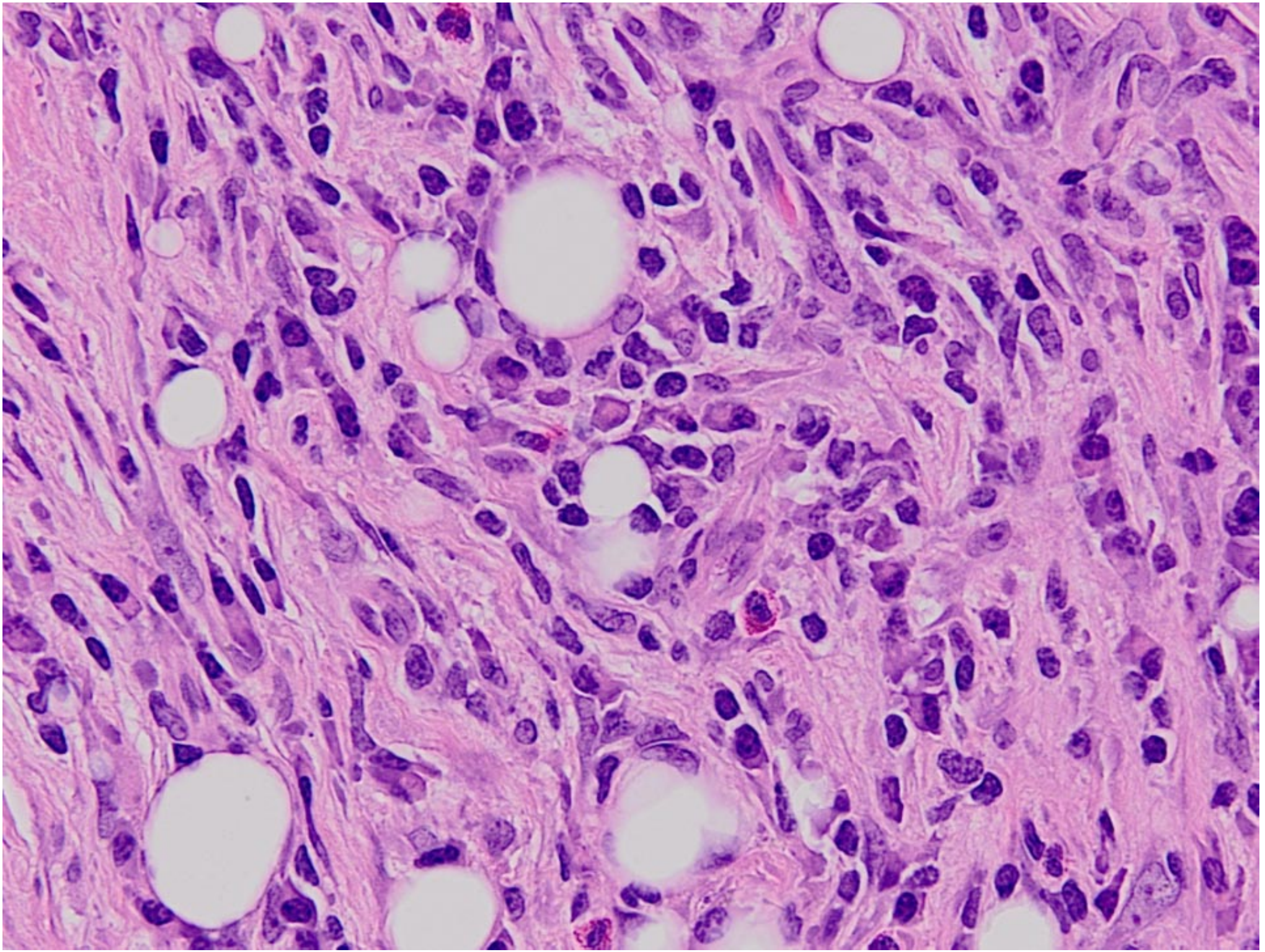
Localisation	Diagnosis	n	Mean IgG4/ hpf	Range IgG4/ hpf	Mean IgG/ hpf	IgG4/IgG mean ratio	Range IgG4/ IgG ratio
Salivary glands	Sclerosing sialadenitis/Küttner tumour	7	40	4–104	74	0.59	0.23–1
	Sialadenitis caused by sialolithiasis	11	3	0–26.8	54.0	0.02	0–0.15
Oral cavity	All lesions	27	79	0–235	235	0.32	0–0.84
	Epulis plasmocellularis	12	69	27–102	232	0.32	0.18–0.77
	Radicular cysts	11	93	23.3–234	278	0.32	0.1–0.84
	Oral lichen ruber	4	67	0–217	126	0.35	0–0.84
Lower gastrointestinal tract	All lesions	24	11	0–40	187	0.06	0–0.2
	Crohn's disease	9	8	1–22	160	0.046	0.008–0.08
	Ulcerative colitis	9	8	0–18	210	0.04	0–0.06
	Diverticulitis	6	19	0–40	194	0.11	0–0.2
Synovitis	All lesions	30	35	0–181	122	0.27	0–1
	Rheumatoid arthritis	15	55	0–181	153	0.4	0–1
	Non-specific synovitis	15	15	0–79	92	0.15	0–0.44
Carcinomas	All lesions	21	24	0–88	117	0.22	0–0.51
	Adenocarcinomas	10	6	0–88	73	0.21	0–0.48
	Squamous cell carcinomas	11	34	1–81	156	0.23	0–0.51
Skin	All lesions	8	26	1–120	85	0.21	0.04–0.67

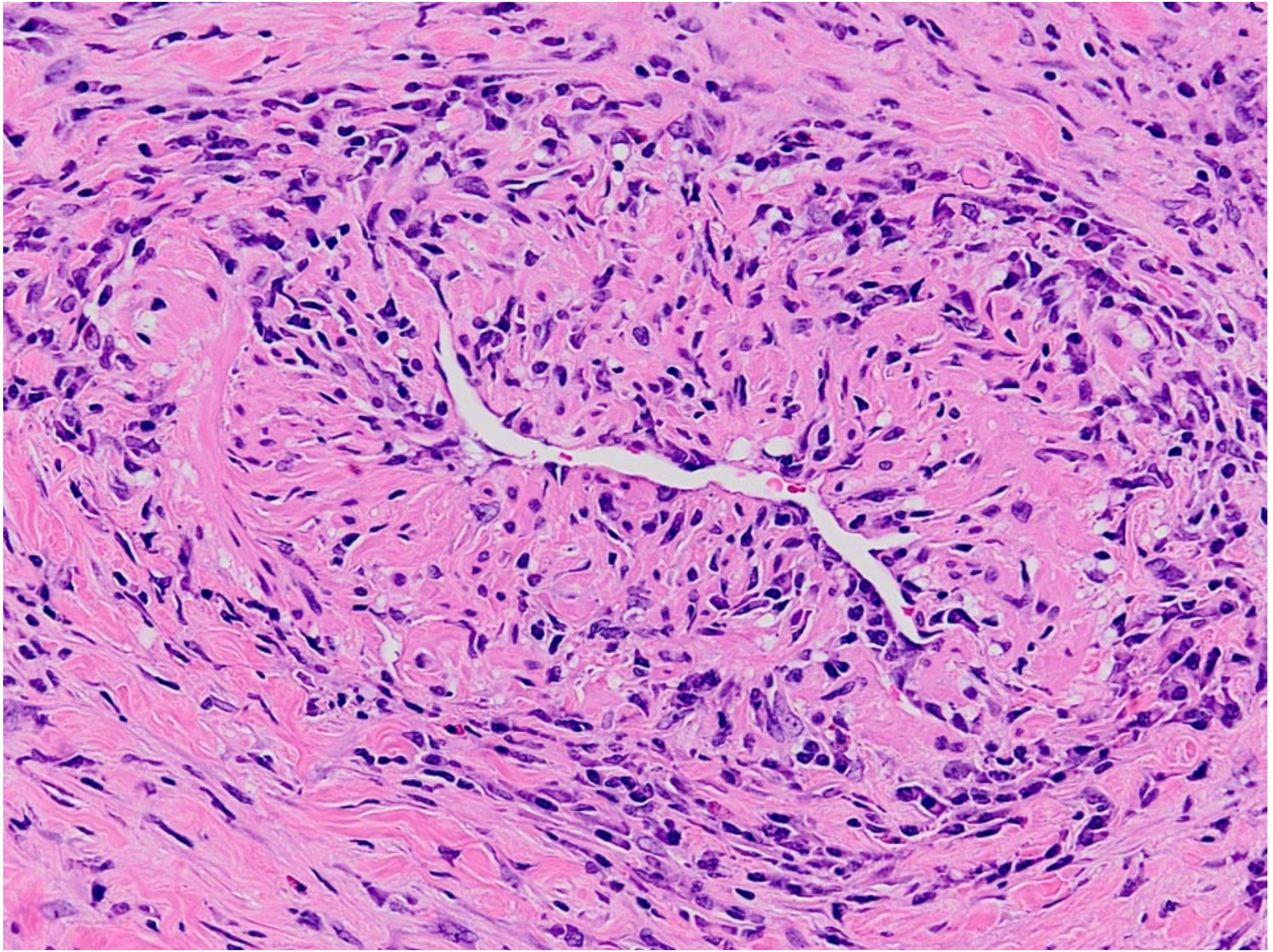
hpf, high-power field.

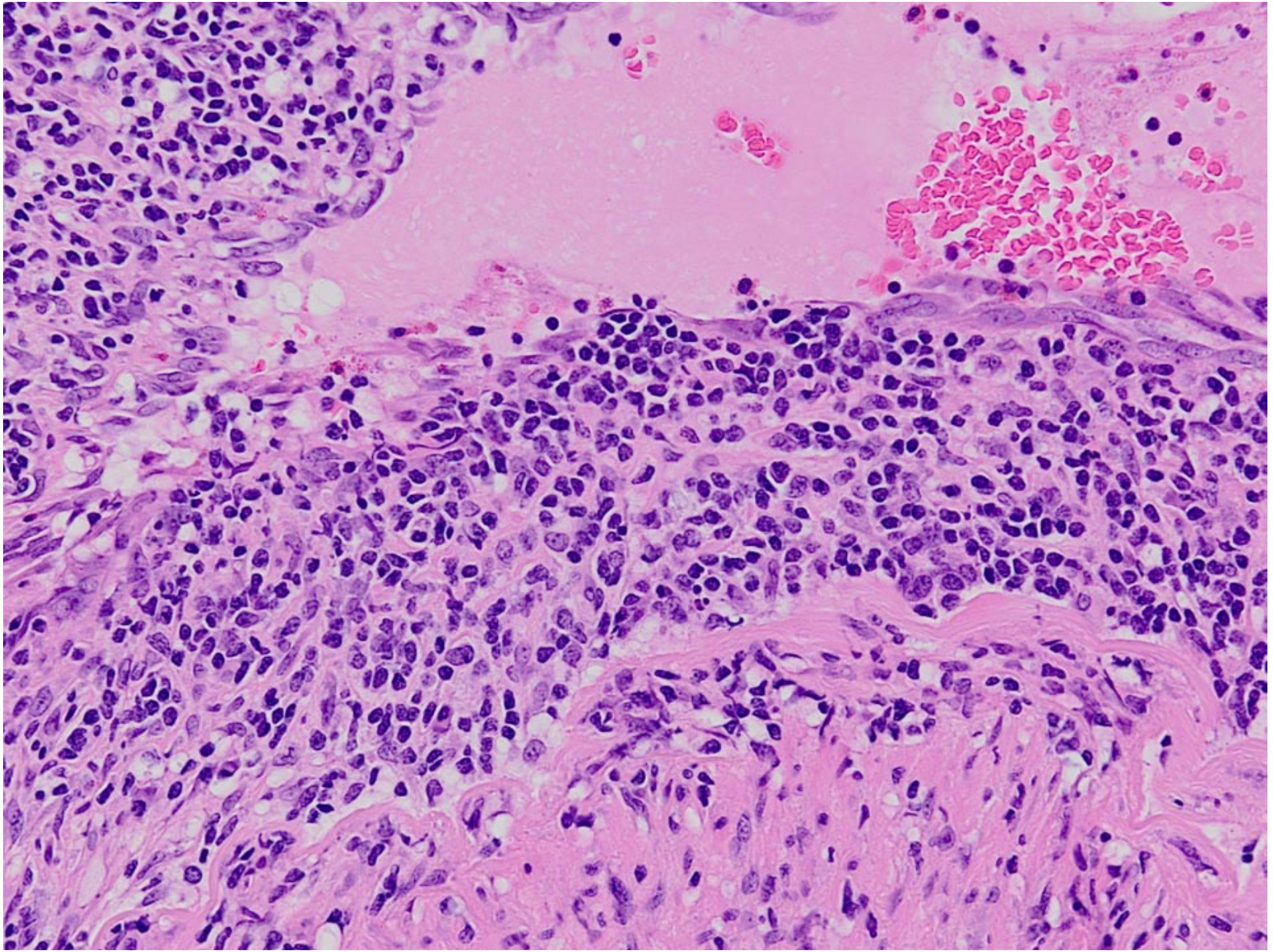












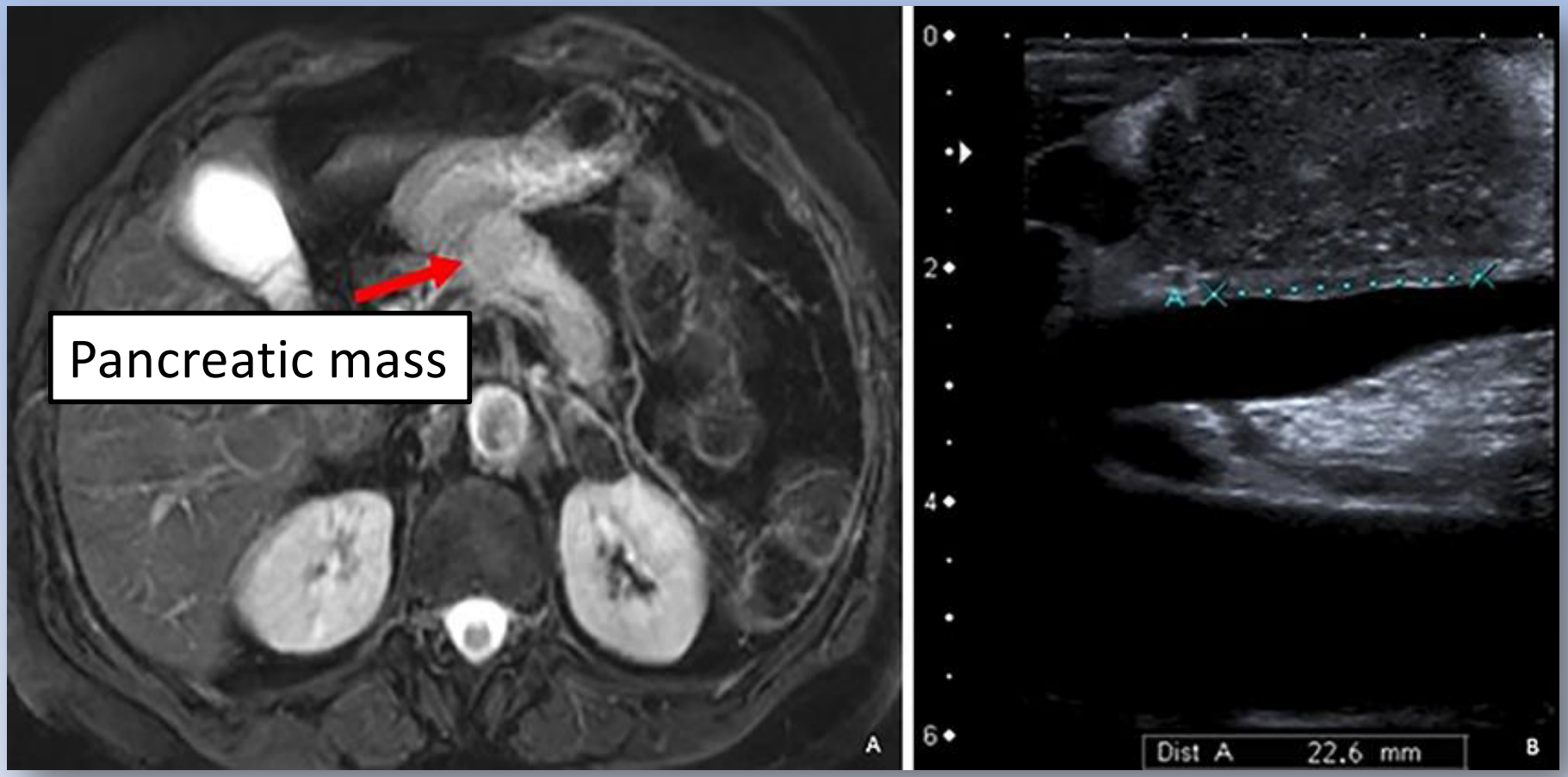
Autoimmune pancreatitis

Autoimmune pancreatitis (T1)

- First commonly described manifestation
- Simulation of neoplasia or diffuse chronic pancreatitis
- May not be diagnosed until after resection
- Commonly co-exists with hepatobiliary involvement

Autoimmune pancreatitis (T1)

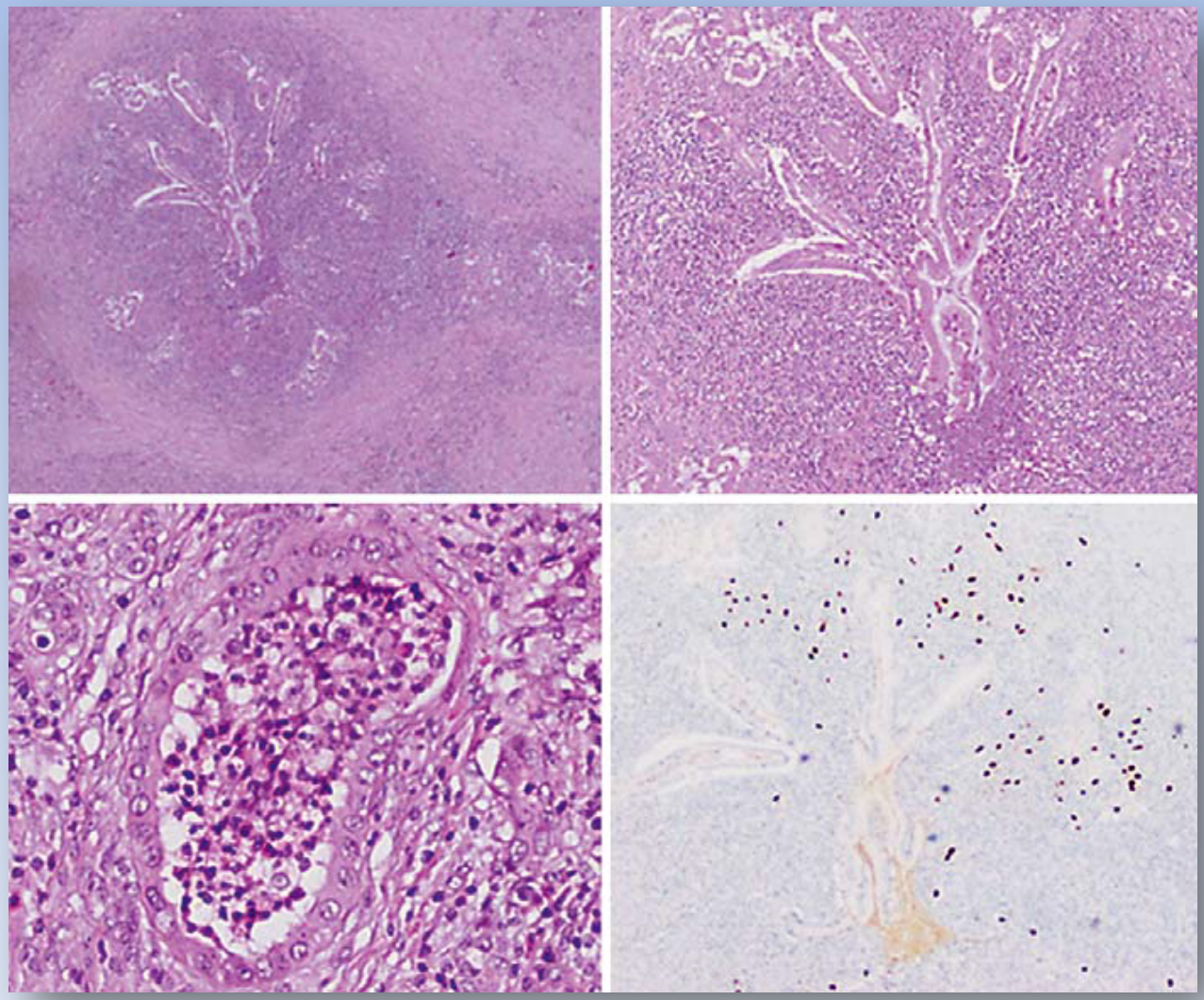
Autoimmune pancreatitis (T2)



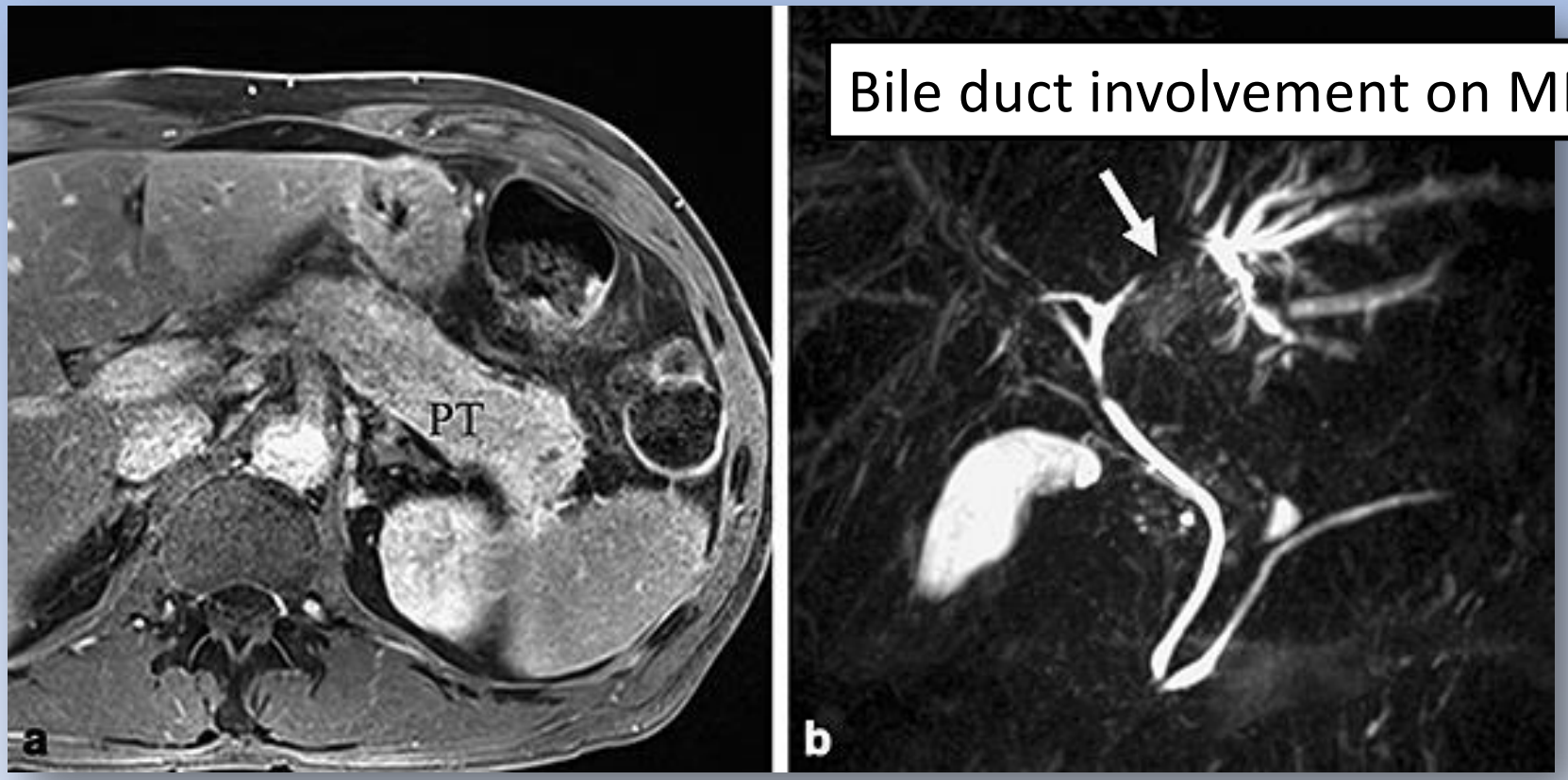
Autoimmune pancreatitis (T2)

- Younger age of presentation
- More common in Europe and North America
- *Not IgG4-related*
- Not a multi-system disease
- Associated with inflammatory bowel disease
- ‘Idiopathic-duct-centric pancreatitis’
- Granulocytic epithelial lesions

Autoimmune pancreatitis (T2)



Autoimmune pancreatitis (T2)



Bile duct involvement on MRCP

Is this really Type 2 AIP?

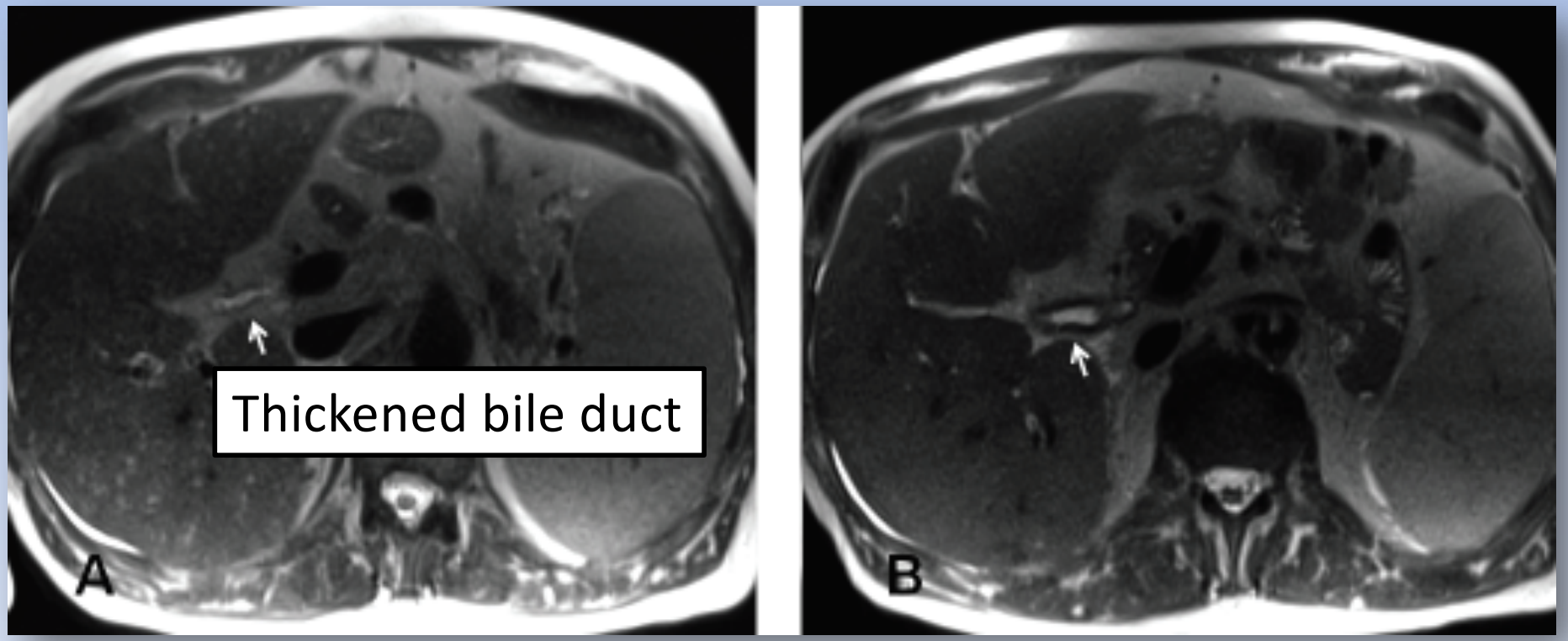
Hepatobiliary involvement

Hepatobiliary involvement

- IgG4-associated cholangitis
- IgG4-associated autoimmune hepatitis
- Pseudotumour formation

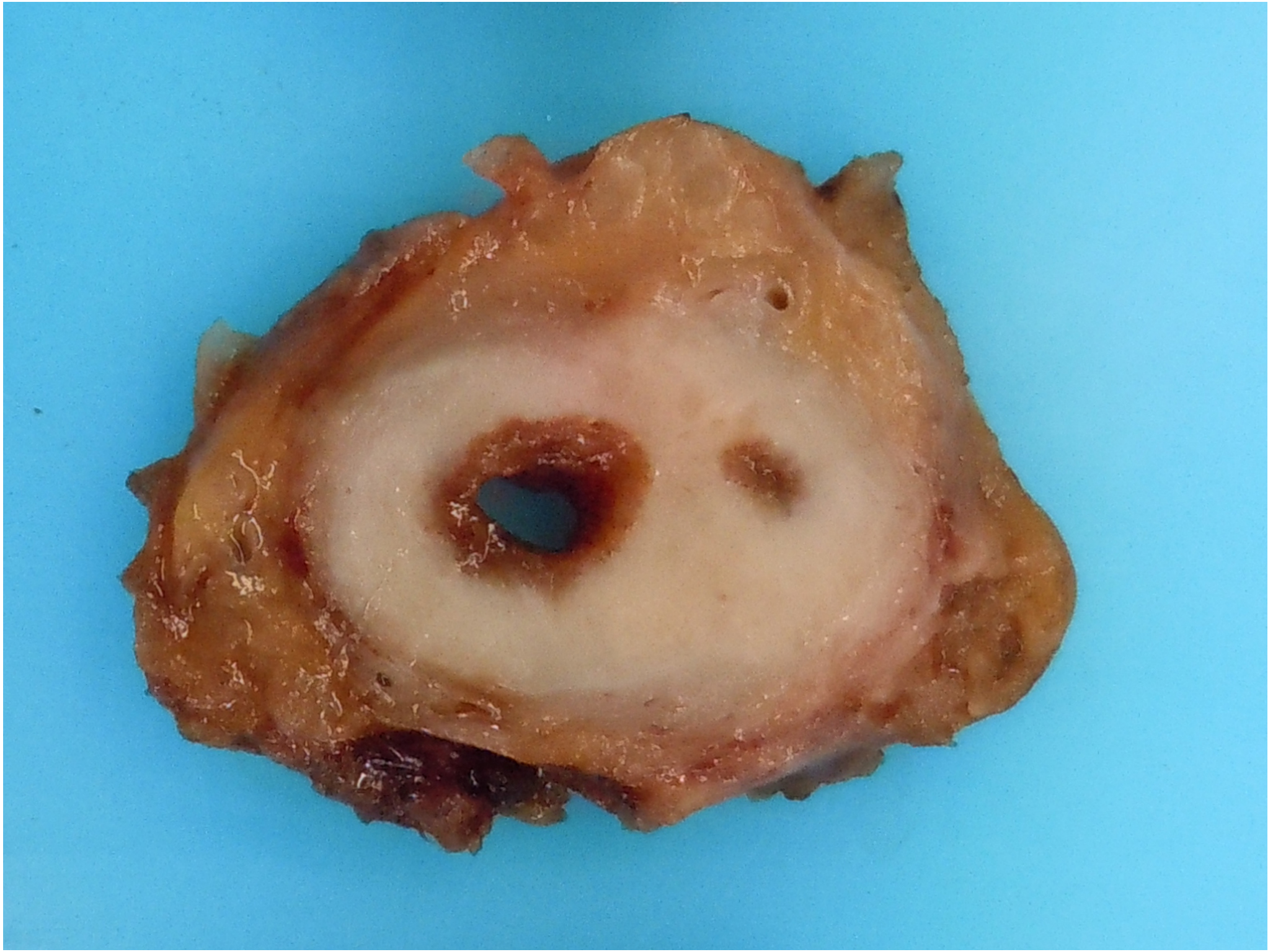
- Gallbladder involvement
- Ampullary/duodenal biopsies

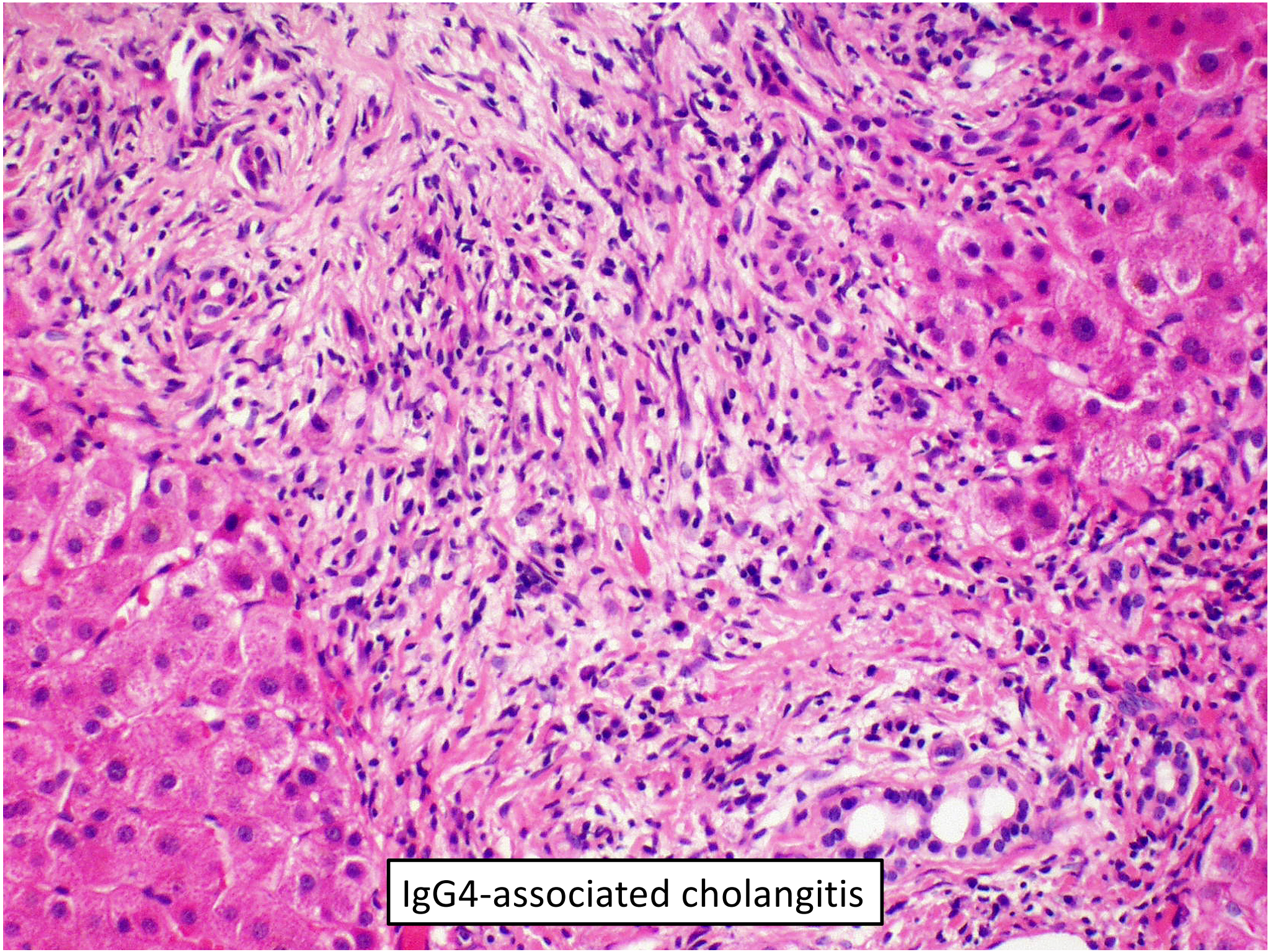
IgG4-associated cholangitis

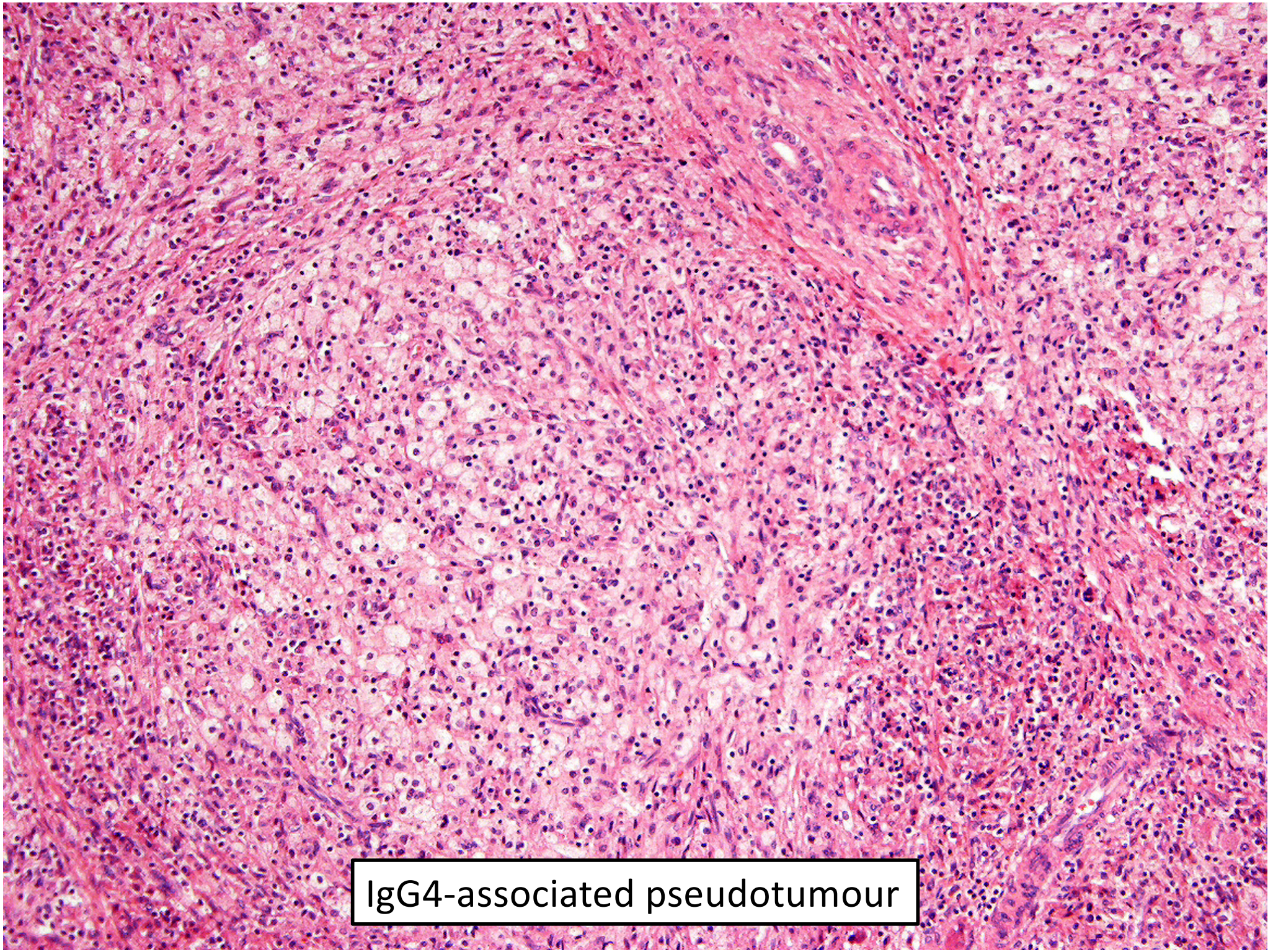


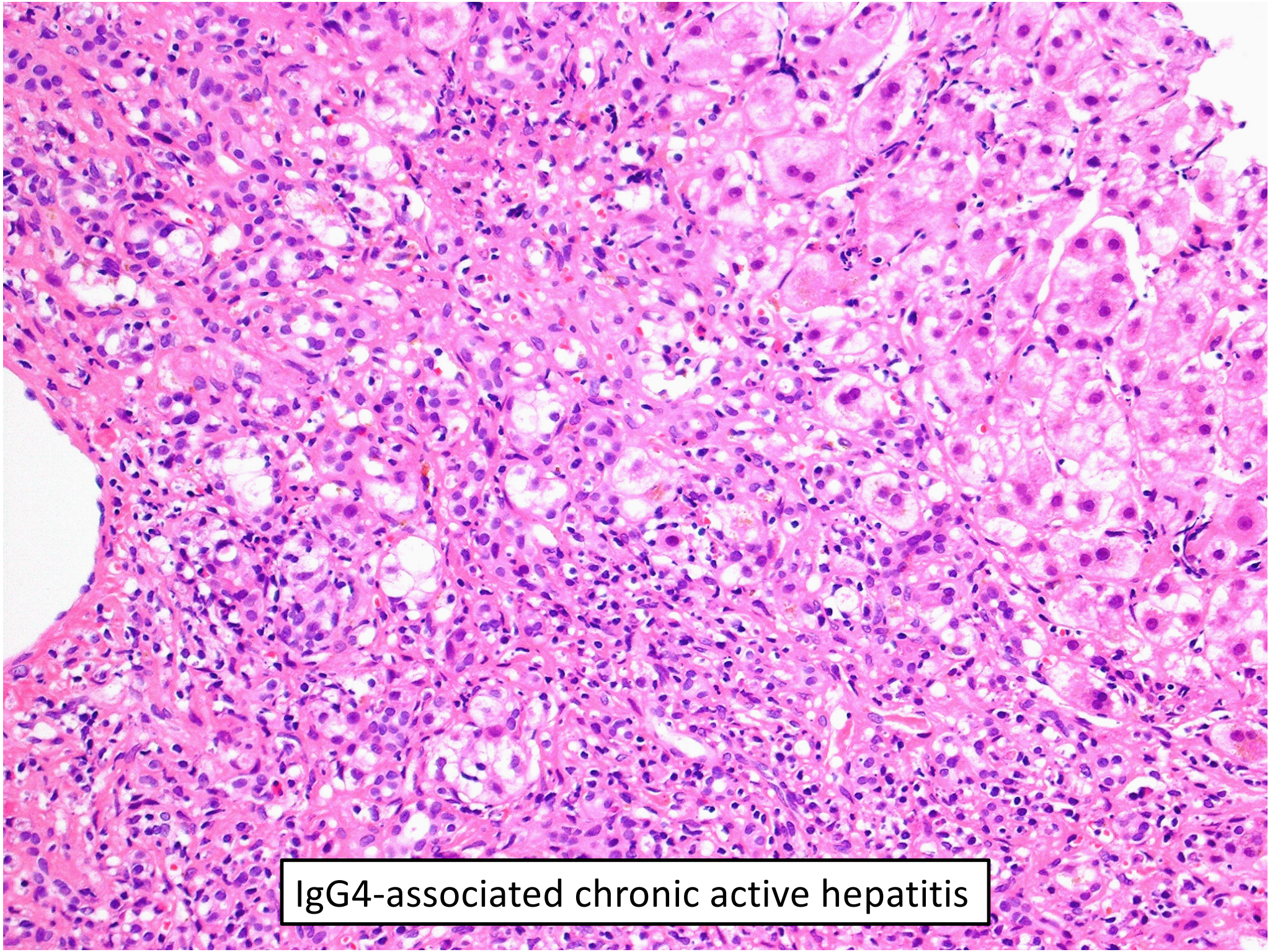
Baseline

Progression




IgG4-associated cholangitis


IgG4-associated pseudotumour


IgG4-associated chronic active hepatitis

Role of liver biopsy

Hindawi
Case Reports in Pathology
Volume 2018, Article ID 2309293, 7 pages
https://doi.org/10.1155/2018/2309293

Case Report

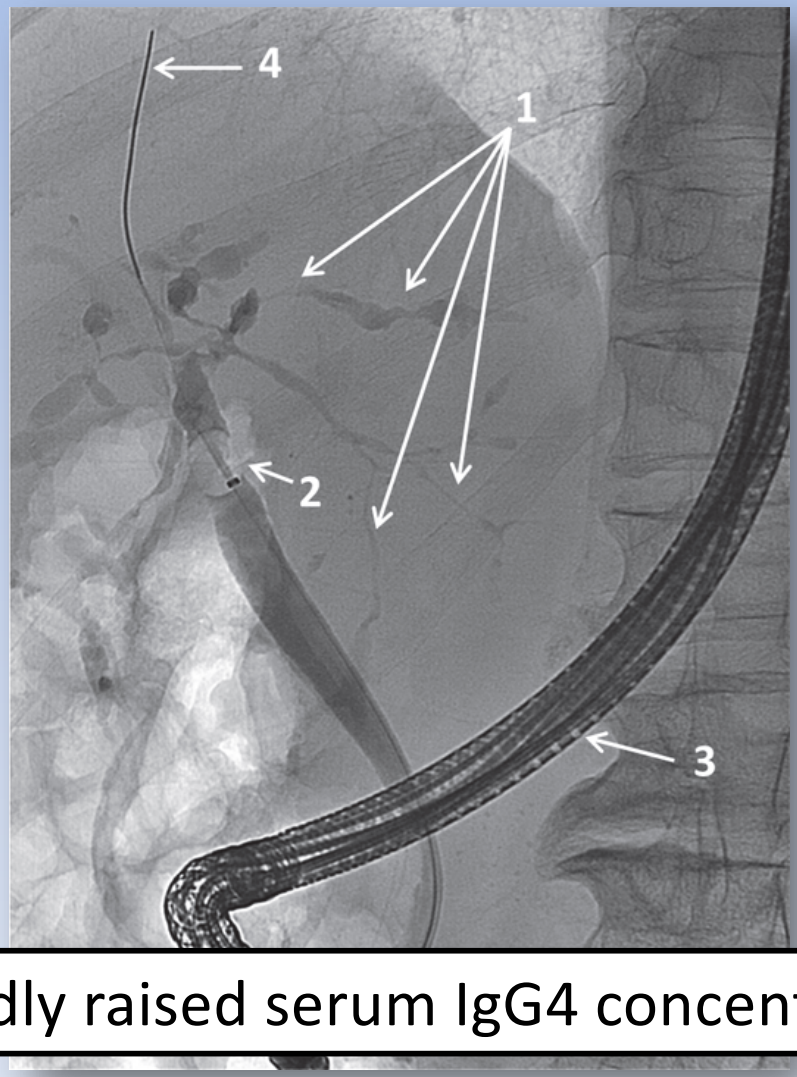
IgG4-Related Sclerosing Cholangitis Involving the Intrahepatic Bile Ducts Diagnosed with Liver Biopsy

Malene Theilmann Thinesen,[1] Ove B. Schaffalitzky de Muckadell,[2] and Sönke Detlefsen[1]

Role of liver biopsy

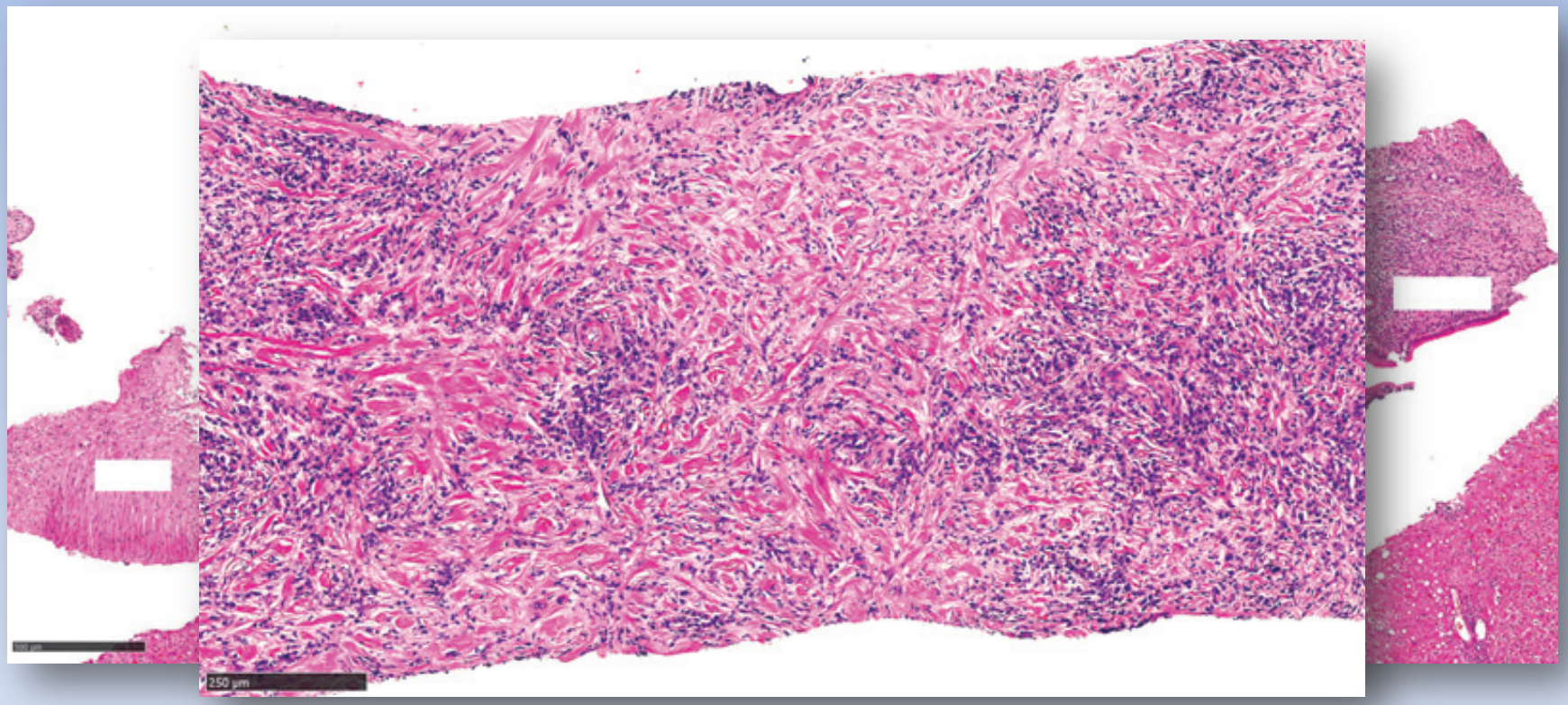
- 74 year old male
- Dysphagia & abdominal pain
- Jaundice
- Abdominal ultrasound – poorly defined pancreas and dilated CBD
- LFTs – predominantly obstructive picture

IgG4-associated cholangitis



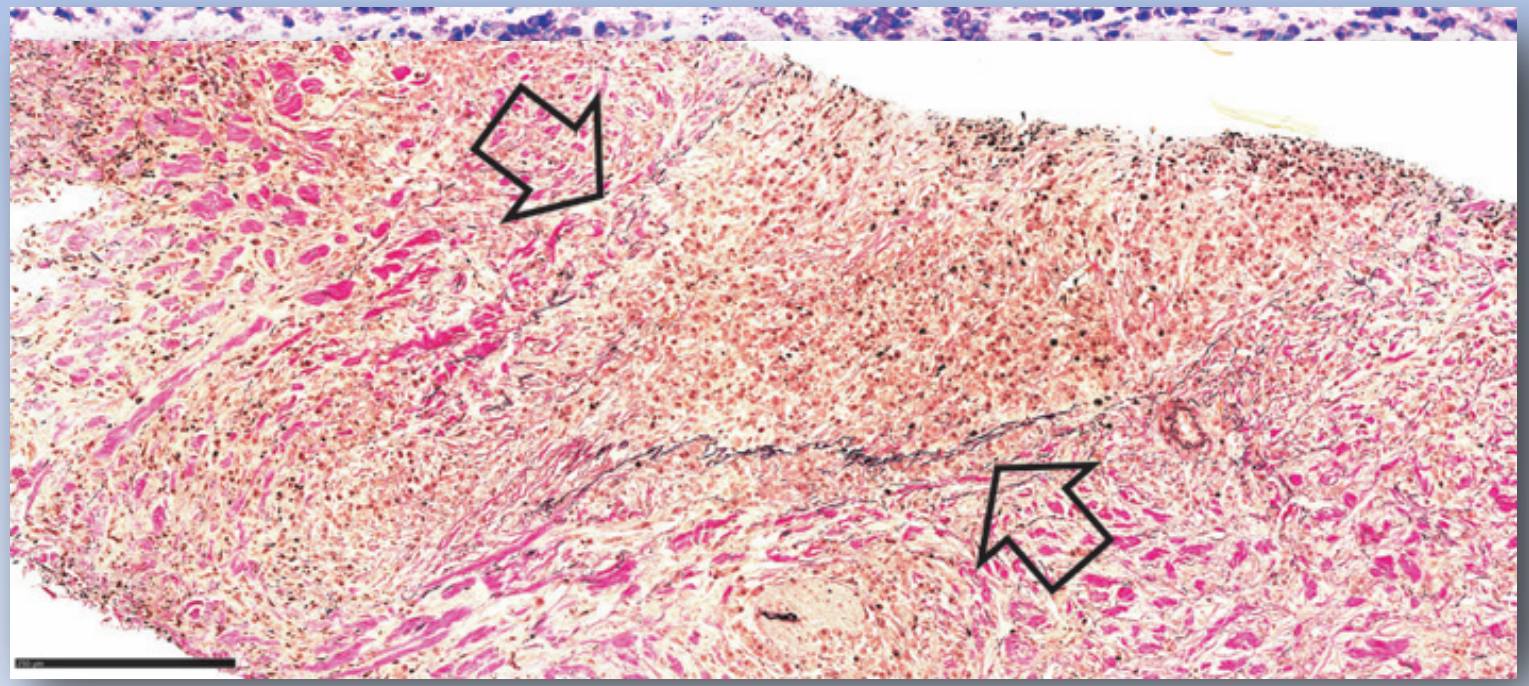
Markedly raised serum IgG4 concentration

IgG4-associated cholangitis



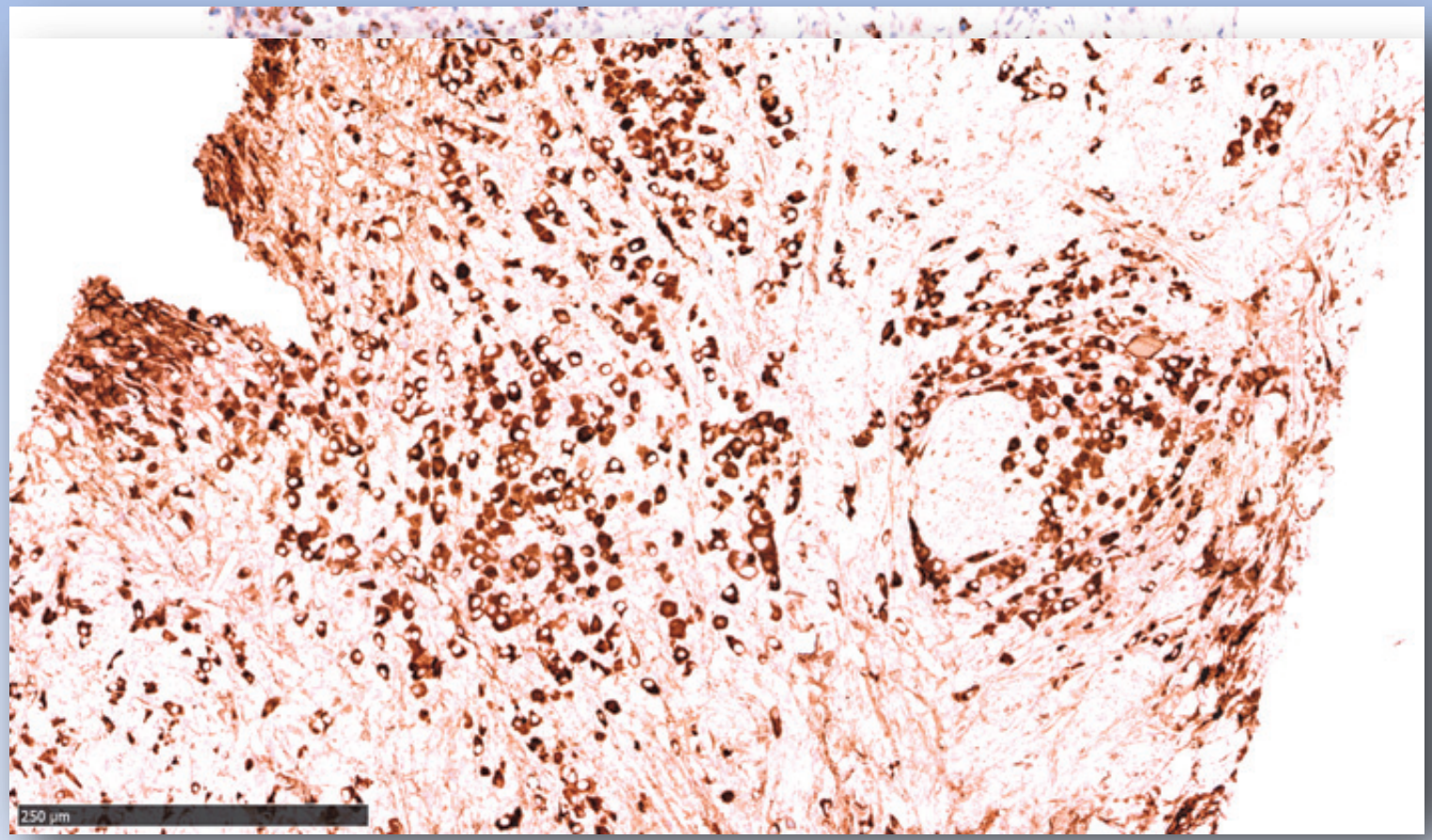
Portal inflammatory nodule

IgG4-associated cholangitis



Lymphocytic & obliterative venulitis

IgG4-associated cholangitis



IgG4 & IgG immunohistochemistry

Duodenal biopsy

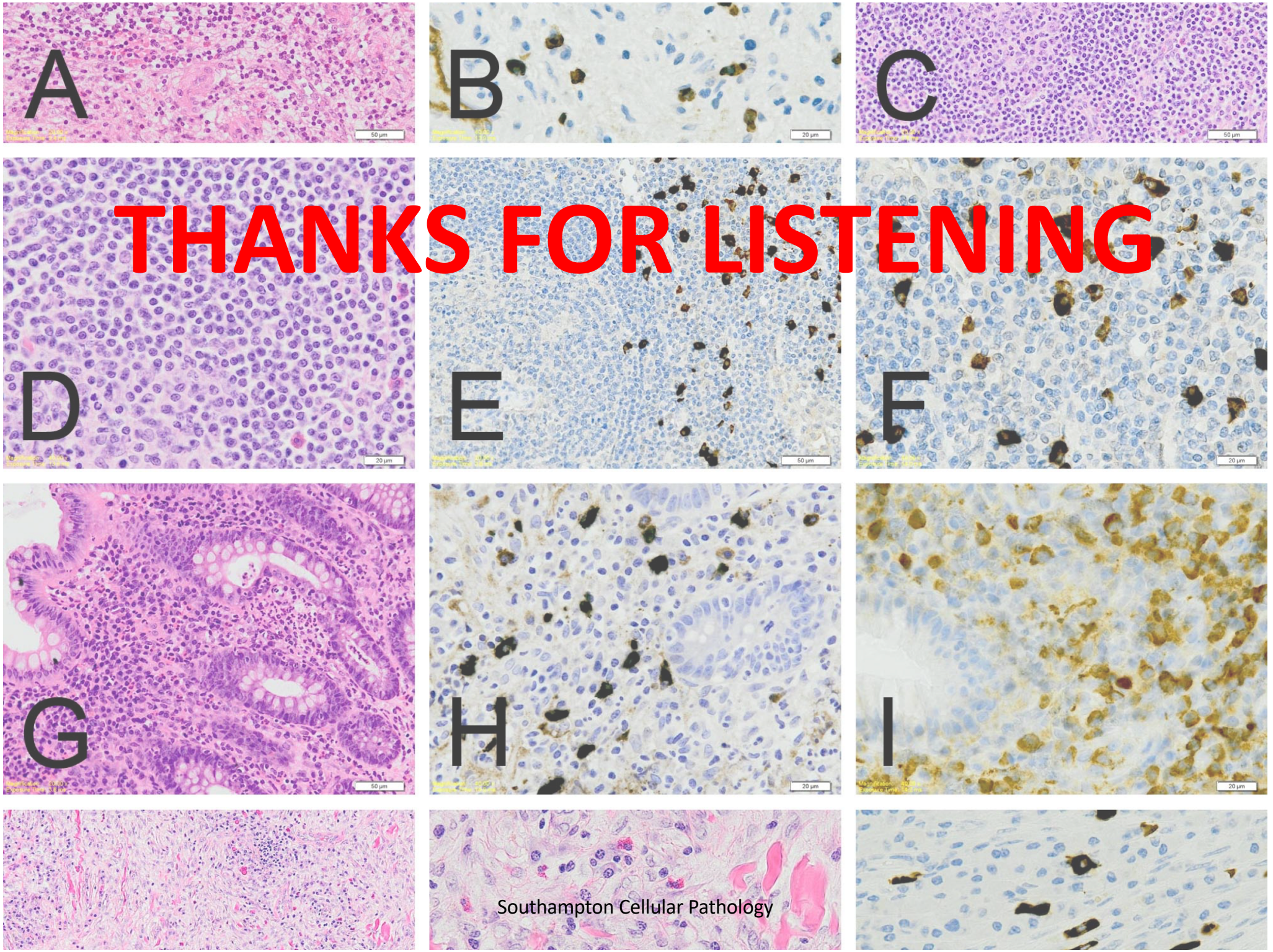
Table 1 Histological features of ampullary and bile duct biopsies

	IgG4-SC ($n = 29$)	PSC ($n = 6$)	PB carcinoma ($n = 27$)
Biopsy from Vater's ampulla			
Number of biopsies (mean and range)	1.4 (1–4)	1.2 (1–2)	1.1 (1–2)
Inflammation (mild/moderate/severe)	3/23/3	1/5/0	13/12/2
Plasma cells (> 20/HPF)	7 (24%)	4 (67%)	14 (52%)
Eosinophils (> 20/HPF)	1 (3%)	0	0
IgG4-positive cells (mean and range/HPF)	27 (0–162)*	3 (0–5)	2 (0–20)
Biopsy from the bile duct			
Number of biopsies (mean and range)	2.4 (1–7)	2.7 (1–7)	2.4 (1–12)
Inflammation (mild/moderate/severe)	18/9/2	4/1/1	22/5/0
Plasma cells (> 20/HPF)	10 (34%)	2 (33%)	3 (11%)
Eosinophils (> 20/HPF)	5 (17%)**	0	0
IgG4-positive cells (mean and range/HPF)	21 (0–157)†	4 (0–12)	1 (0–4)

*$P < 0.01$ versus PSC and PB carcinoma; **$P < 0.05$ versus PB carcinoma; †$P < 0.05$ versus PSC and $P < 0.01$ versus PB carcinoma.
HPF, high power field; IgG4, immunoglobulin G4; IgG4-SC, IgG4-related sclerosing cholangitis; PB carcinoma, pancreatobiliary carcinoma; PSC, primary sclerosing cholangitis.

Summary

- IgG4-RD is still an evolving concept
- Multisystem involvement is common
- May be mass-forming or diffuse
- Hepatobiliary & pancreatic disease often co-exist
- IgG4-associated cholangitis may progress more rapidly than PSC but steroid-responsive
- Histopathology very important but only one component of a multidisciplinary approach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THANKS FOR LISTENING
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