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Rosai-Dorfman Disease of the Pancreas Shows Significant Histologic Overlap With IgG4-related Disease

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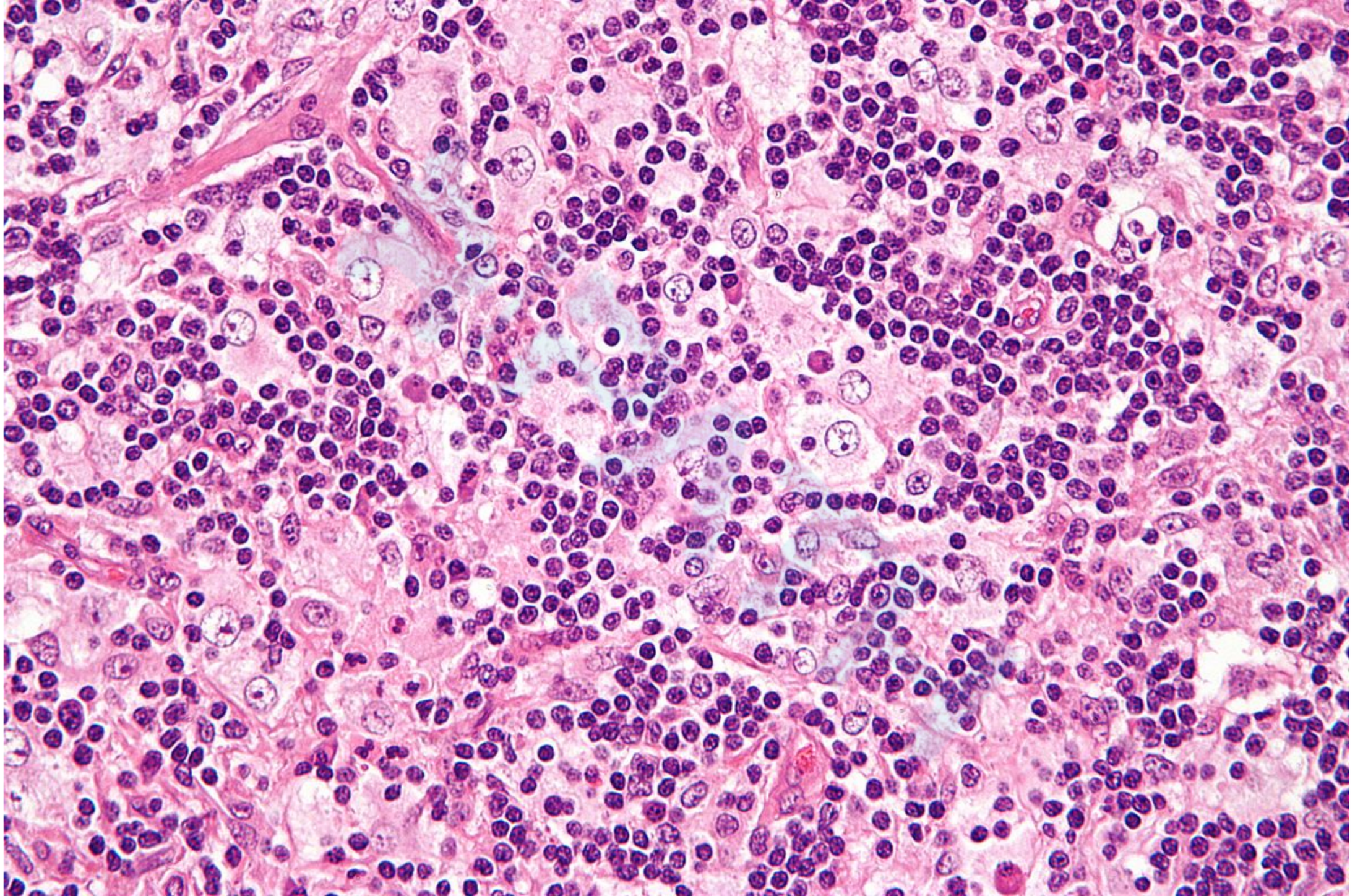
2019-12-23

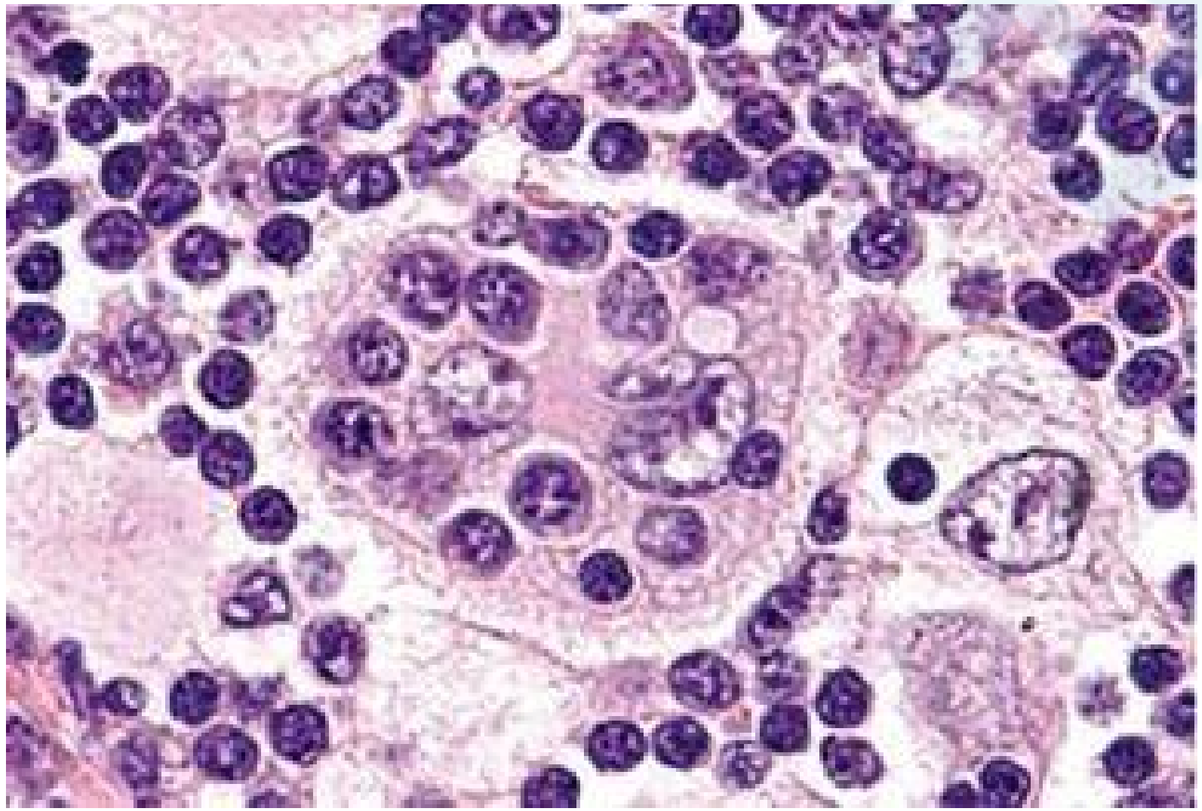
Rosai-Dorfman Disease (RDD)

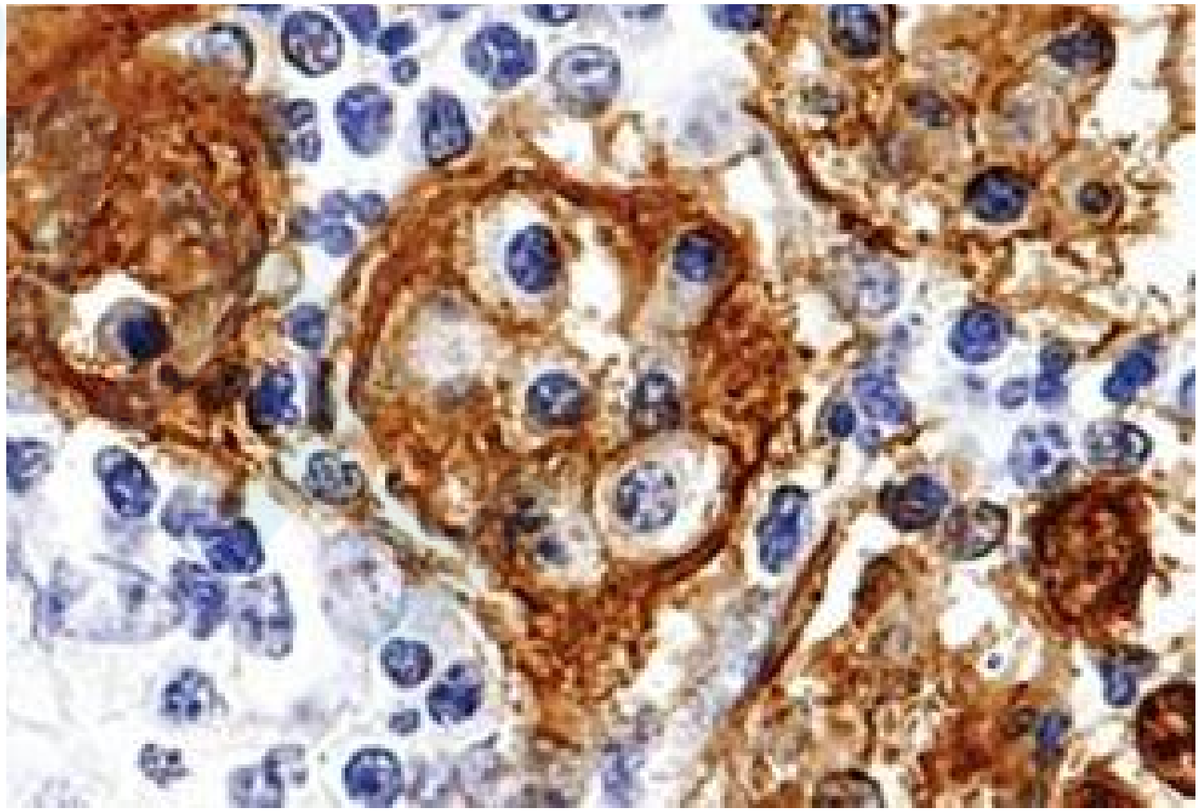
Sinus histiocytosis with massive lymphadenopathy (SHML)

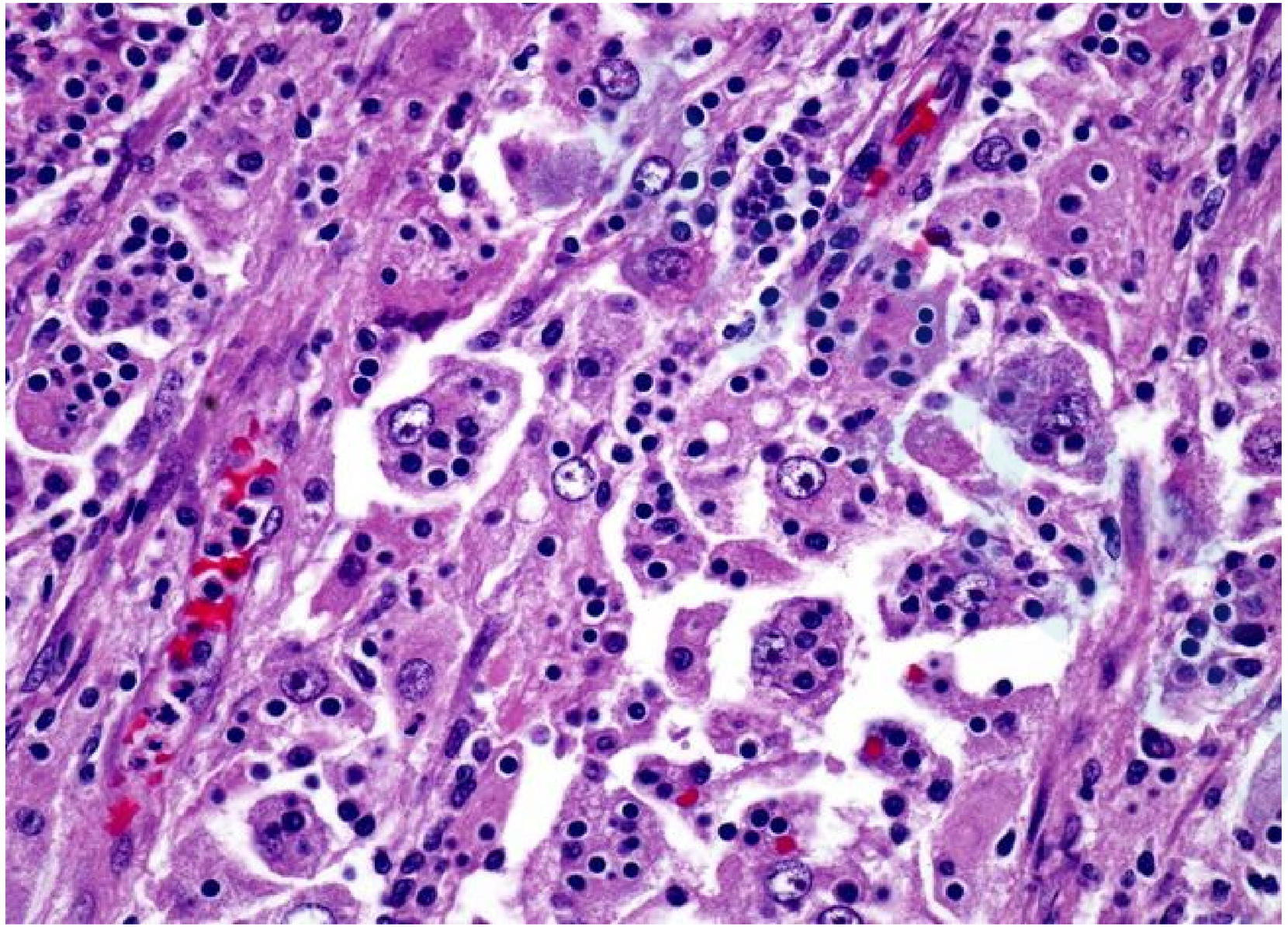
- RDD was first described by Rosai and Dorfman in 1969
- It is a **benign disease** which is characterized by over-production and accumulation of a specific type of histiocytes in the lymph nodes
- The cause remains unknown, although altered immune responses and infectious agents may play a role
- RDD is a self-limited and seldom life-threatening disease which commonly does not require therapy



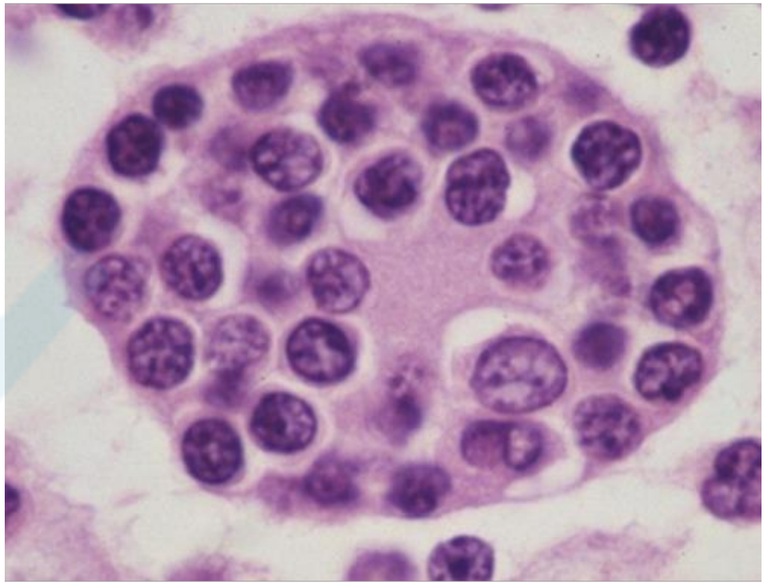
RDD is characterized by a proliferation of nonclonal histiocytes with abundant cytoplasm, large nuclei and conspicuous nucleoli that stain with histiocytic markers such as CD163 or CD68. Unlike normal histiocytes, these cells are also positive for S100







Classic finding of RDD is that of **emperipolesis**, which consists of inflammatory cells within the cytoplasm of the proliferating histiocytes



- **Extranodal involvement** can be seen in the skin, soft tissue, bone or breast, and involvement of essentially every site has been reported
- The spectrum of histomorphologic features of RDD in extranodal sites can be highly variable. Some cases may show only patchy areas of classical RDD, making the diagnosis in unusual sites very difficult

- Gastrointestinal involvement by RDD is extremely rare and <10 cases of **pancreatic** involvement have been reported in the literature
- This diagnostic challenge is further compounded by an overlap between RDD and autoimmune pancreatitis type 1

IgG4-related disease

IgG4-related Disease (IRD)

- First described by Hamano et al, in the form of sclerosing pancreatitis, which is also known as autoimmune pancreatitis type 1
- The current diagnostic criteria for IRD in all organ systems is outlined in a 2012 consensus statement by Deshpande et al

3 major histopathological features

(1) Dense **lymphoplasmacytic** infiltrate

(2) **Fibrosis**, arranged at least focally in a storiform pattern

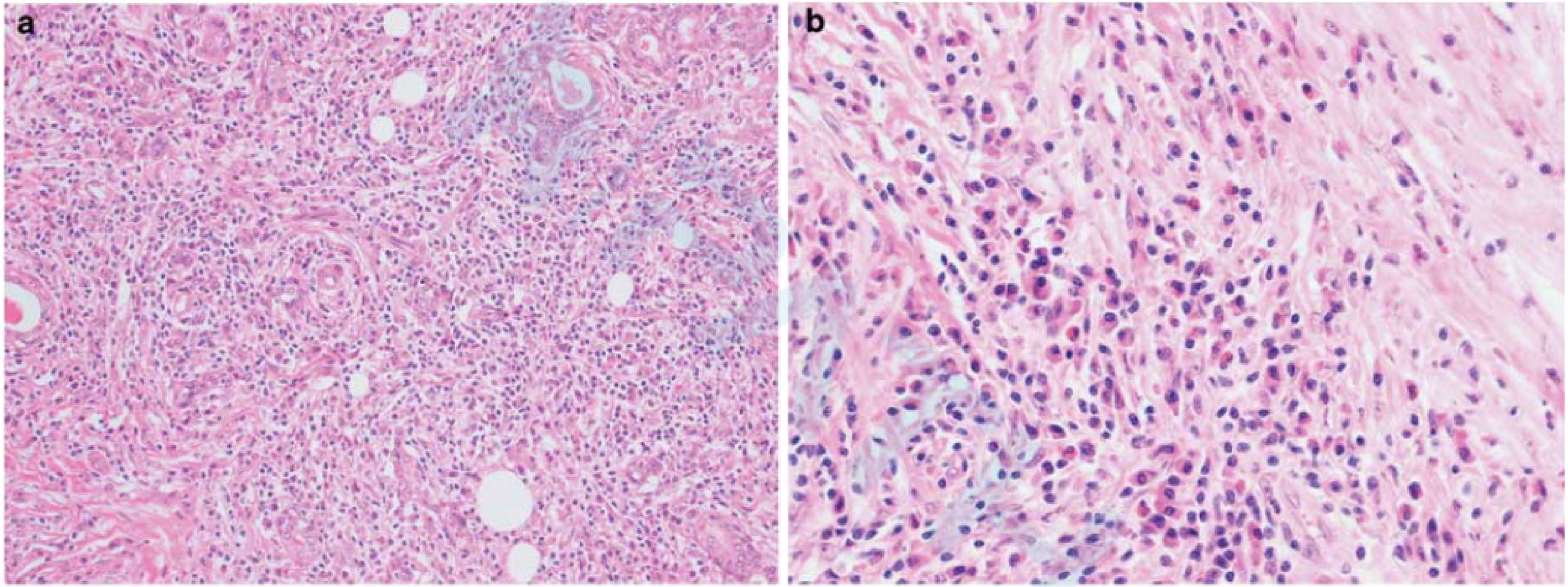
(3) **Obliterative phlebitis**

Other histopathological

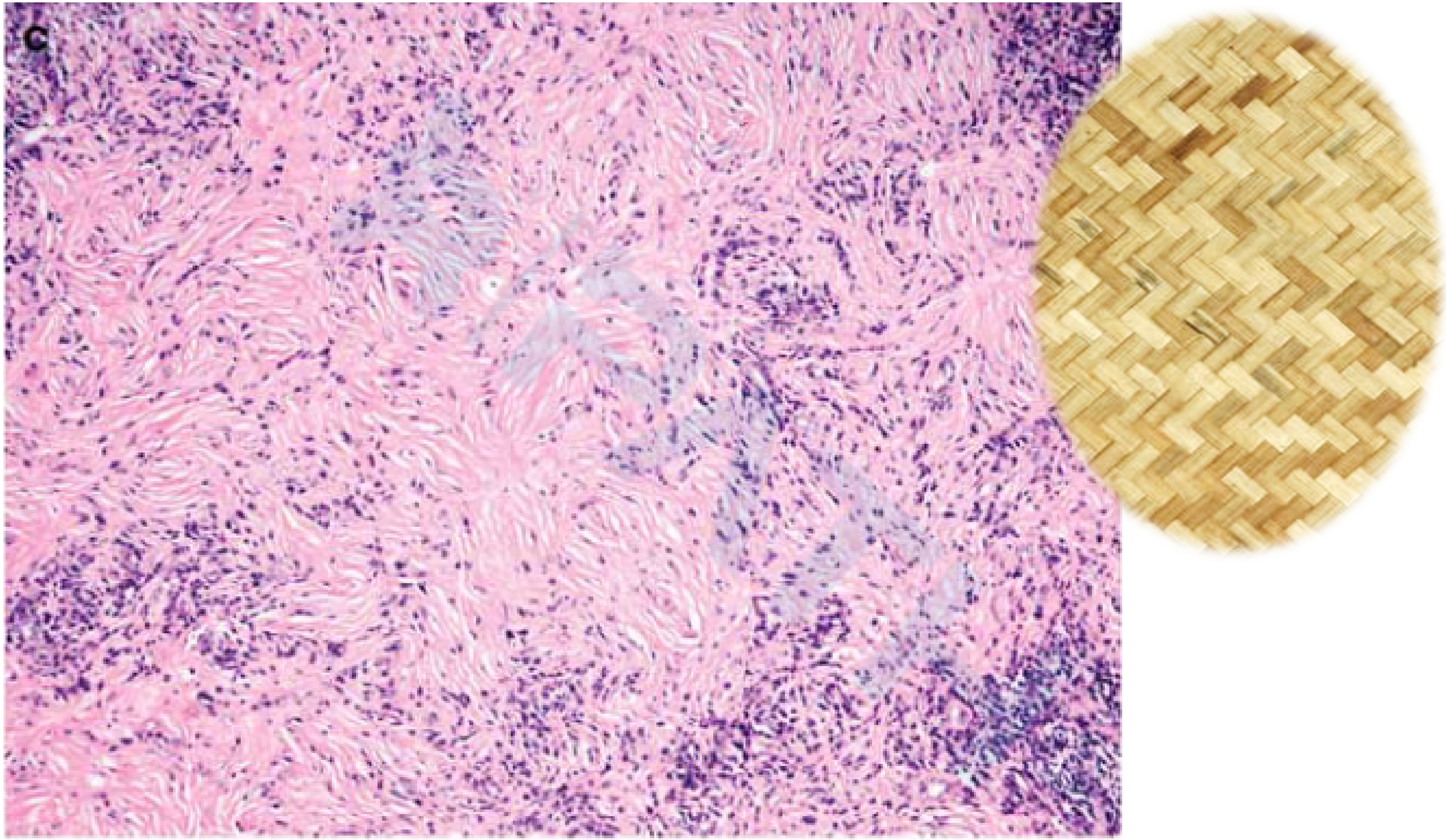
(1) Phlebitis without obliteration of the lumen

(2) Increased numbers of eosinophils

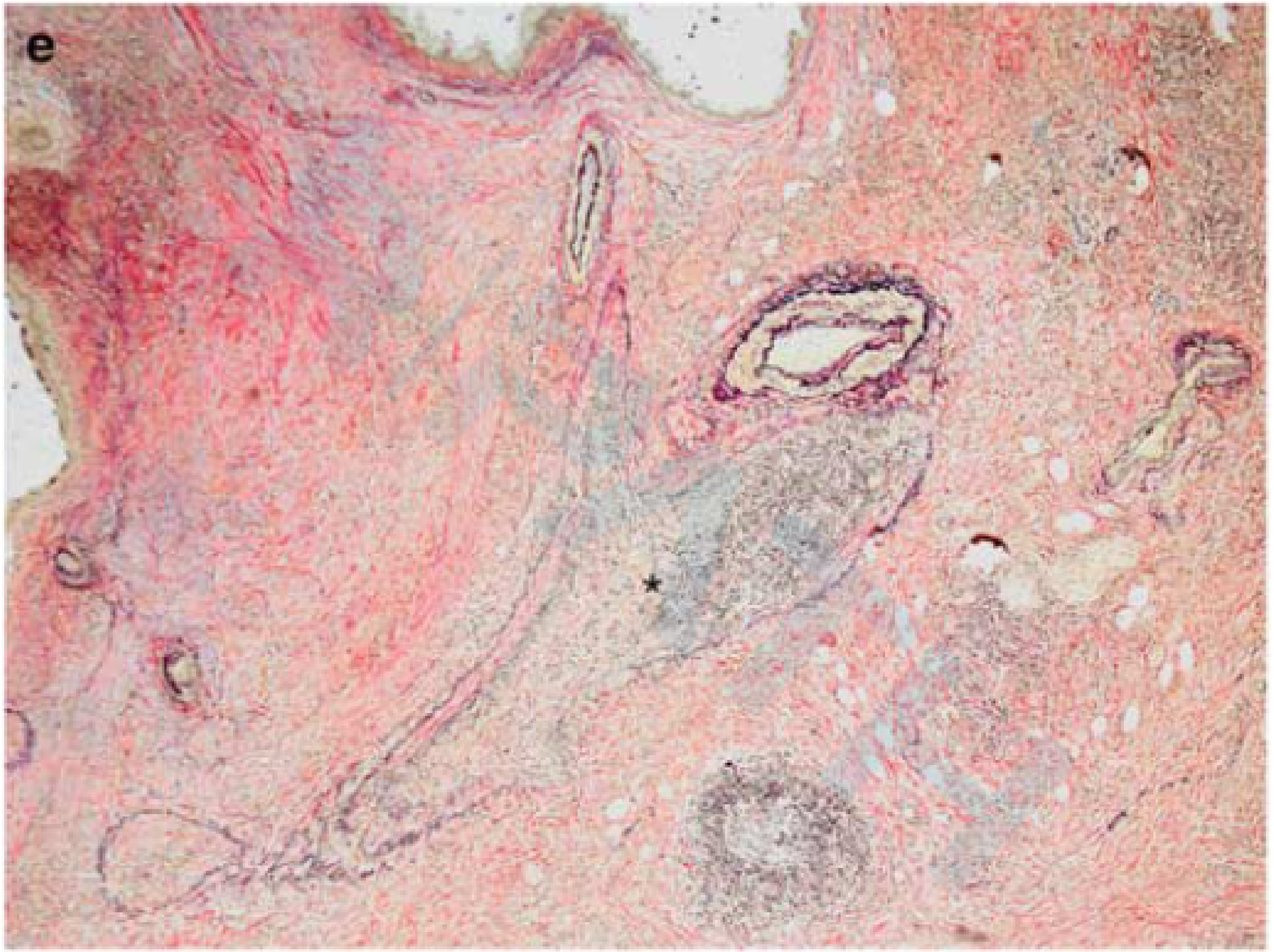
Modern Pathology 25(9):1181-92. 2012



Modern Pathology 25(9):1181-92. 2012

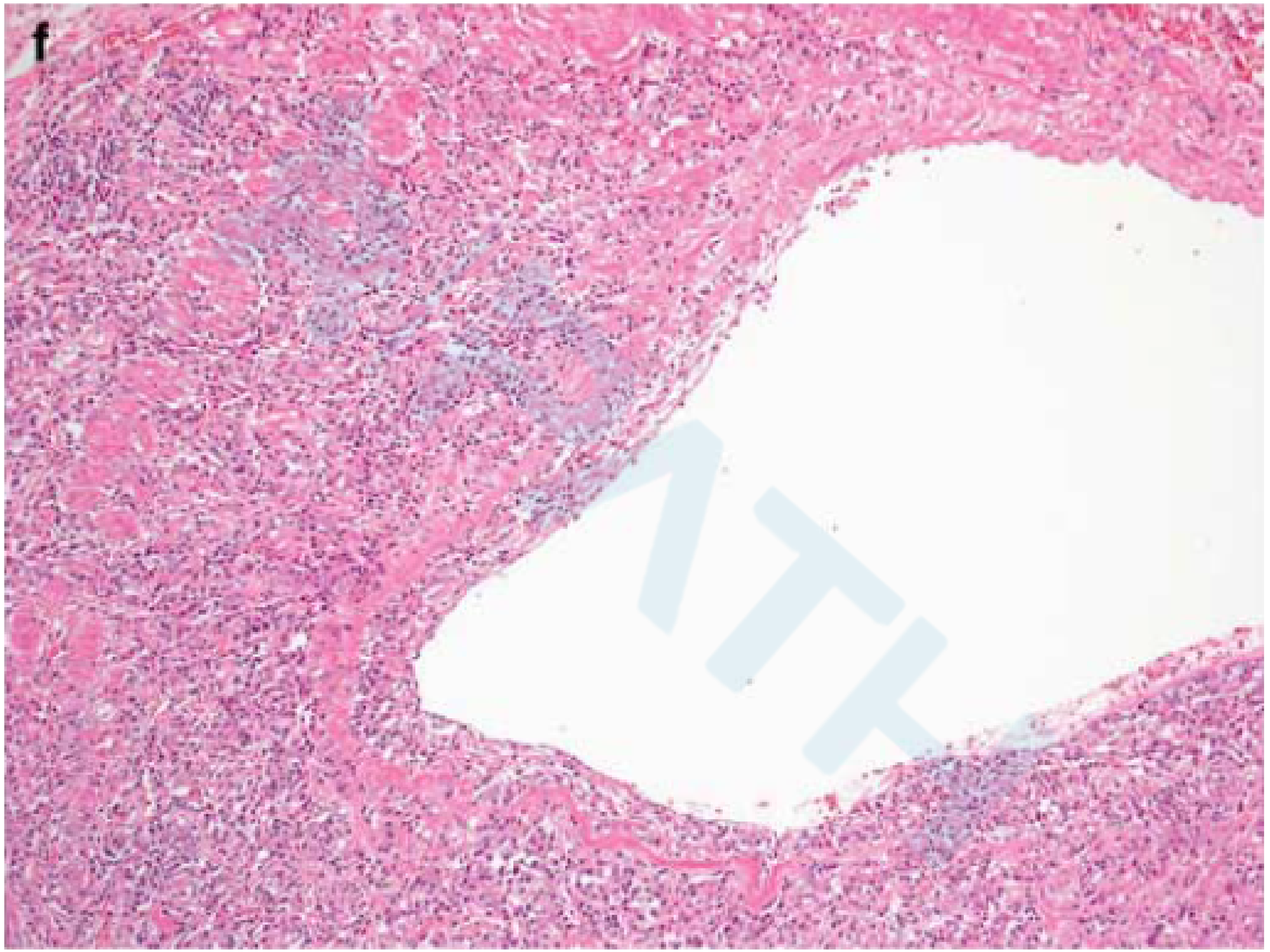


Modern Pathology 25(9):1181-92. 2012

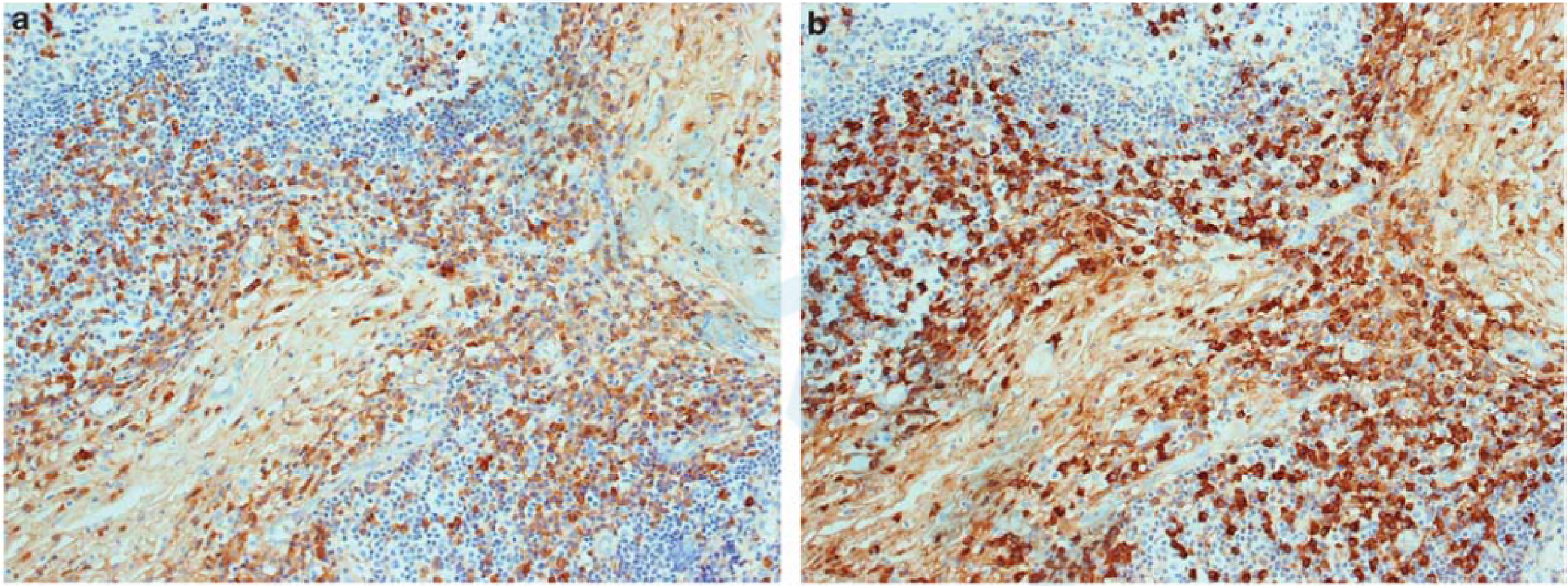


Elastin stain

Modern Pathology 25(9):1181-92. 2012



Modern Pathology 25(9):1181-92. 2012



IgG

IgG4

Modern Pathology 25(9):1181-92. 2012

Characteristic histological features
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform in character
3. Obliterative phlebitis

	Cases with ≥ 2 pathology features	Cases with 1 pathology feature
	Numbers of IgG4+ plasma cells (/hpf)	
Meningus	>10	>10
Lacrimal gland	>100	>100
Salivary gland	>100	>100
Lymph node	>100	>50
Lung (surgical specimen)	>50	>50
Lung (biopsy)	>20	>20
Pleura	>50	>50
Pancreas (surgical specimen)	>50	>50
Pancreas (biopsy)	>10	>10
Bile duct (surgical specimen)	>50	>50
Bile duct (biopsy)	>10	>10
Liver (surgical specimen)	>50	>50
Liver (biopsy)	>10	>10
Kidney (surgical specimen)	>30	>30
Kidney (biopsy)	>10	>10
Aorta	>50	>50
Retroperitoneum	>30	>30
Skin	>200	>200

IgG4+/IgG+ 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

Modern Pathology 25(9):1181-92. 2012

- The presence of increased IgG4-positive plasma cells with varied major histologic criteria of IRD has been described in numerous cases of extranodal RDD but never examined in pancreatic RDD

- RDD is no uniform approach to treatment, with modalities including observation, surgery, steroids, chemotherapy, and immunotherapy depending on the site and presentation
- Steroids are the established treatment for IRD

The **PURPOSE** of this study was to

•Examine new cases of pancreatic RDD and assess them for defining histomorphologic features and the presence of diagnostic histologic and immunohistochemical features of IRD

•These features were then assessed in nonpancreatic, extranodal RDD cases to determine if overlapping IRD features are present in all locations

MATERIALS AND METHODS

- Patient Selection
- cases from 2002 to 2018 in Emory University Hospital
- diagnoses of extranodal RDD occurring specifically in the pancreas and deep-seated intraabdominal locations
- Histopathologic / Cytologic Evaluation
- Immunohistochemical / Special Stain Analysis

RESULTS

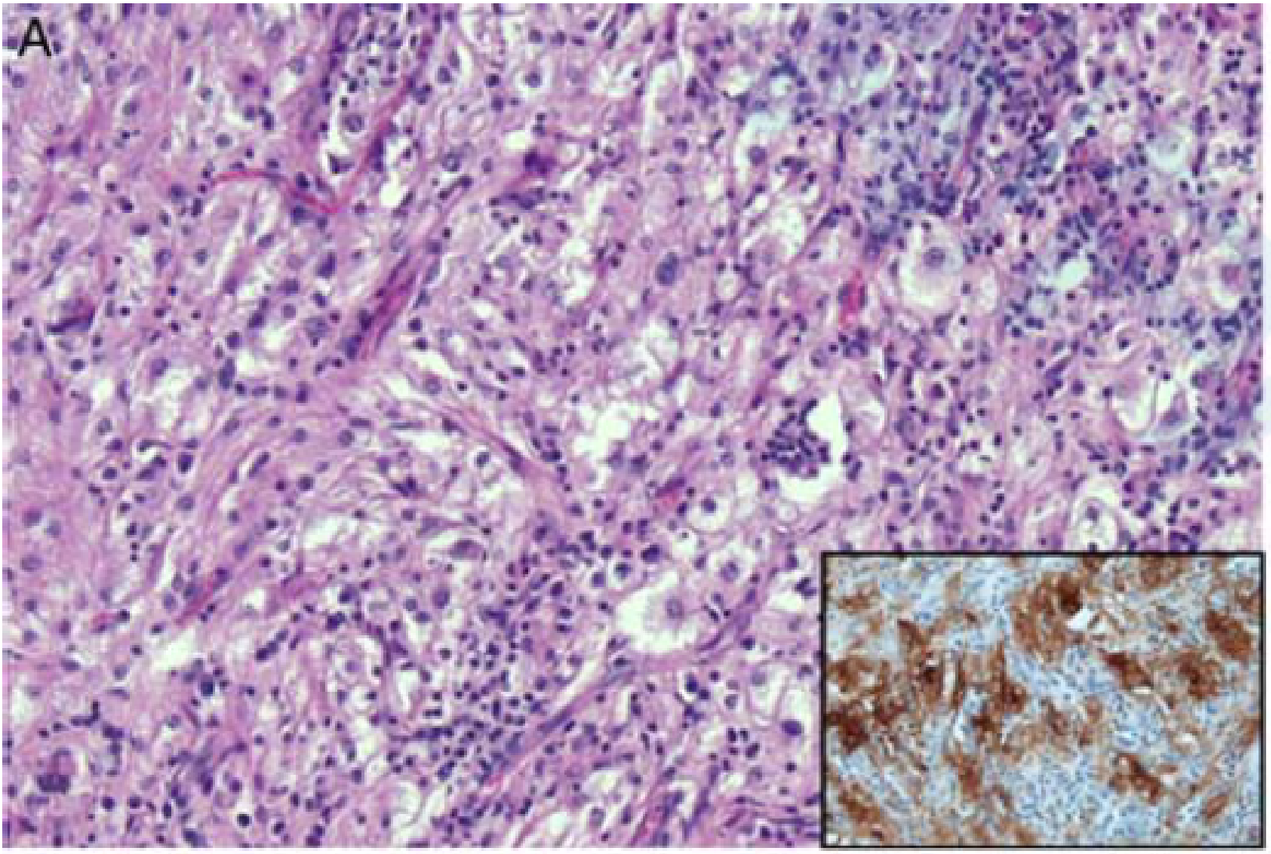
- Pancreatic RDD (4+5)

TABLE 1. Clinical and Pathologic Features of Previous and Current Cases of Pancreatic RDD

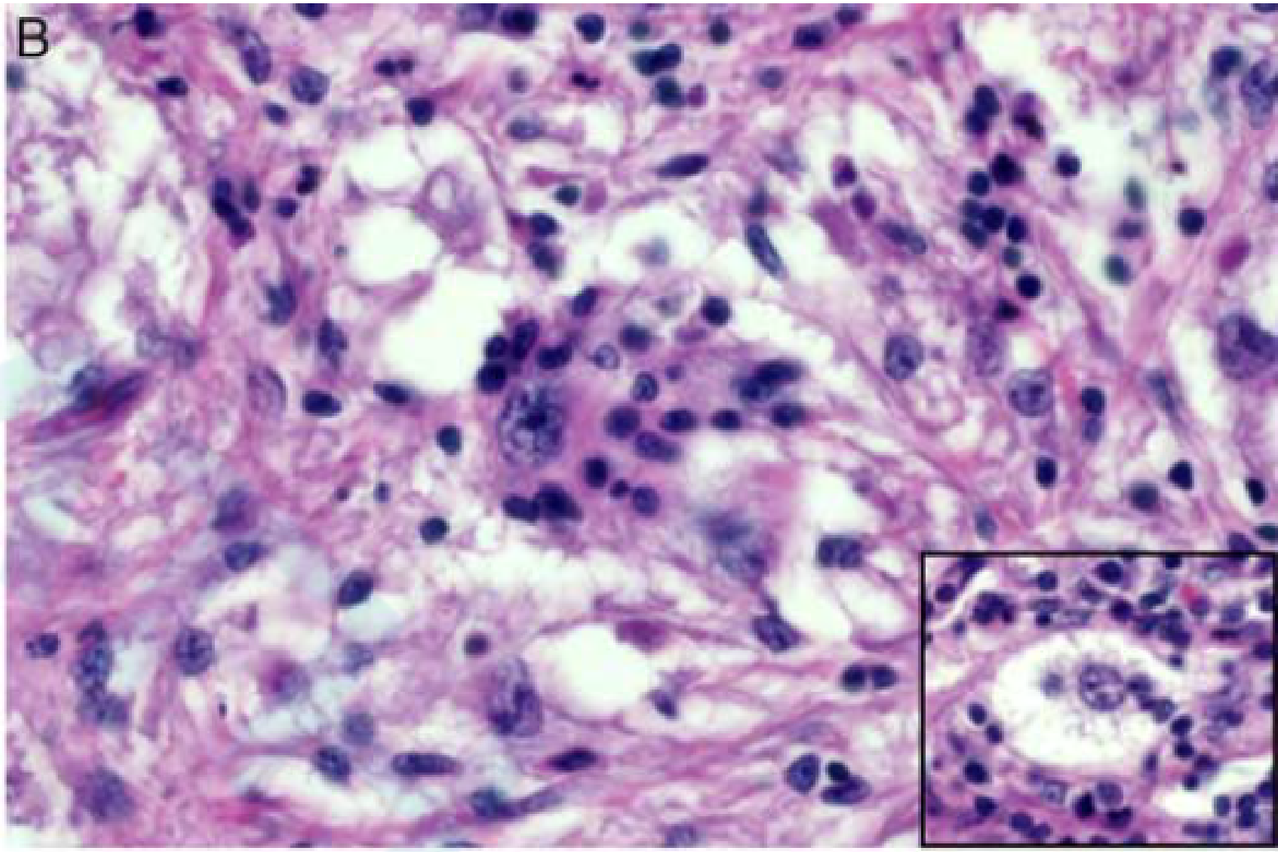
Case	Location	Size (cm)	Age (y)	Sex	Race	Presentation
Esquivel et al[2] (same as Lauwers et al[3])	Distal pancreas	4	48	Female	AA	Abdominal pain
Zivin et al[4]	Pancreatic head	NA	63	Female	AA	Obstructive jaundice
Romero Arenas et al[6]	Uncinate process	2	74	Female	AA	Abdominal pain
Podberezin et al[5]	Distal pancreas	10.2	35	Female	H	Abdominal pain
1	Distal pancreas	2.1	65	Female	AA	Incidental
2	Distal pancreas	2.9	51	Female	AA	Incidental
3	Distal pancreas	4.2	47	Male	NA	Abdominal pain
4	Distal Pancreas	2.3	69	Male	AA	Abdominal pain
5 (same as Smith et al[7])	Pancreatic head	4.5	75	Female	AA	Weight loss

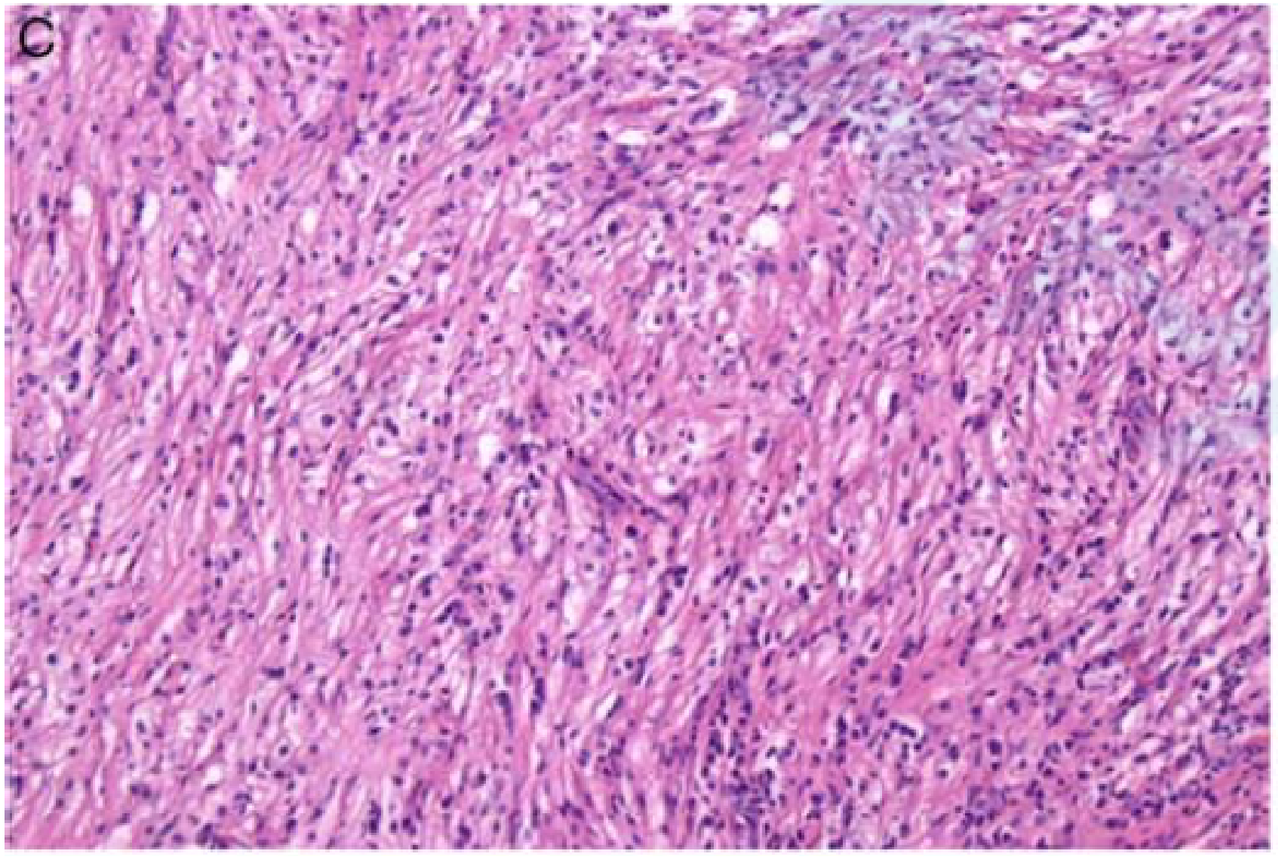
*Additional sites not resected are stable or growing.
AA indicates African American; H, Hispanic; NA, information not available; NC, noncontributory.

Case 1 of pancreatic RDD: A 65-year-old African American woman



S100

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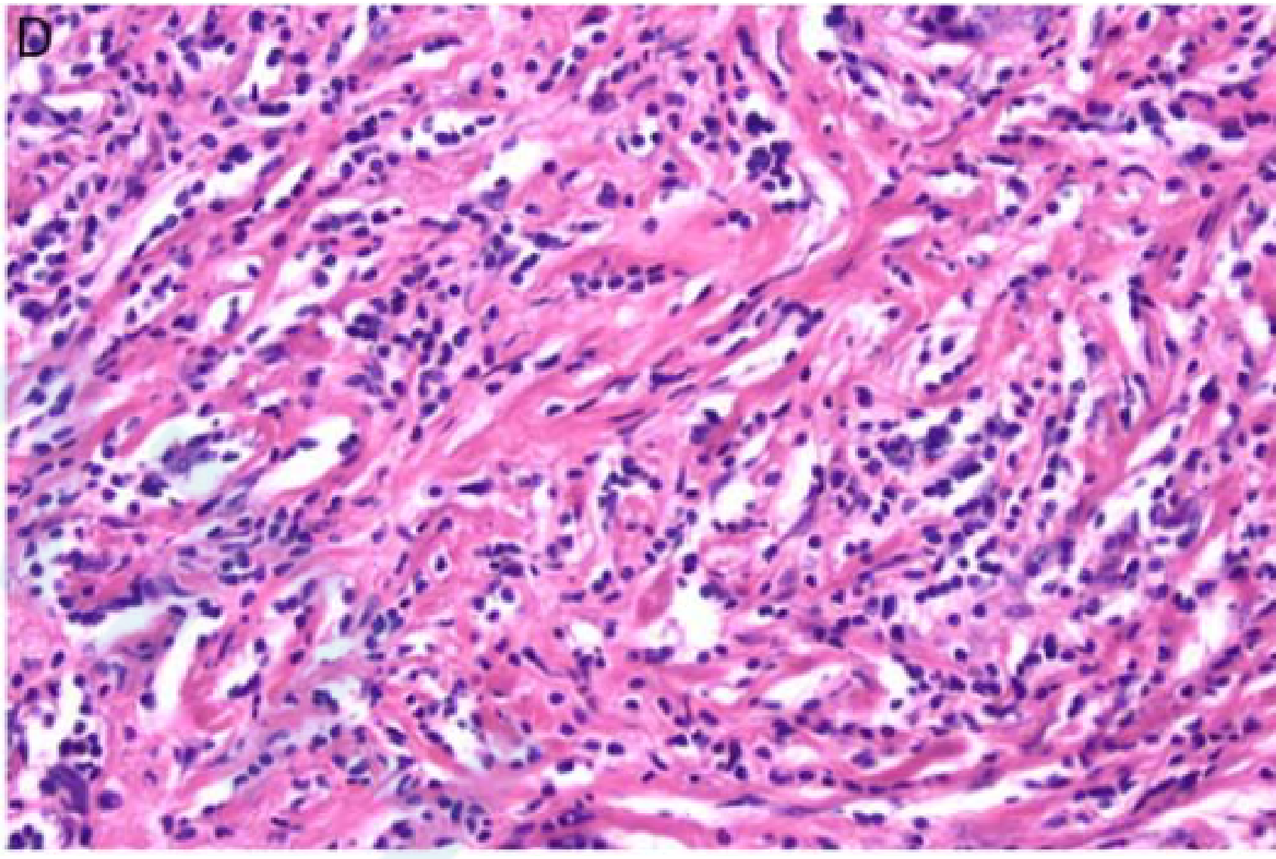
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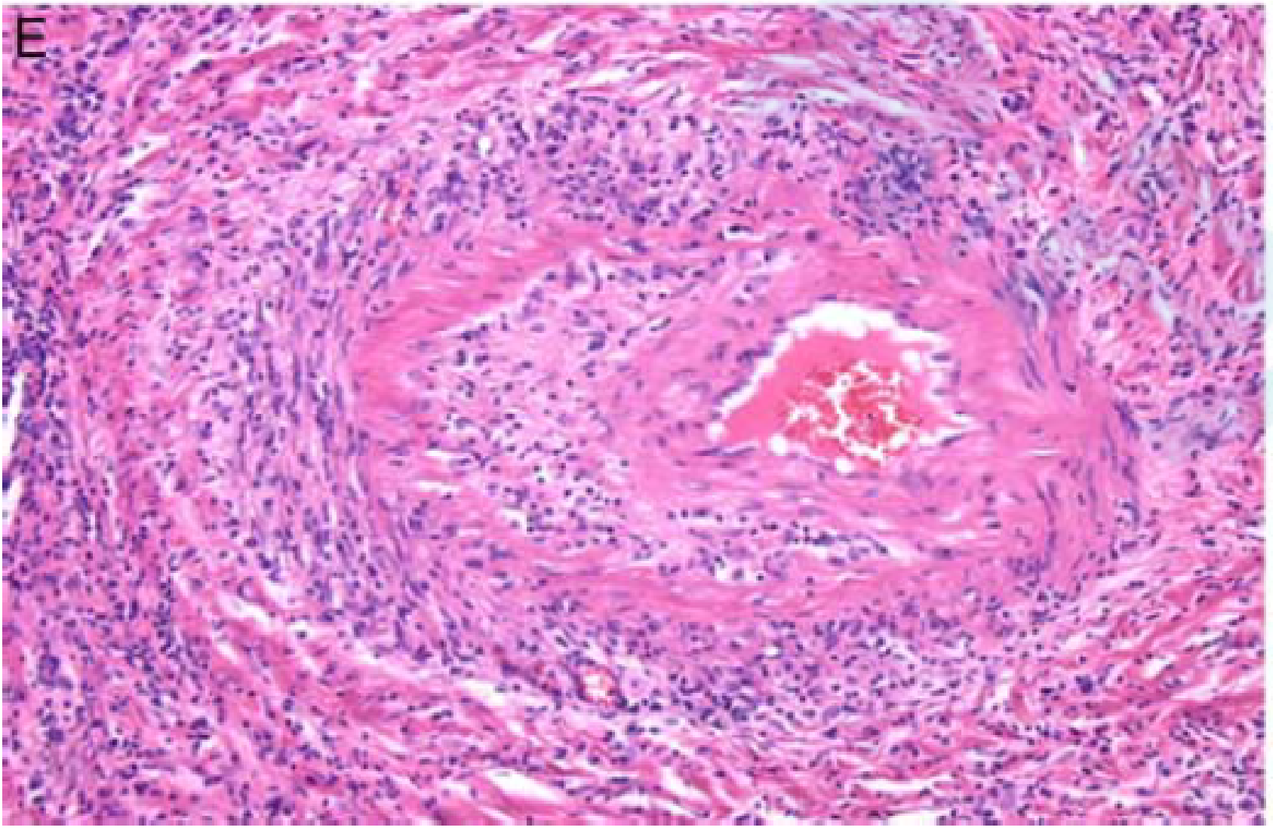
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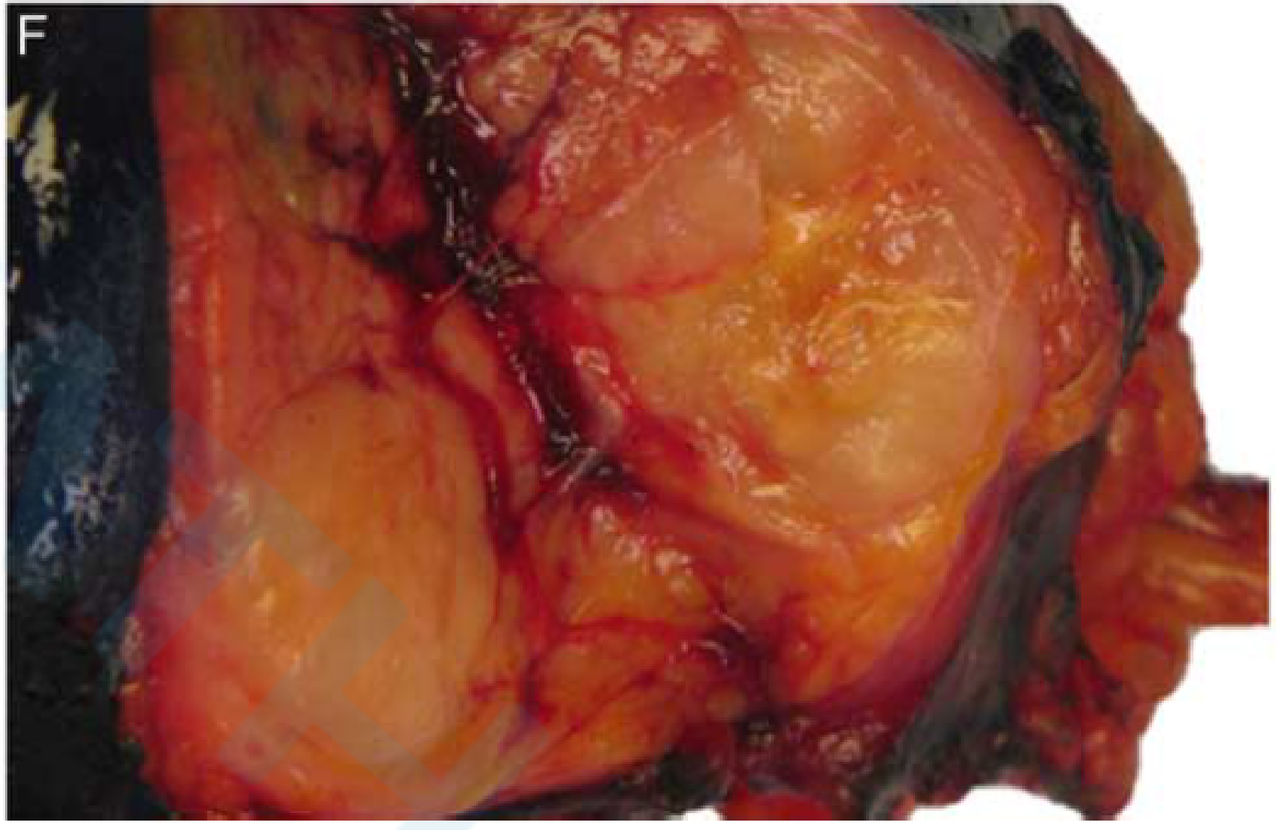
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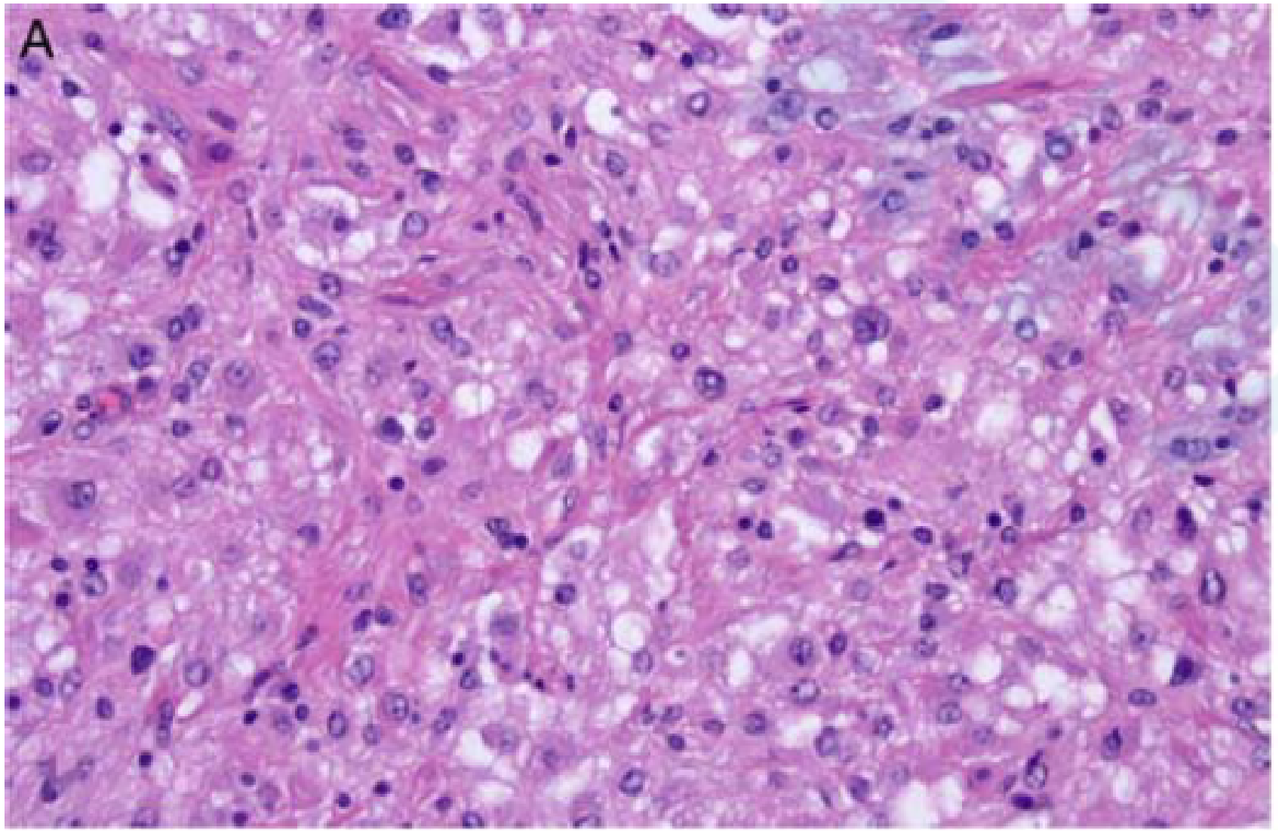
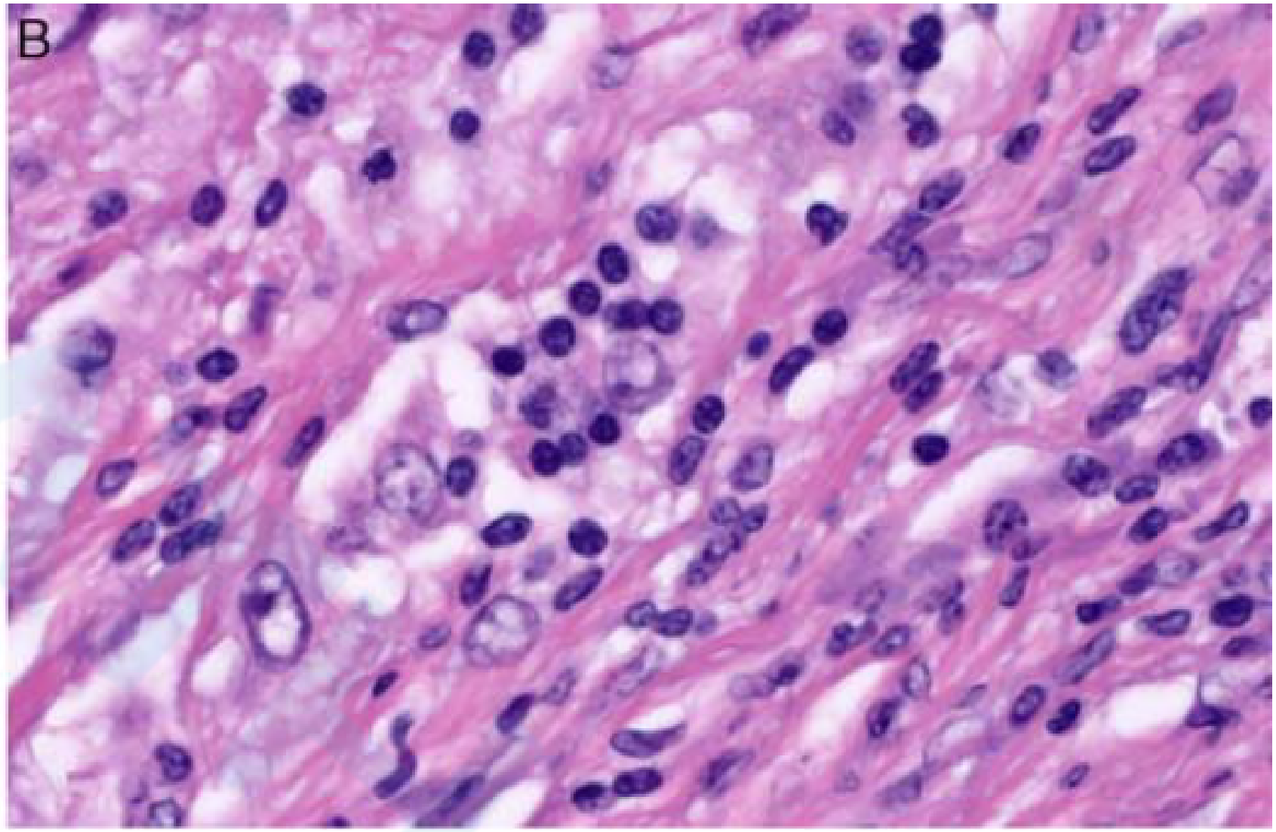
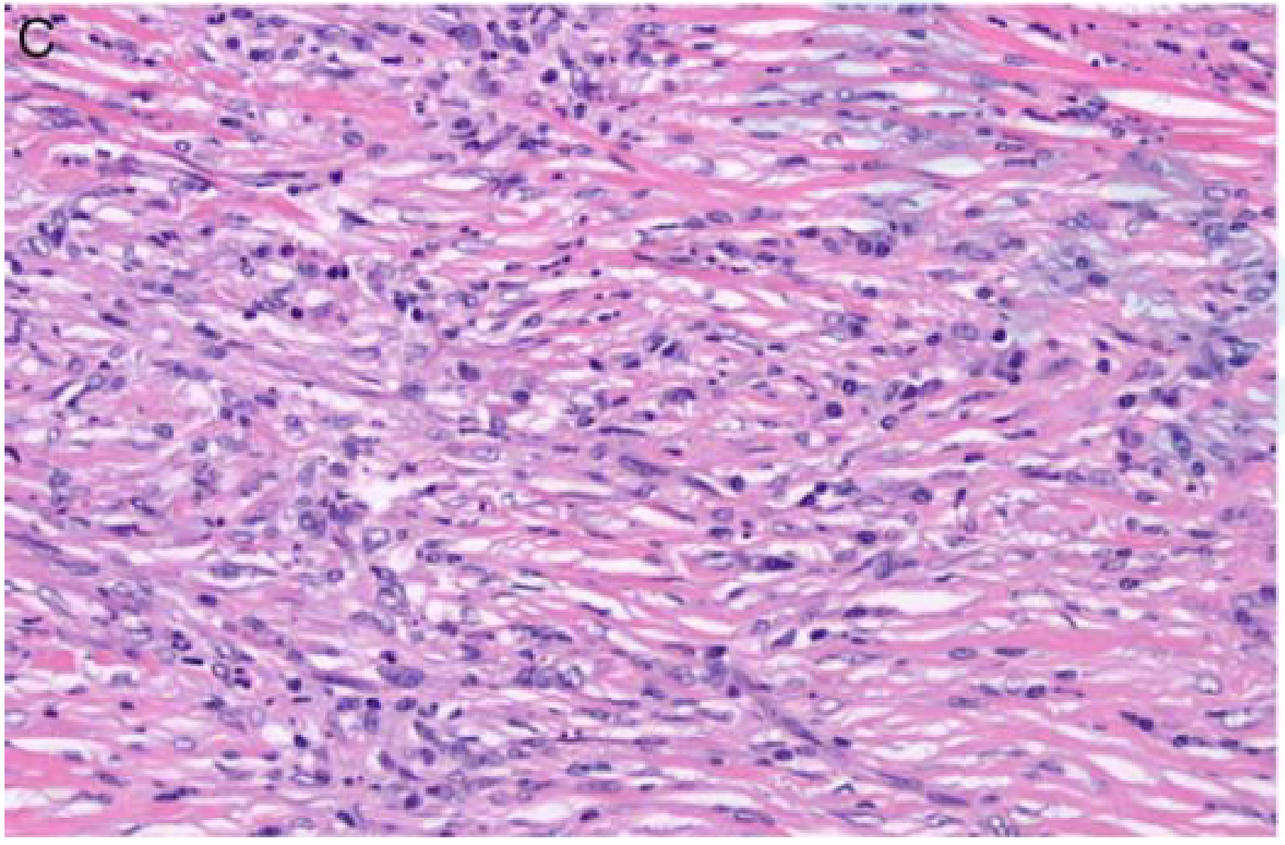
Case 2 of pancreatic RDD: A 51-year-old African American woman





emperipolesis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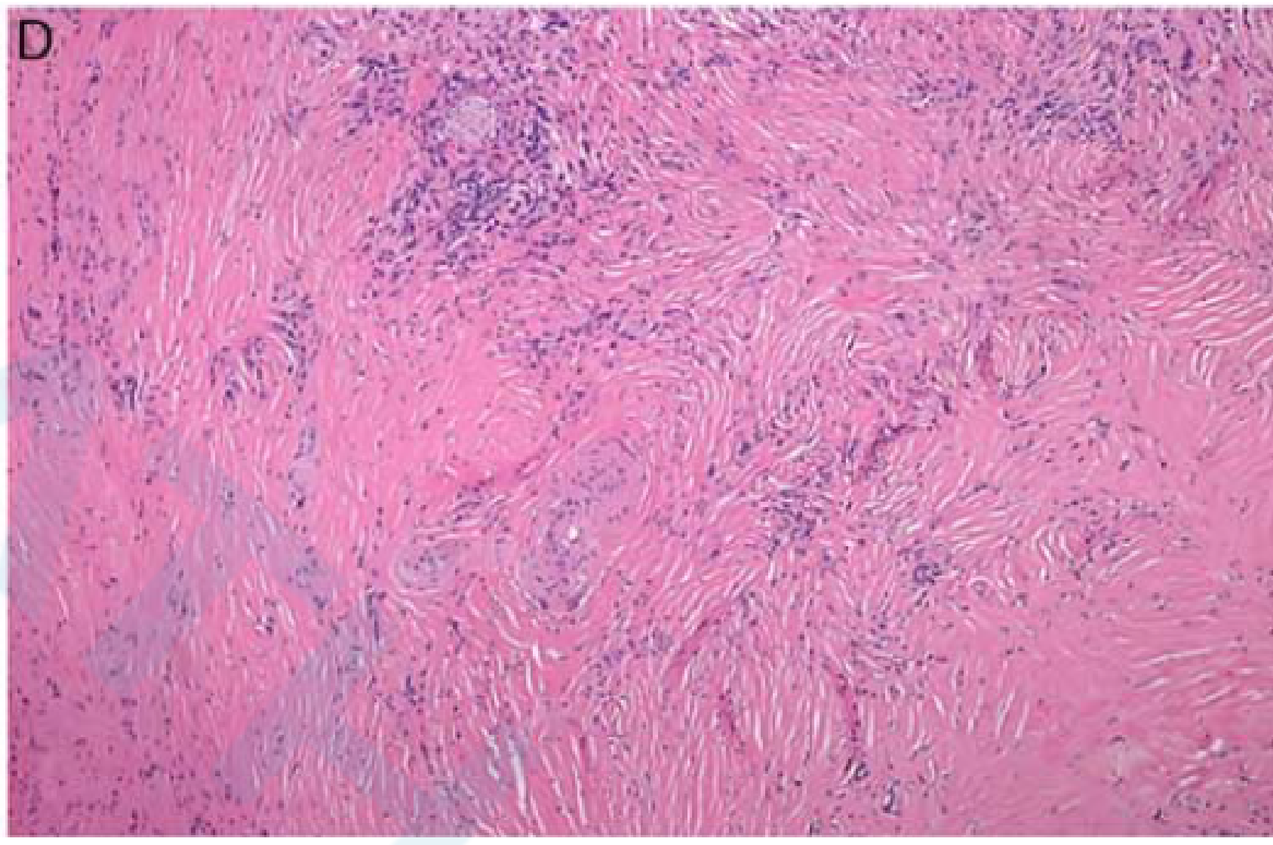
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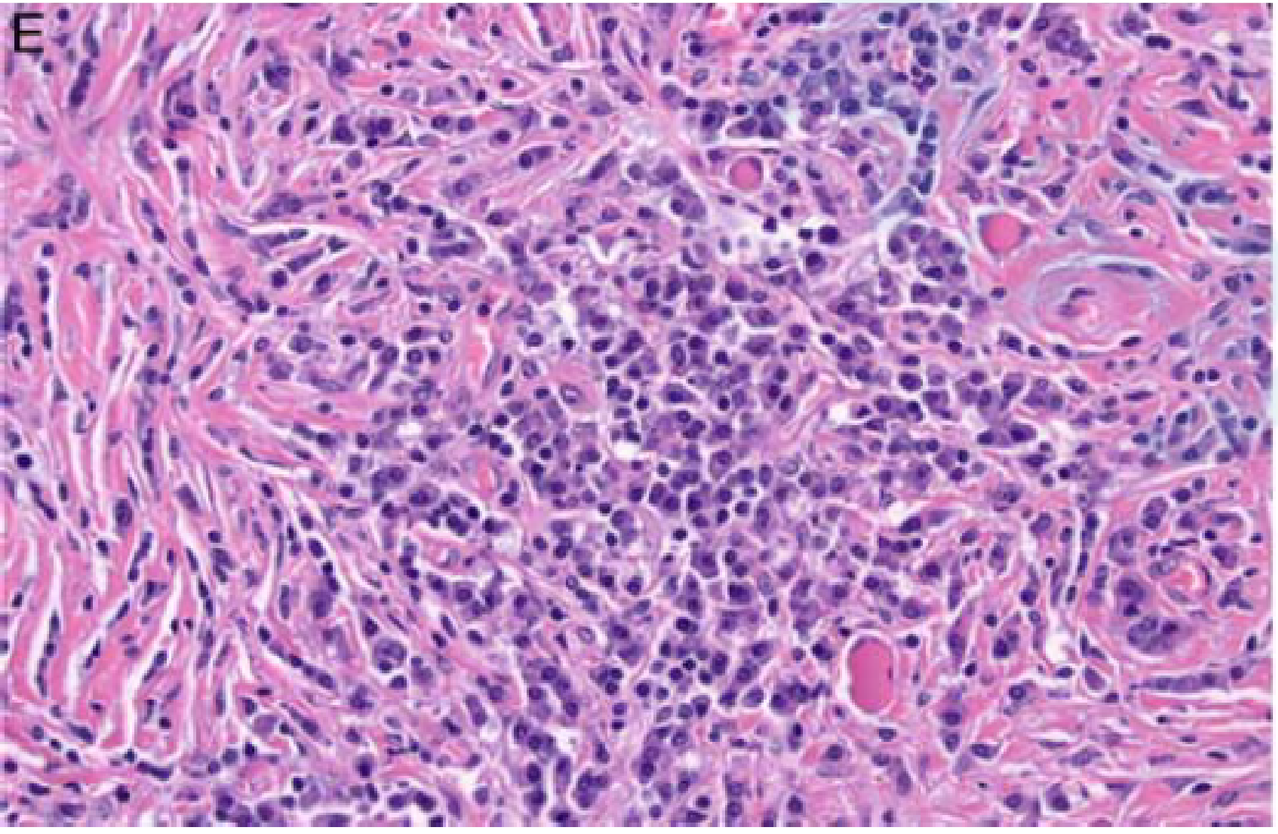
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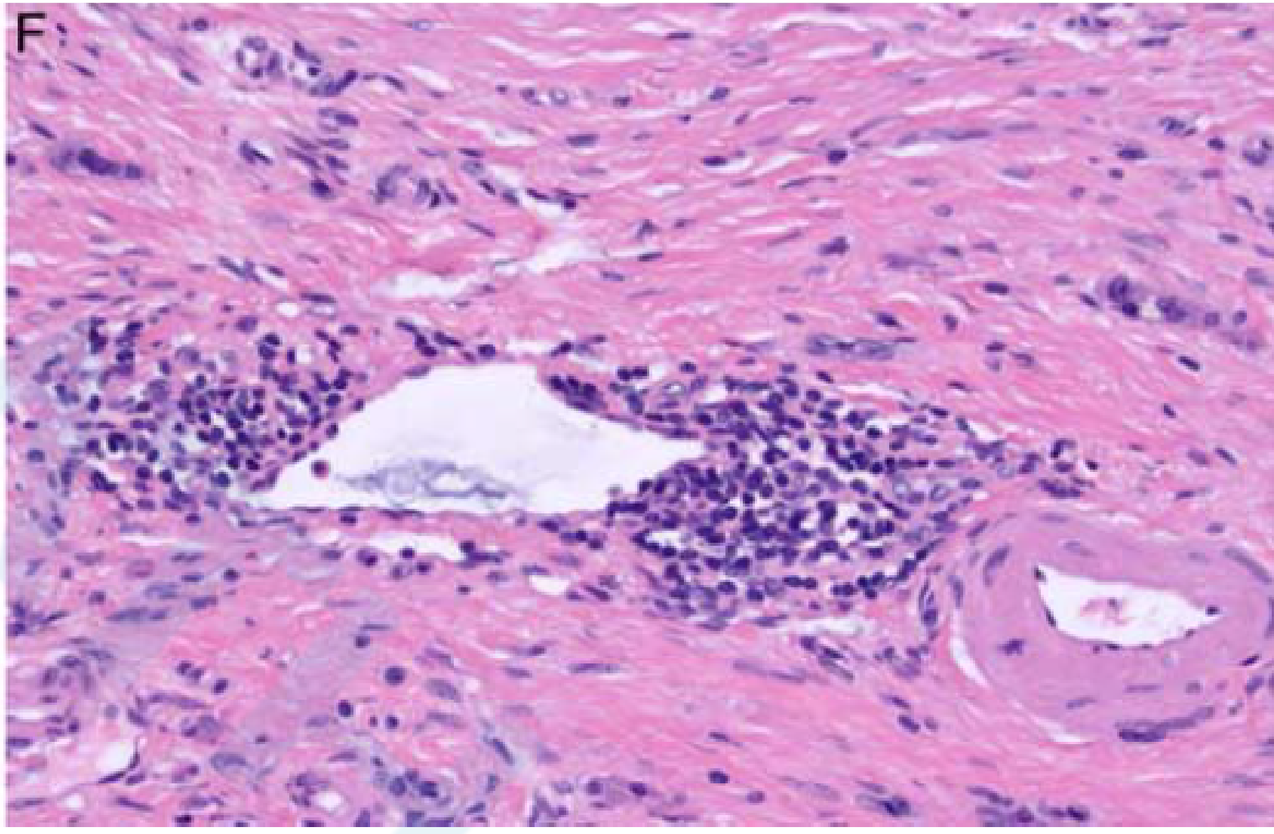
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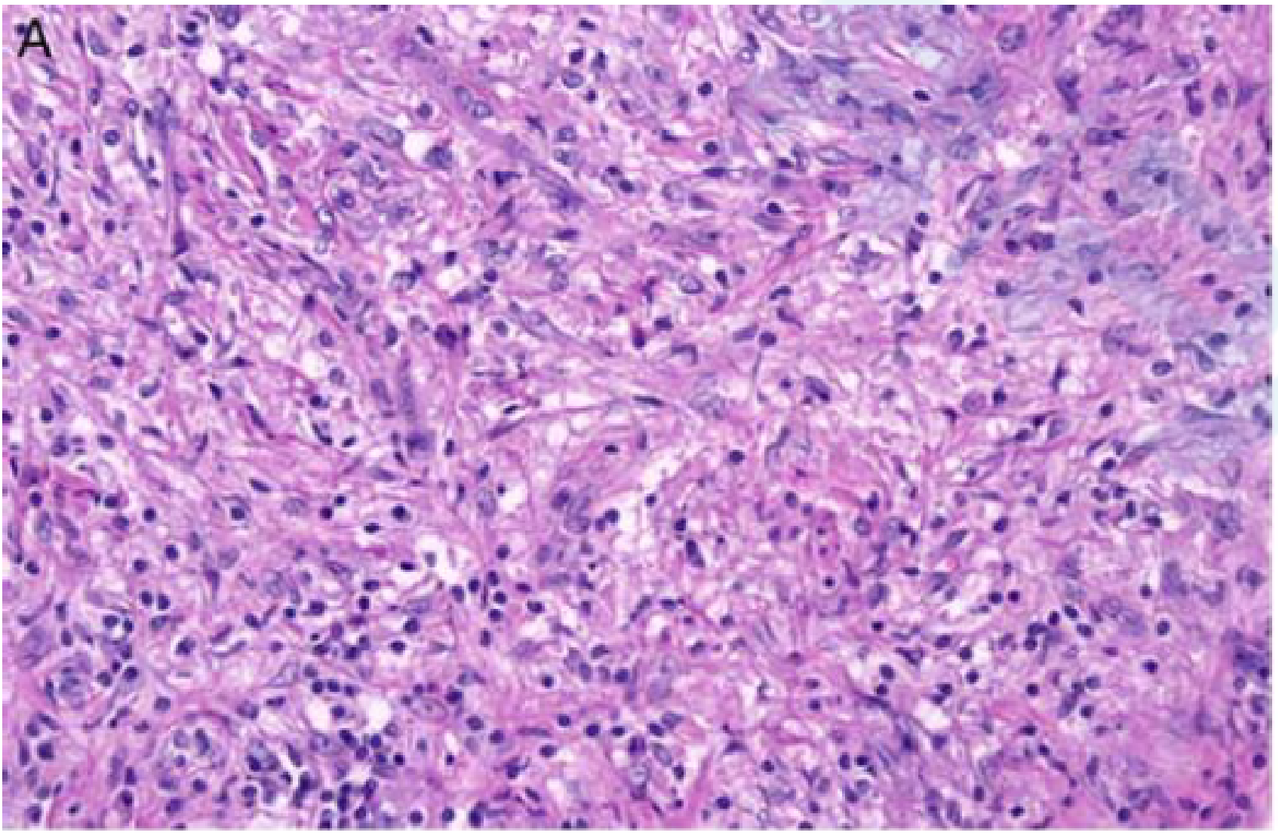
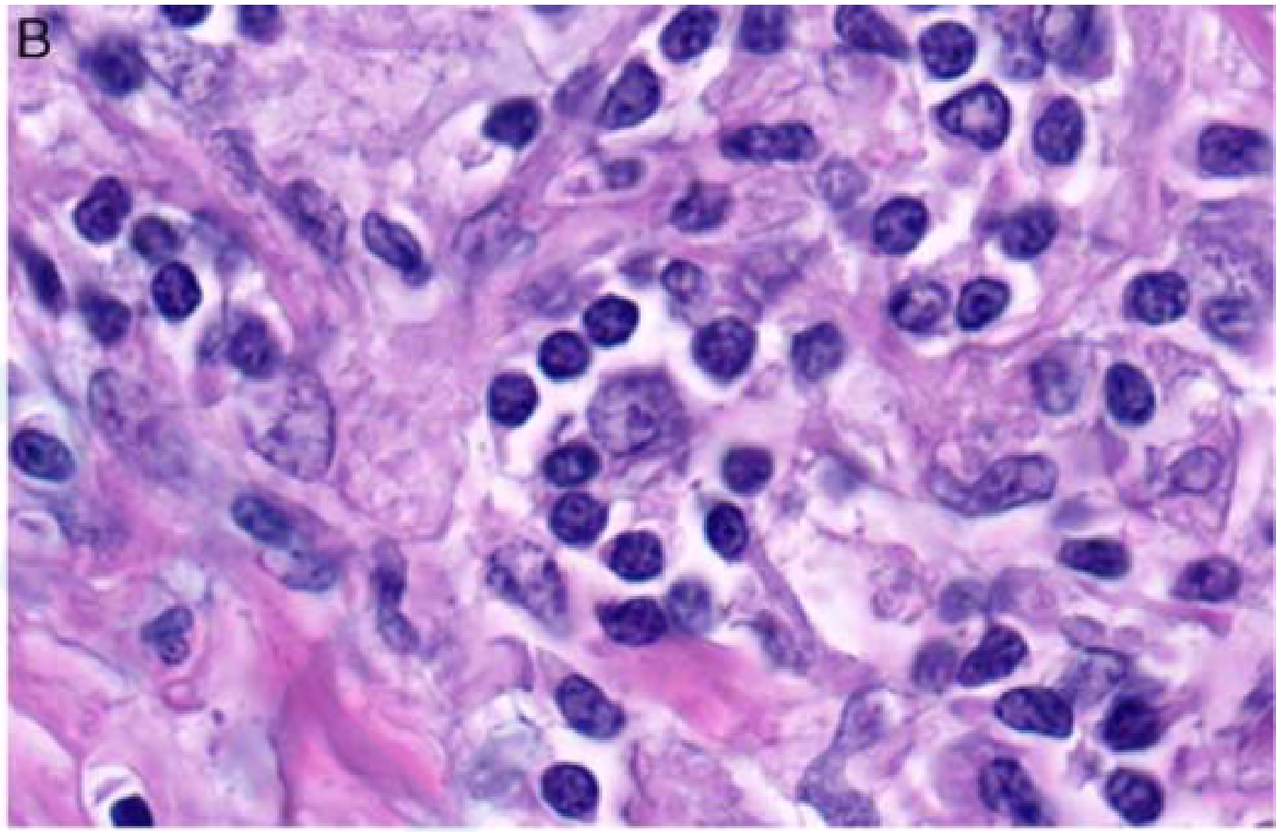
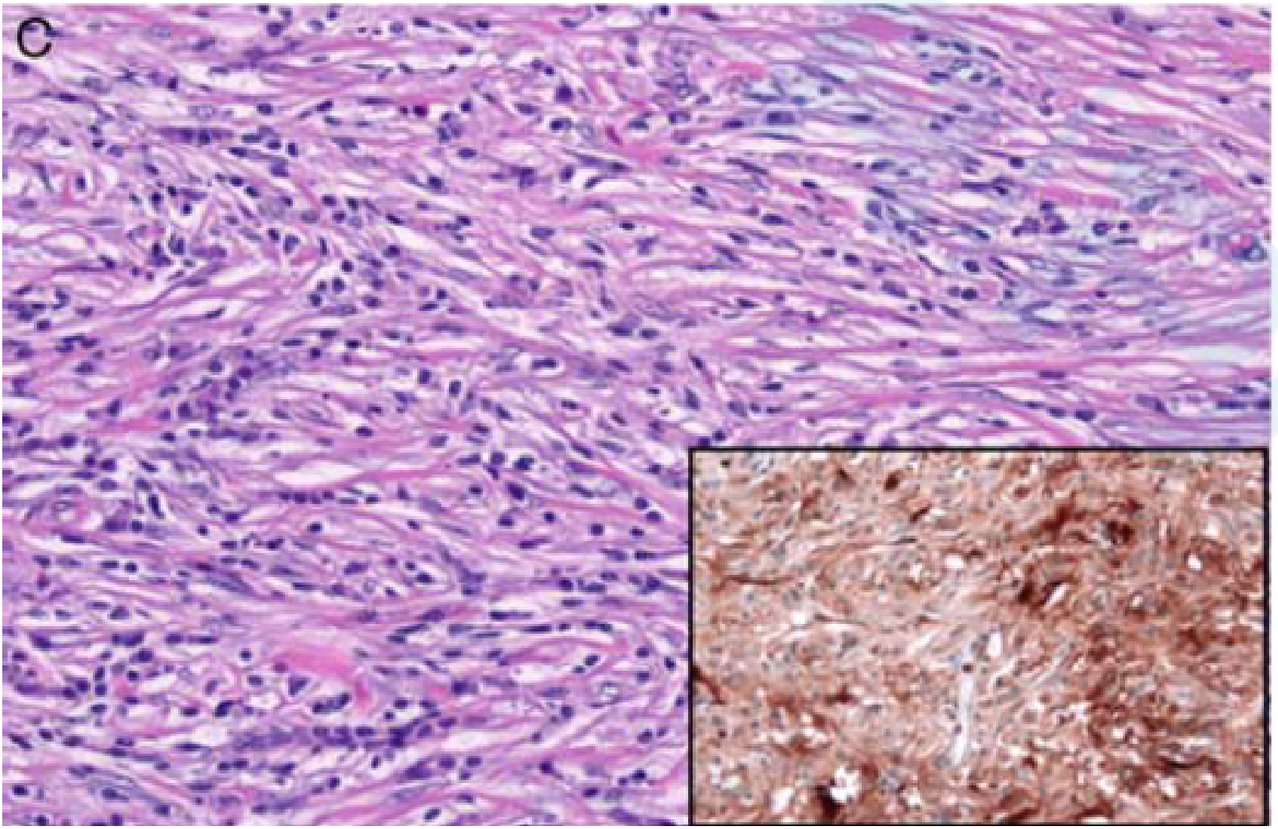
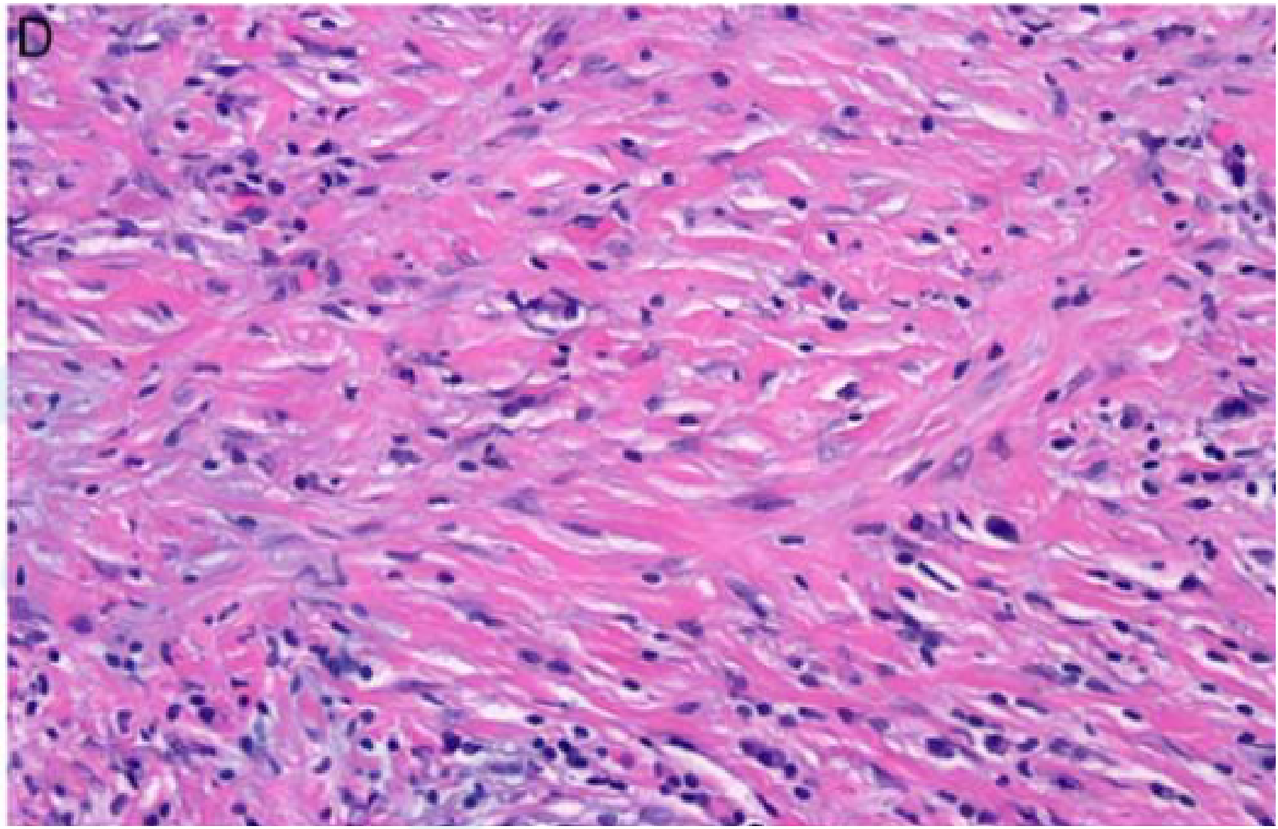
Case 3 of pancreatic RDD: A 47-year-old man

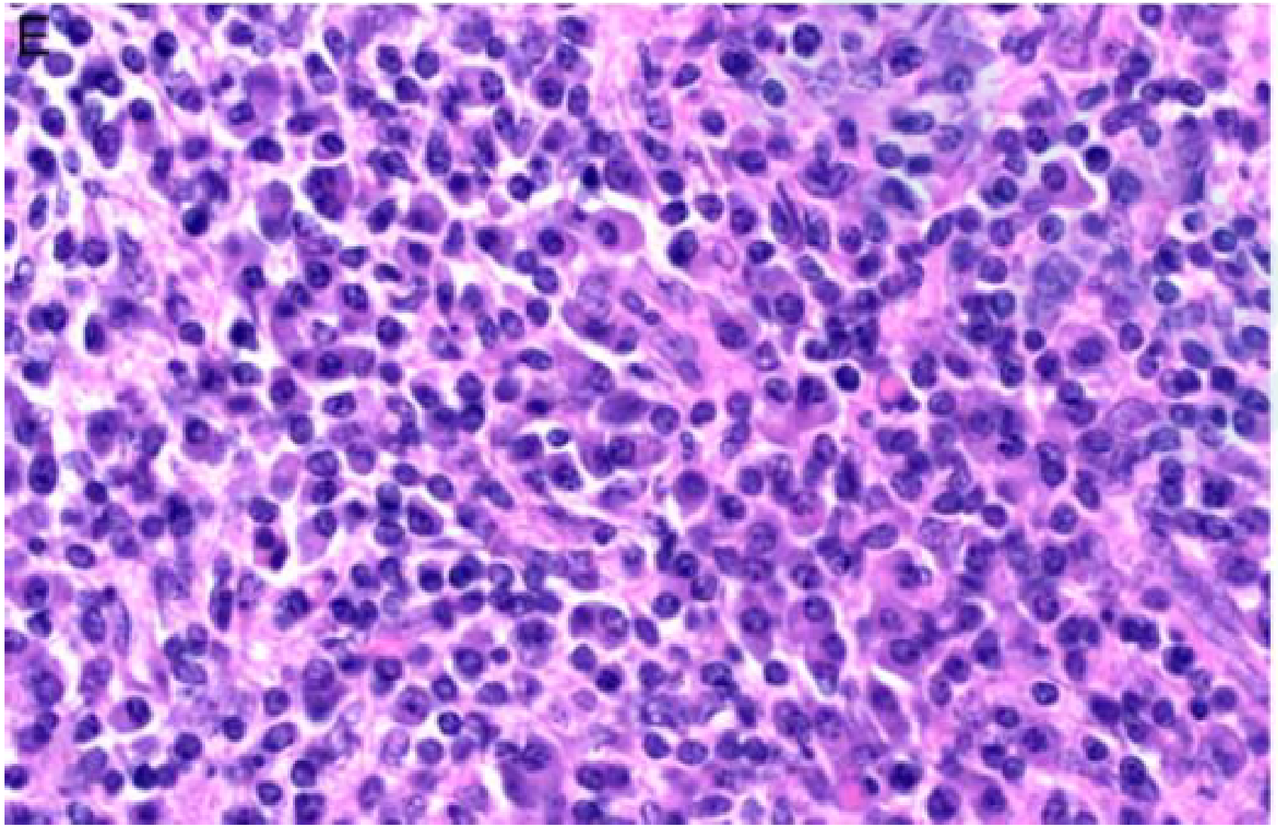






S100

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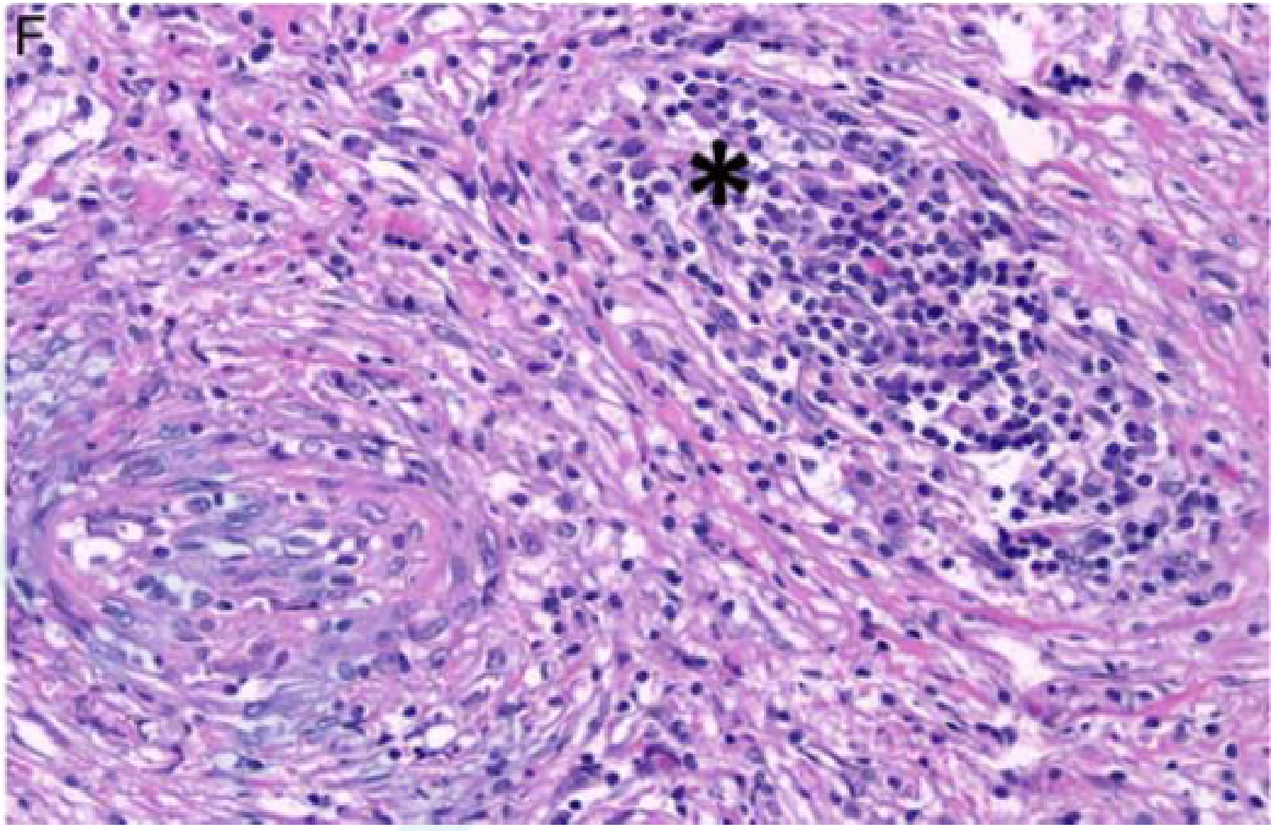
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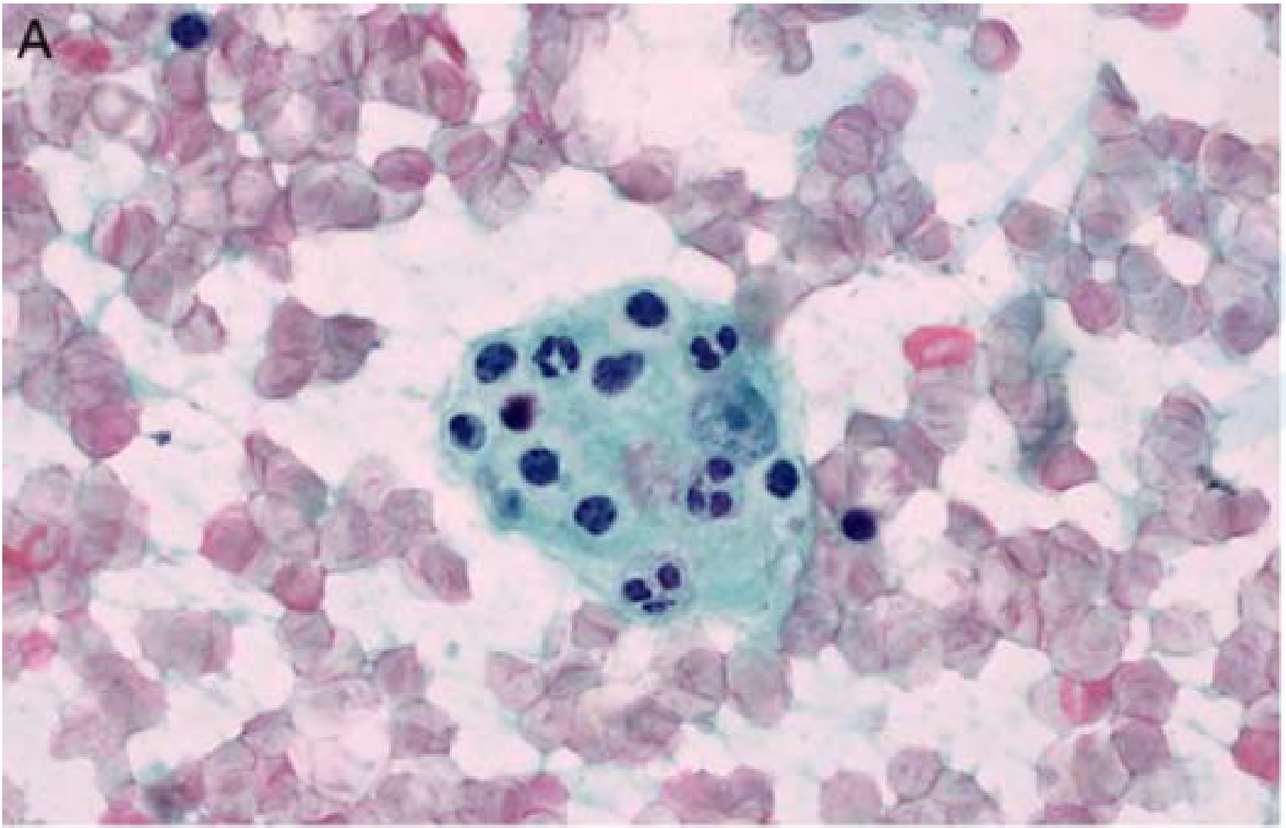
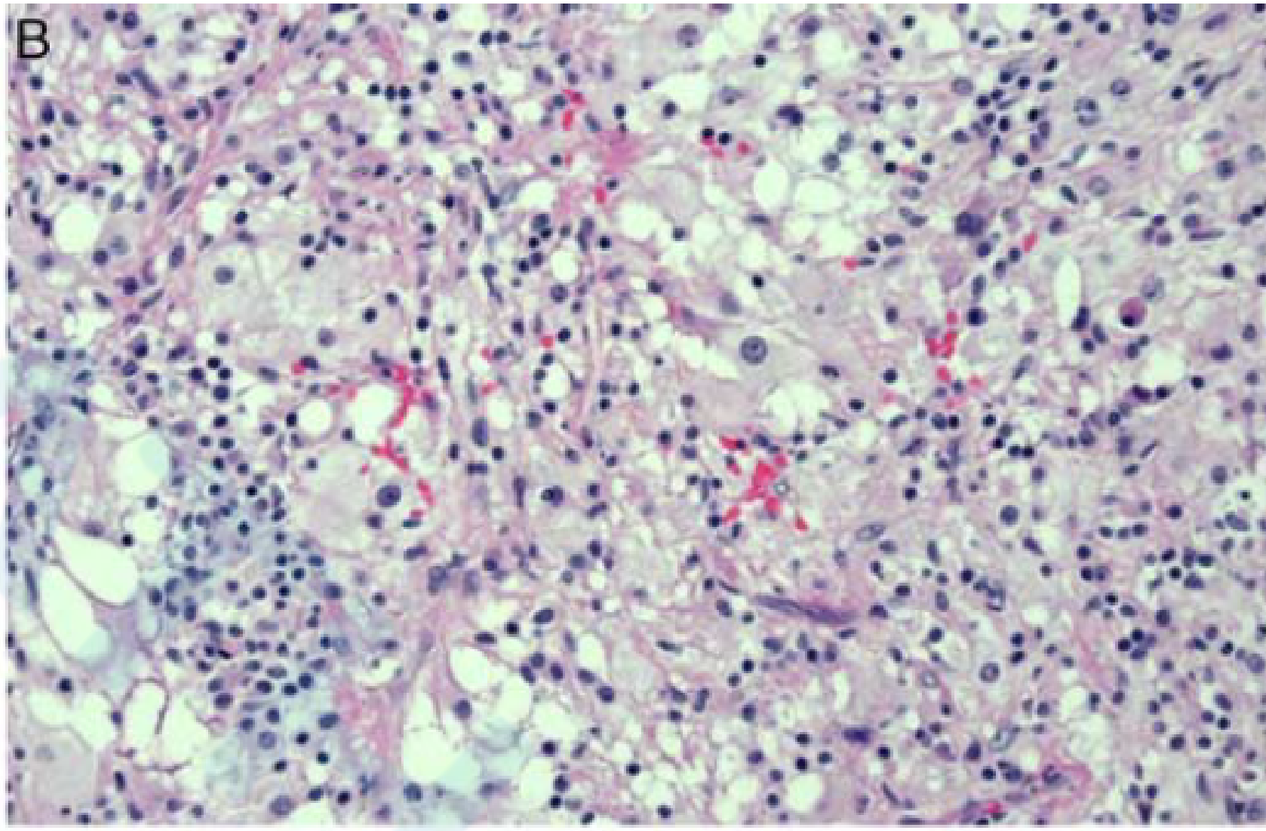
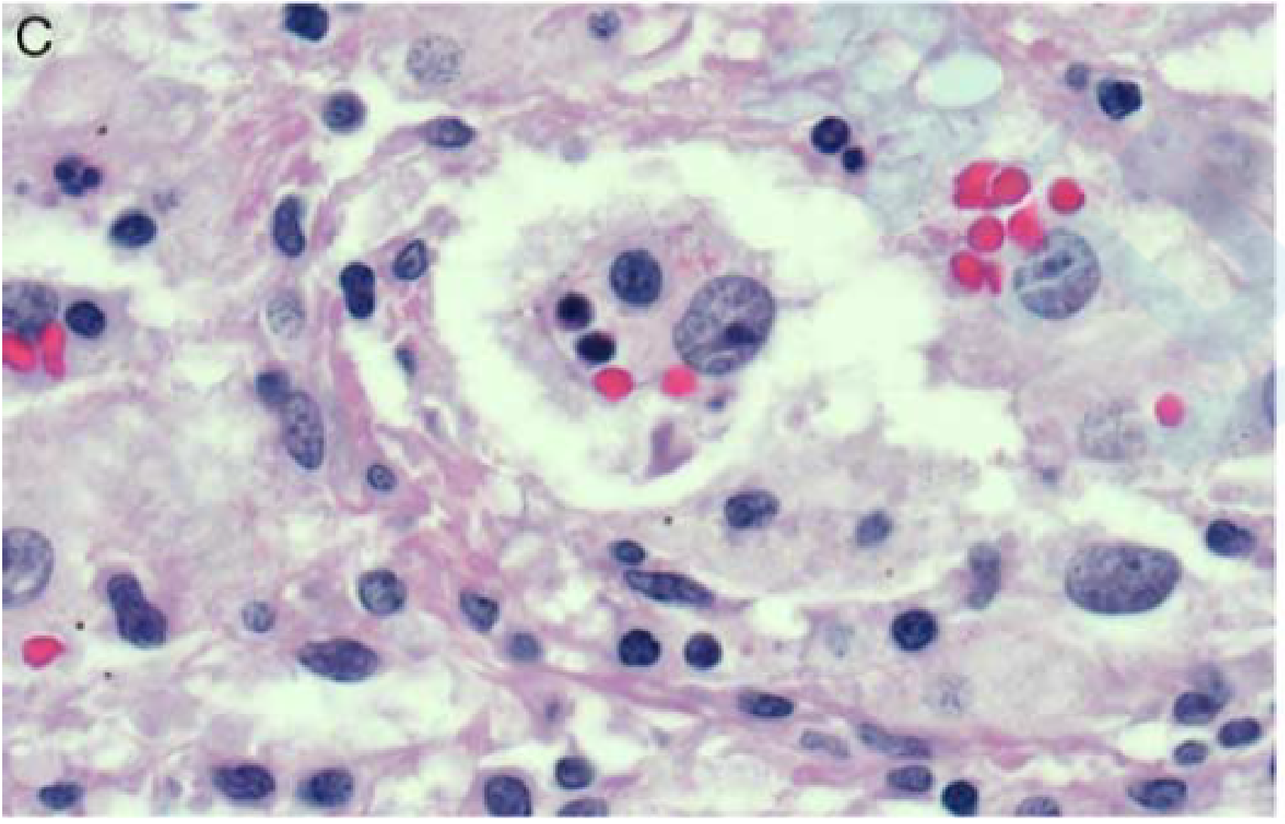
Case 4 of pancreatic RDD: A 69-year-old African American woman





EUS-FNA / air-dried Diff-Quick / Papanicolaou stain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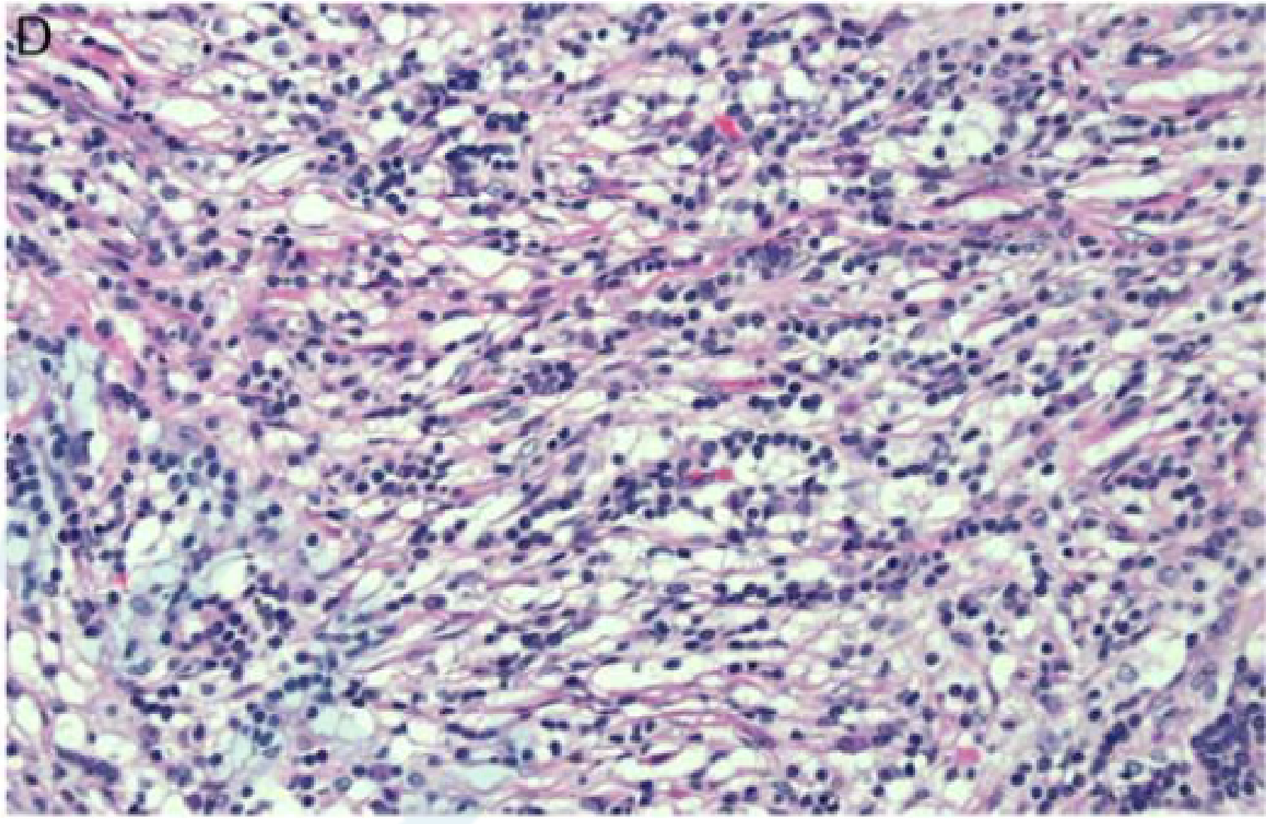
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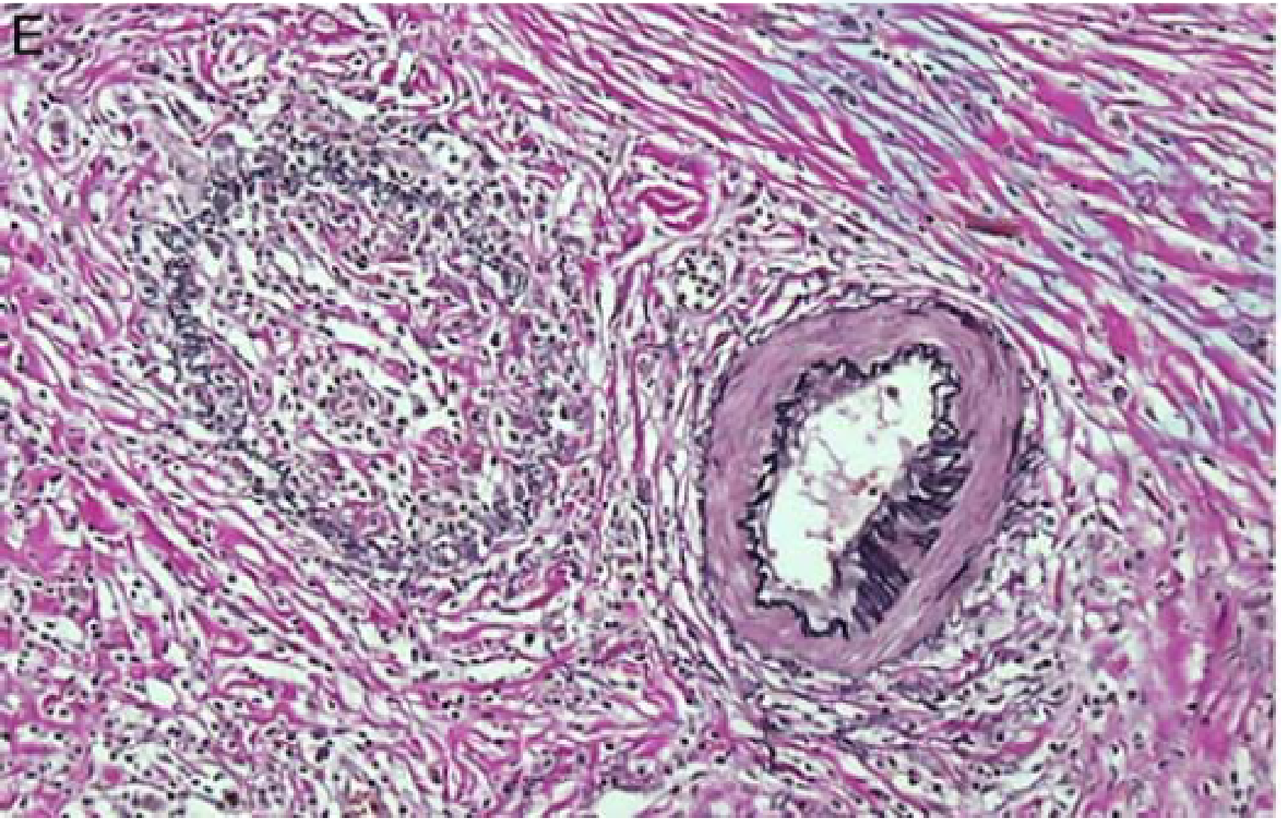
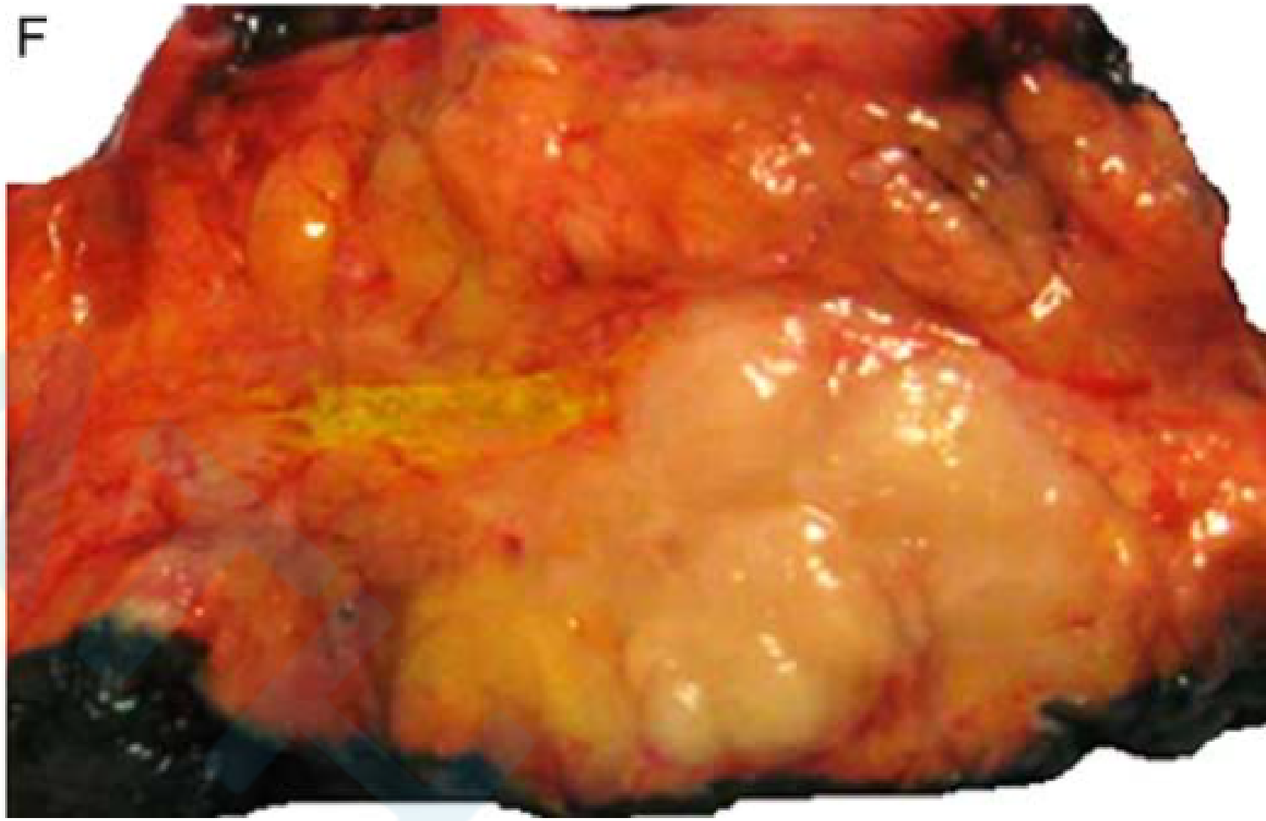
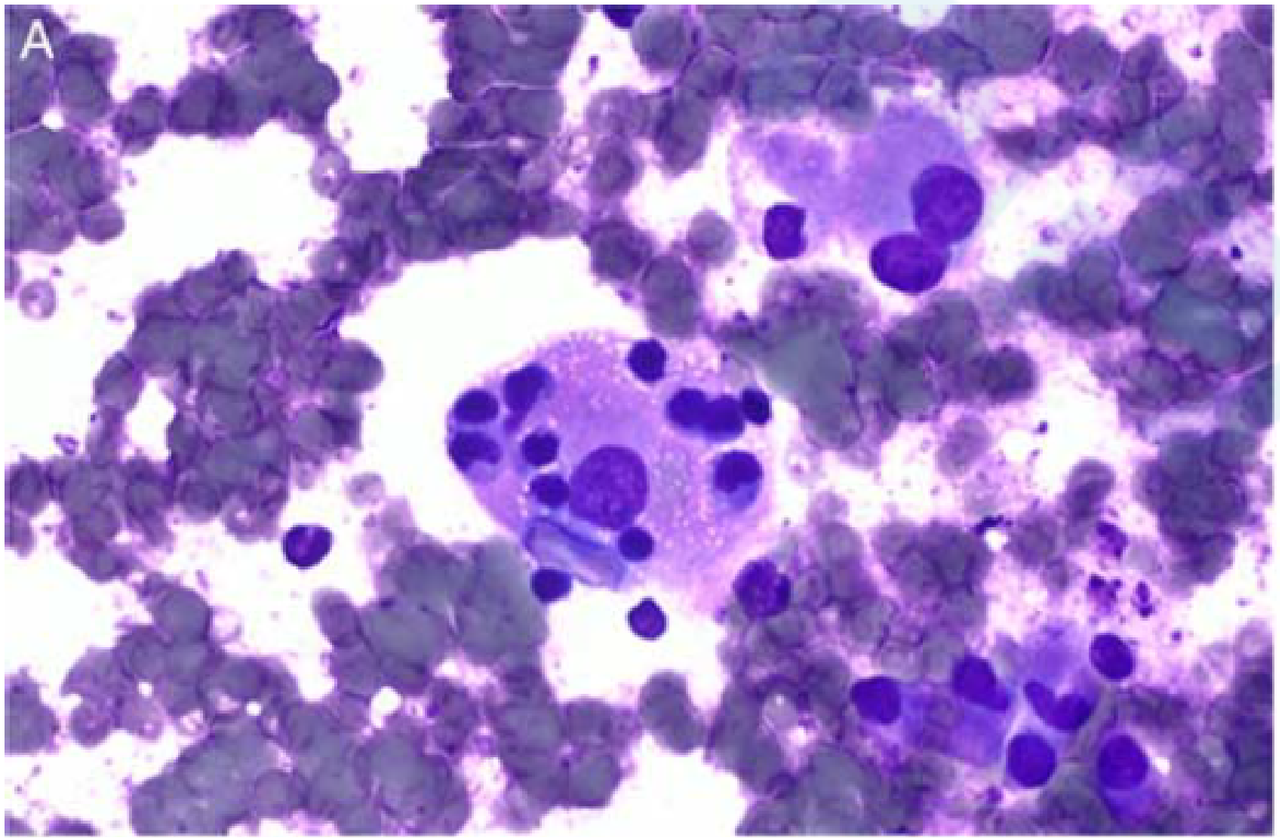
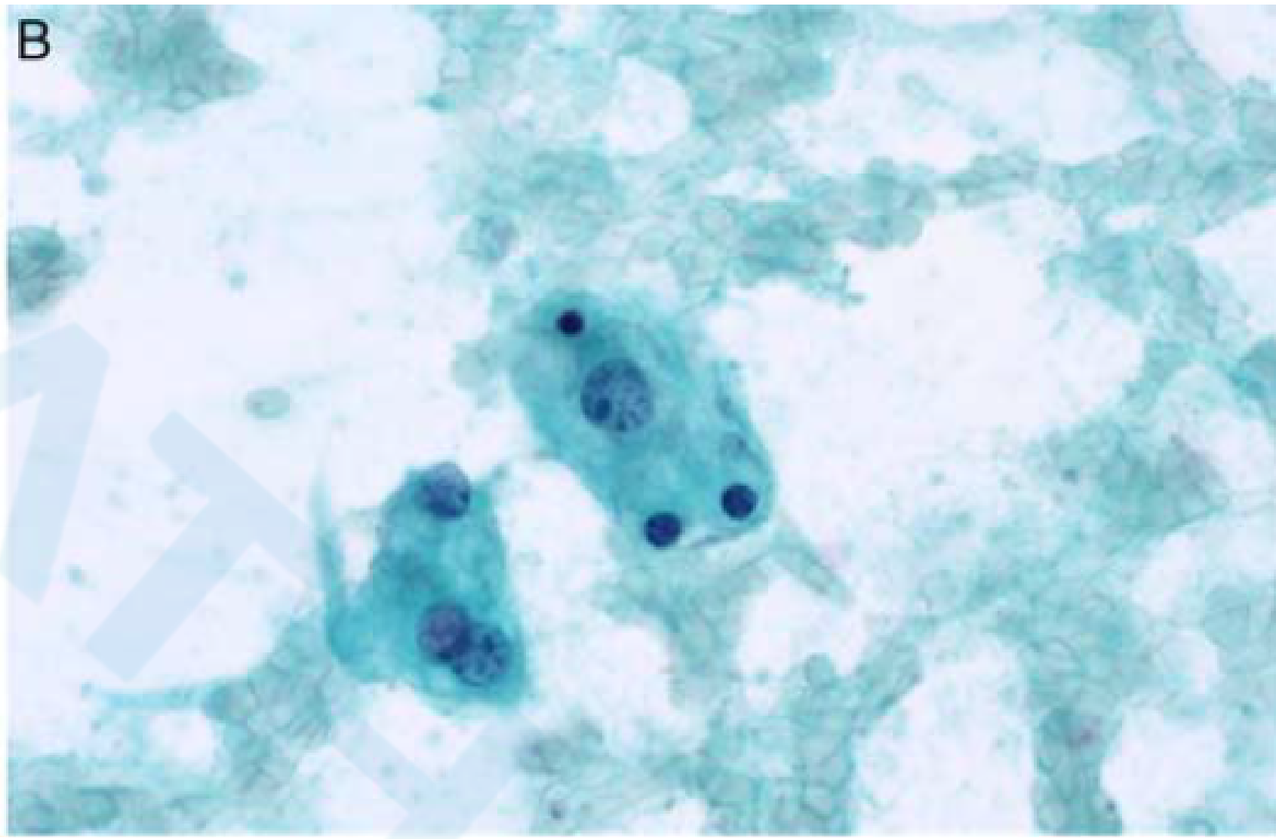




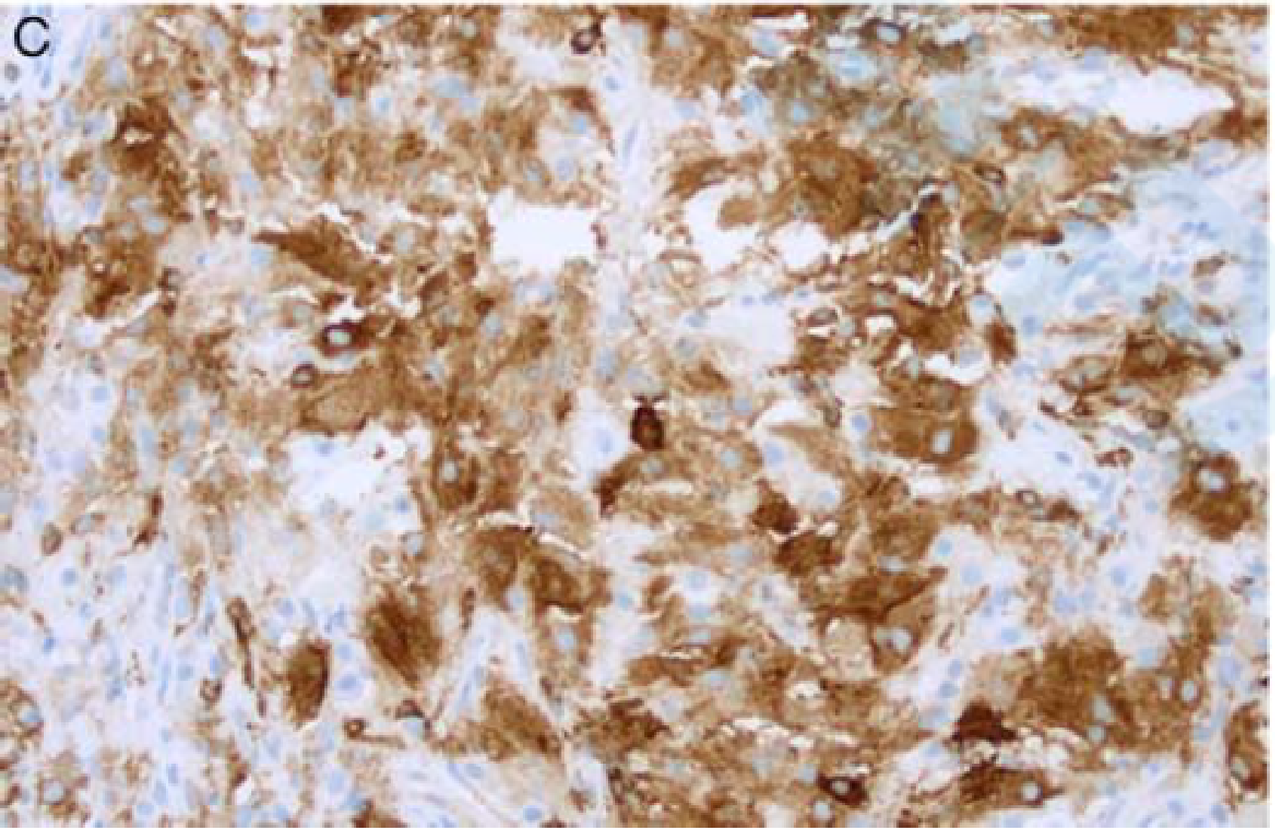
Elastin stain: obliterative periphlebitis

Case 5 of pancreatic RDD: A 75-year-old African American woman

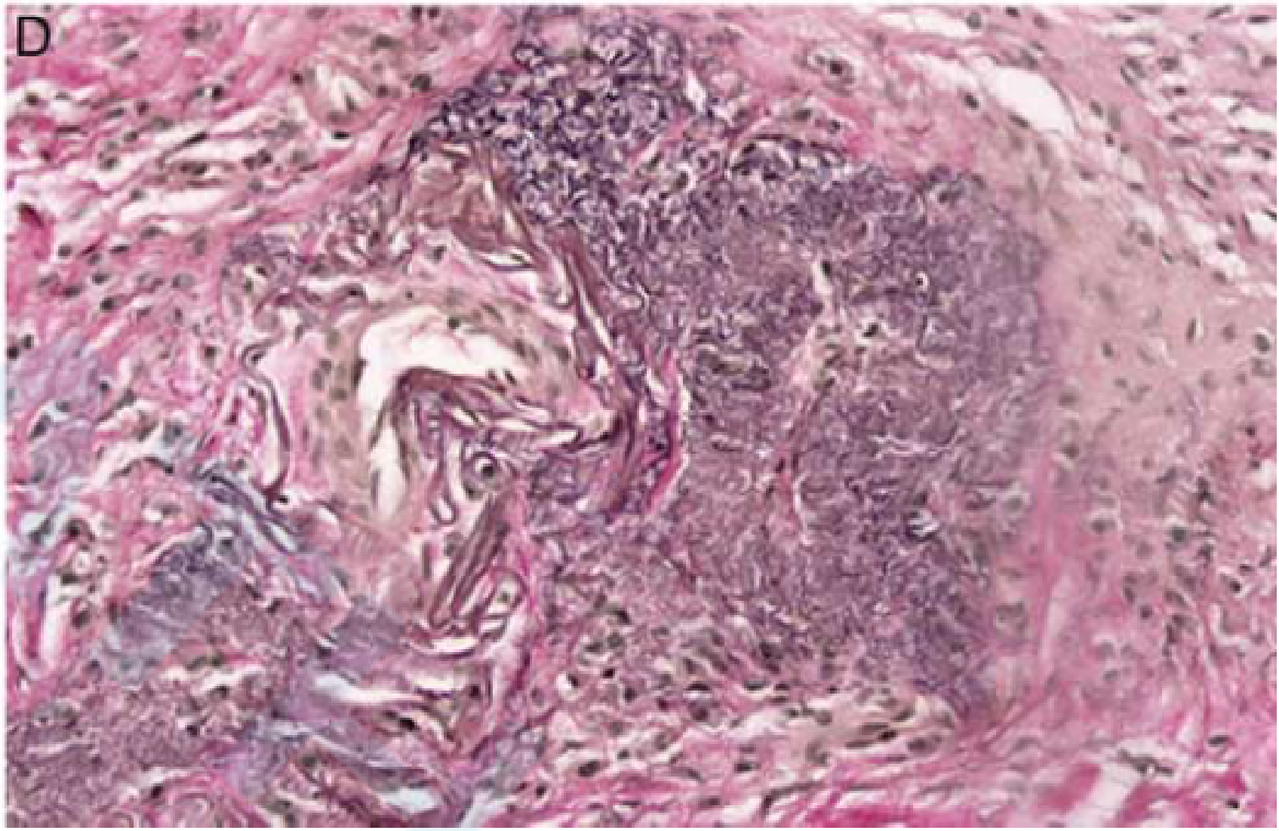




EUS-FNA / Diff Quik / Papanicolaou stains



CD163, S100 (not shown)



Elastin stain: nonobliterative periphlebitis

Case	Dense Lymphoplasmacytic Infiltrate	Fibrosis	Obliterative Phlebitis/Vasculitis
Esquivel et al[2] (same as Lauwers et al[3])	Yes	Yes	No
Zivin et al[4]	NA	Yes	NA
Romero Arenas et al[6]	NA	NA	NA
Podberezin et al[5]	Yes	Yes	NA
1	Yes	Focal storiform	Yes
2	Yes	Extensive storiform	No
3	Yes	Storiform	Yes
4	Yes	Storiform	Yes
5 (same as Smith et al[7])	Yes	Storiform	No

54% (n= 7) had 2 major histologic features
13% (n= 3) had 3

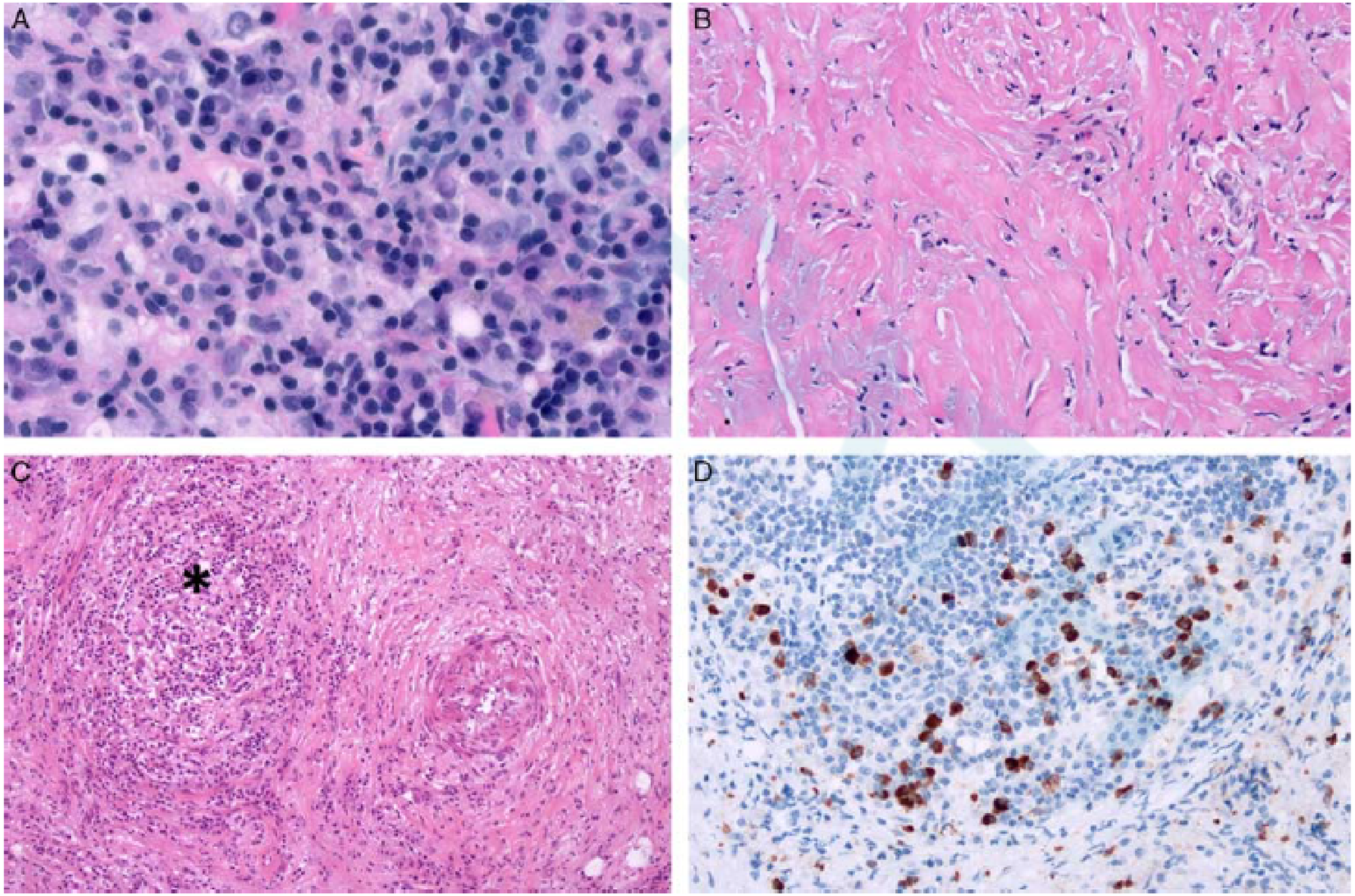
Case	Increased Eosinophils	IgG4/HPF	Treatment	Spindled Histiocytes	Recurrence
Esquivel et al[2] (same as Lauwers et al[3])	NA	NA	Surgical	Yes	No
Zivin et al[4]	NA	Normal serum IgG4	Surgical	Yes	No
Romero Arenas et al[6]	NA	NC	Surgical	Yes	No
Podberezin et al[5]	Rare	NA	Surgical	Yes	No*
1	No	2	Surgical	Yes	No
2	No	10	Surgical	Yes	No
3	No	Rare cells	Surgical	Yes	NA
4	No	11	Surgical	Yes	No
5 (same as Smith et al[7])	No	5	Radiation	Yes	No

- Nonpancreatic Extranodal RDD (13)

TABLE 2. Clinical and Pathologic Features of 13 Additional Cases (nonpancreatic) of Extranodal RDD

Case No.	Location	Size (cm)	Age (y)	Sex	Race	Dense Lymphoplasmacytic Infiltrate	Fibrosis	Obliterative Phlebitis/ Vasculitis	Increased Eosinophils	IgG4/ HPF	Treatment	Recurrence
1	Right breast	NA	15	Female	AA	Yes	Yes	No	No	60	Surgical	No
2	Left breast	1.8	35	Female	AA	Yes	Yes	Yes	No	NA	Surgical	No
3	Left breast	NA	52	Female	NA	Yes	Focal storiform	Yes	No	NA	NA	NA
4	Right breast	NA	50	Female	NA	Yes	Yes	No	No	NA	NA	NA
5	Pararenal	5	48	Female	AA	Yes	Storiform	No	No	12	Azothiaprine	No
6	Right perinephric soft tissue	NA	60	Male	NA	Yes	No	No	No	9	NA	NA
7	Retroperitoneum	8	52	Female	AA	Yes	Focal storiform	Yes	No	2	Surgical	No
8	Retroperitoneum	NA	53	Male	NA	Yes	Focal storiform	No	No	NA	NA	NA
9	Retroperitoneum	NA	61	Male	NA	Yes	Yes	No	No	NA	NA	NA
10	Retroperitoneum	NA	68	Male	NA	Yes	No	No	No	NA	NA	NA
11	Retroperitoneum	NA	42	Male	NA	Yes	Storiform	Yes	No	NA	NA	NA
12	Sigmoid mesentery	NA	71	Female	NA	Yes	Focal storiform	No	No	NA	NA	NA
13	Right upper quadrant abdomen	NA	32	Female	NA	Yes	Yes	No	No	1	NA	NA
Total				8 female/ 5 male	4 AA	13/13 (100%)	Any: 11/ 13 (85%), storiform: 6/13 (46%)	4/13 (31%)	0/13	Range: 1-60		

Features of IRD in other cases of extranodal RDD



Increased IgG4+ plasma cells were present in 2 cases with up to 60/HPF

DISCUSSION

- Numerous cases showing RDD with positive IgG4 plasma cells and overlapping histologic features of IRD

Study	Cases	Location	Diagnosis	IgG4 /HPF	IgG4 ratio	Histologic features	Raf	Conclusion
1	10	cutaneous	RDD	21-204	34%	F&L	Kuo, 2009	RDD may belong in IRD
2	1	Parotid gland	RDD	121	33.4%	F&L	Chen, 2011	suggested a link between RDD and IRD
3	4	lung	RDD	increased		F&L F&L F&L F&L&OP	Roberts SS, 2010 de Jong WK, 2012 El-Kersh K, 2013 Hasegawa M, 2017	a possible relationship between RDD and IRD
4	1	GI	RDD	122	>40%	F&L	Wimmer DB, 2013	
5	4	breast	RDD	increased	increased	L&OP(2)	Liu M, 2018	
6	1	breast	RDD	increased	increased	L&OP	Wang Q, 2015	

- Two larger studies have been done investigating the possible link between 2 entities

Study	Cases	Location	Diagnosis	IgG4 /HPF	IgG4 ratio	Histologic features	Raf	Conclusion
1	15(26)	LN Estranodal (testes, breast, left atrium, colon)	RDD	>30 (46.2%)	>40% (30%)	F(30%) L	Zhang, 2013	There may be some overlap in these 2 disease processes
2	29(32)	13 LN 19 extranodal (skin, soft tissue)	RDD	3 cases		L	Liu, 2013	RDD does not belong to IRD although increased IgG4 plasma cells. Increased plasma cells is most likely due to a T-cell–mediated response and point out that other features of IRD were not seen in

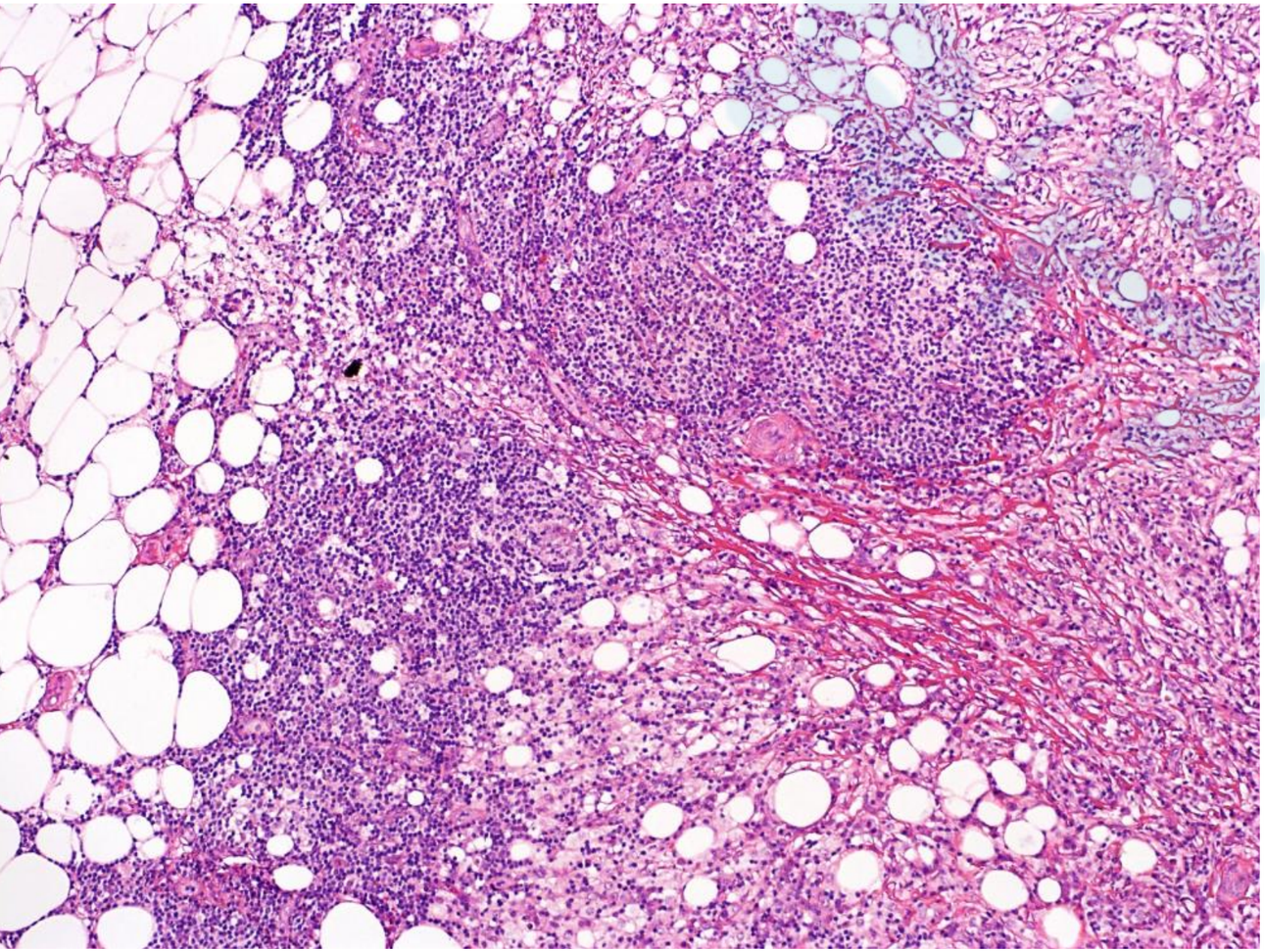
- Overlapping histologic features of RDD and IRD of the pancreas and other deep-seated extranodal sites despite lack of significant IgG4 staining

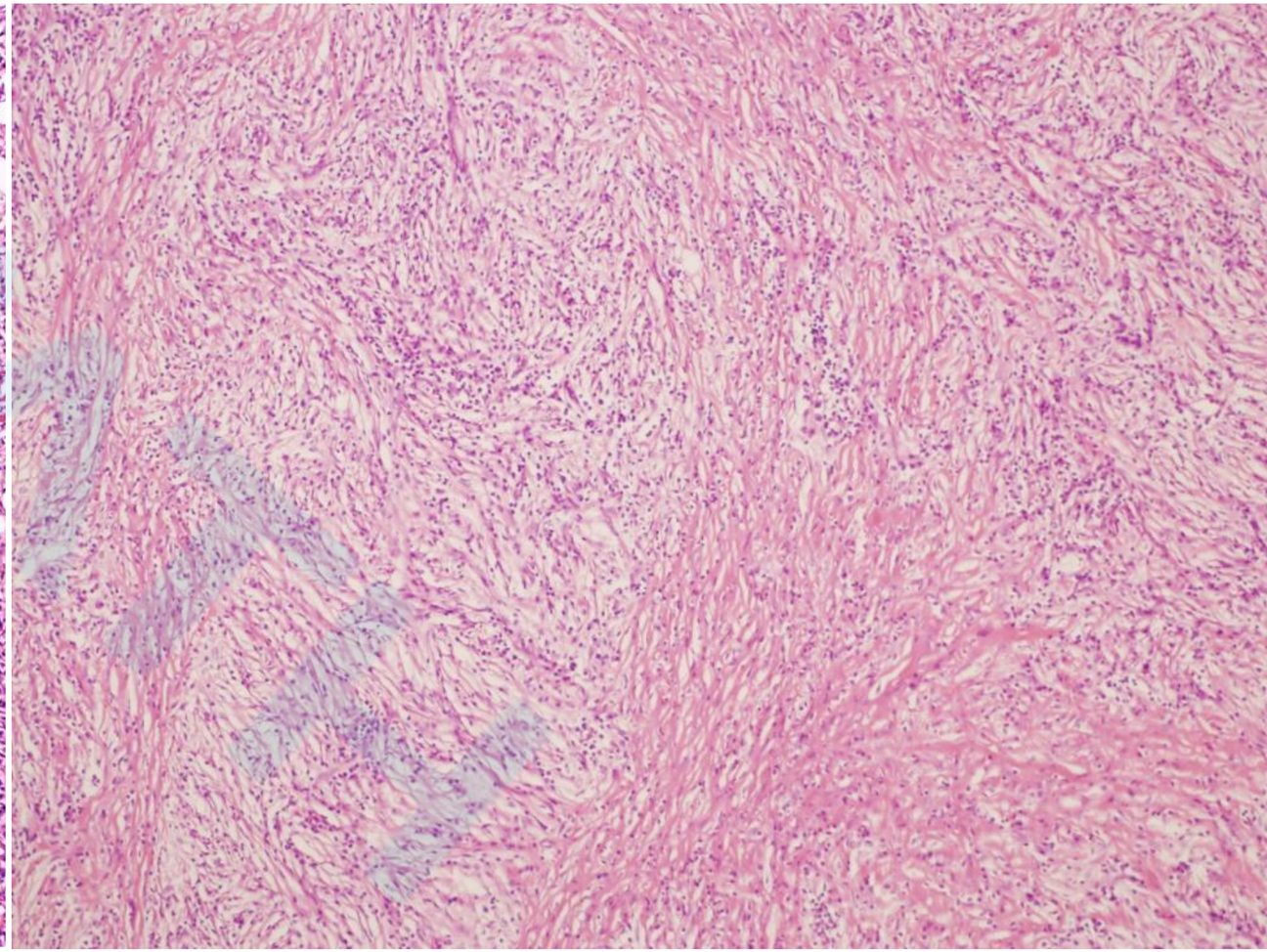
1. Dense lymphoplasmacytic infiltrates
2. Increased fibrosis with storiform fibrosis
3. And/or obliterative phlebitis/vasculitis
4. Spindled and elongated histiocytes（more abundant than classic RDD）

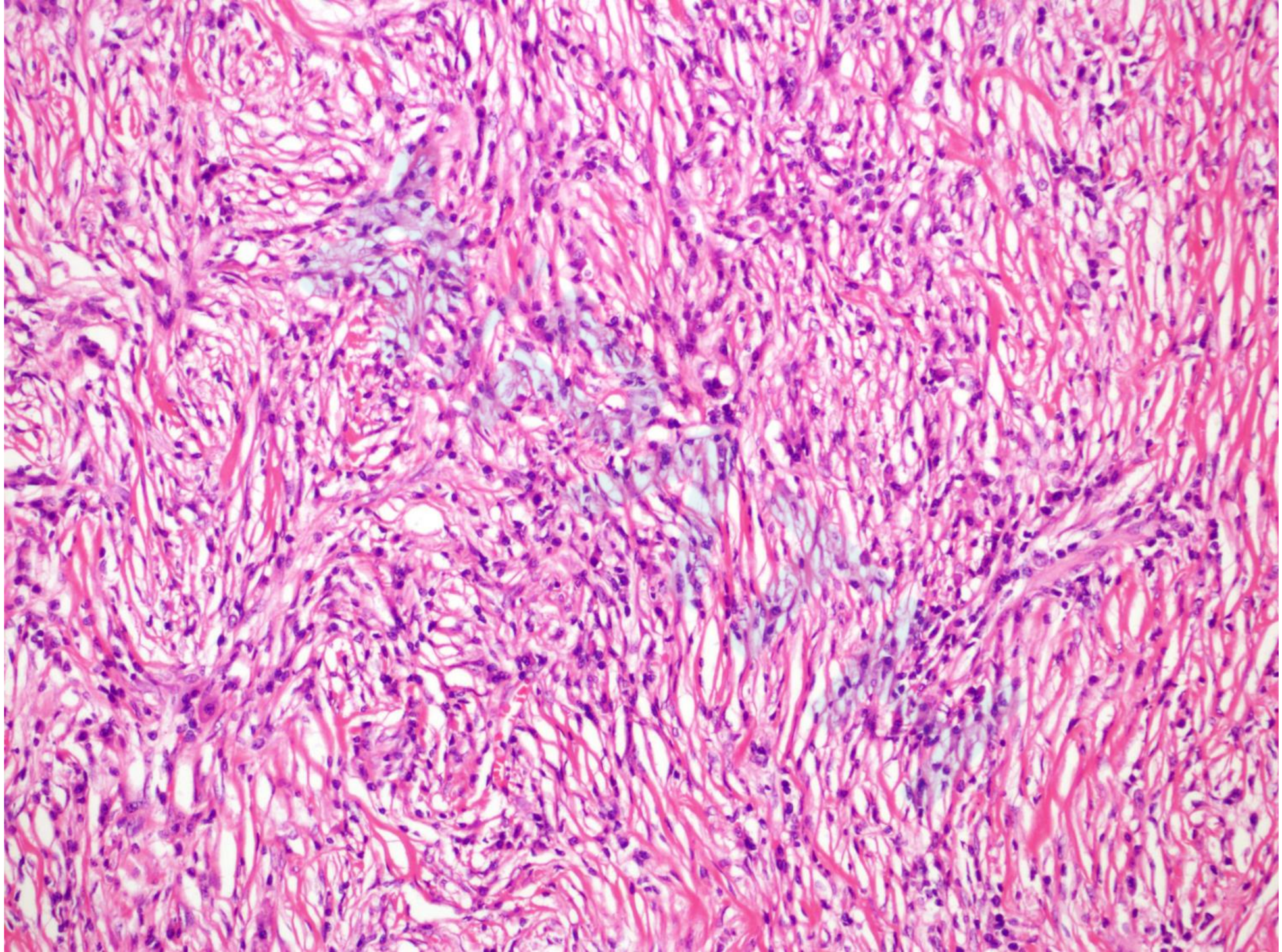
- When evaluating a mass forming lesion of the pancreas, even in the presence of 2 or 3 major histologic criteria for IRD and even with increased numbers of IgG4-positive cells, RDD should be considered in the differential diagnosis and excluded using an IHC stain for **S100**

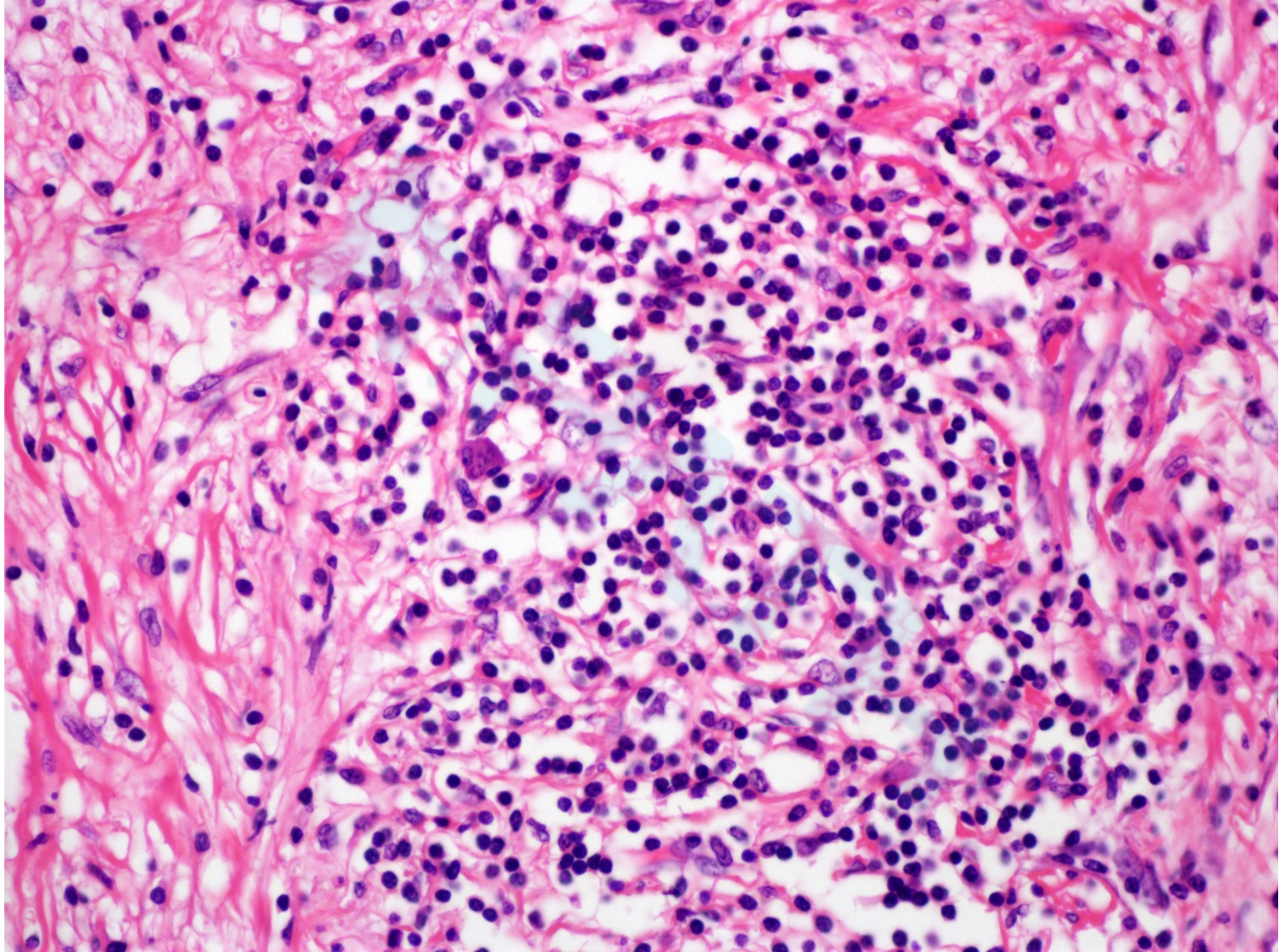
THANK YOU

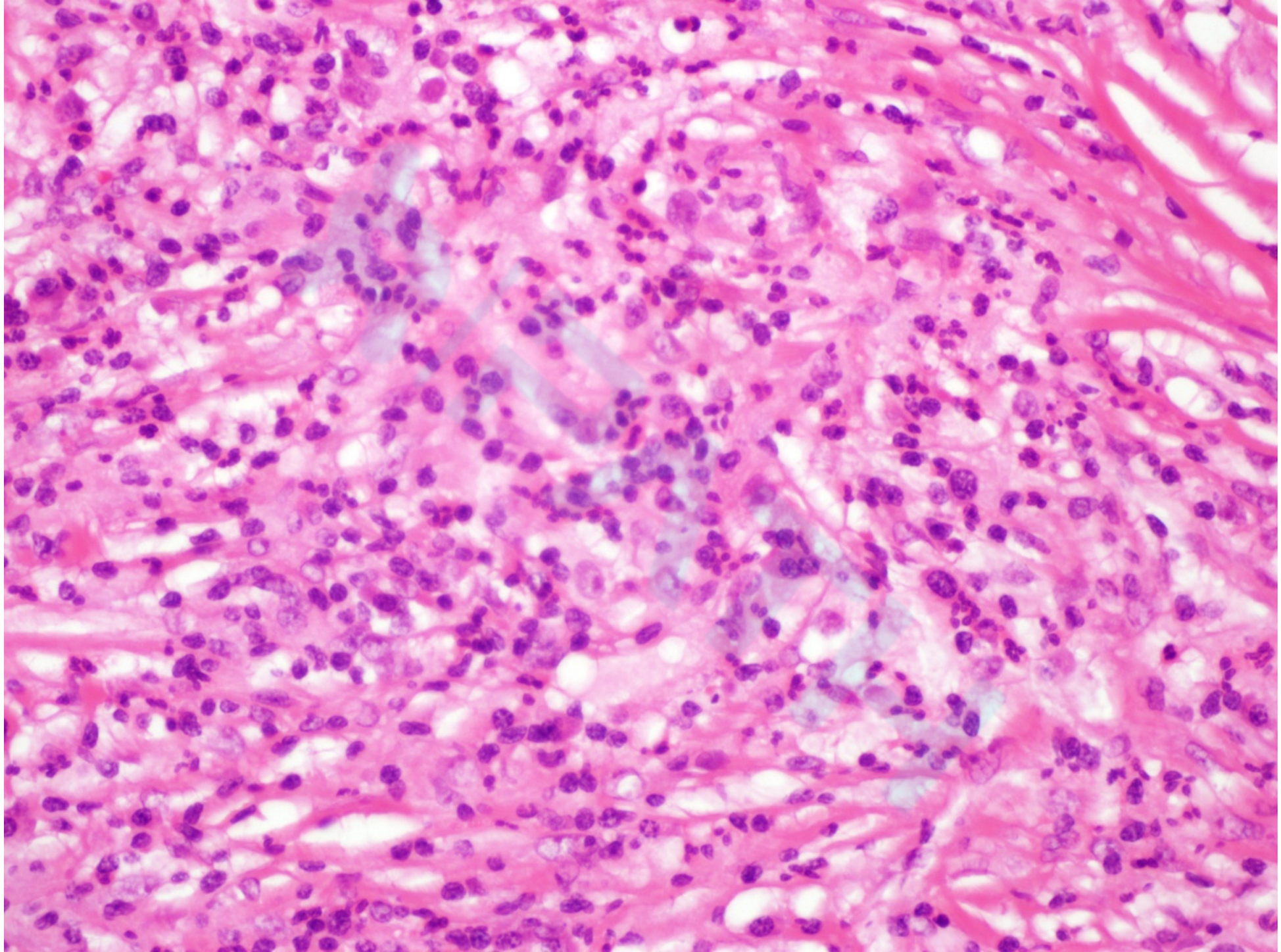
Case 1 M 68 Retroperitoneum mass

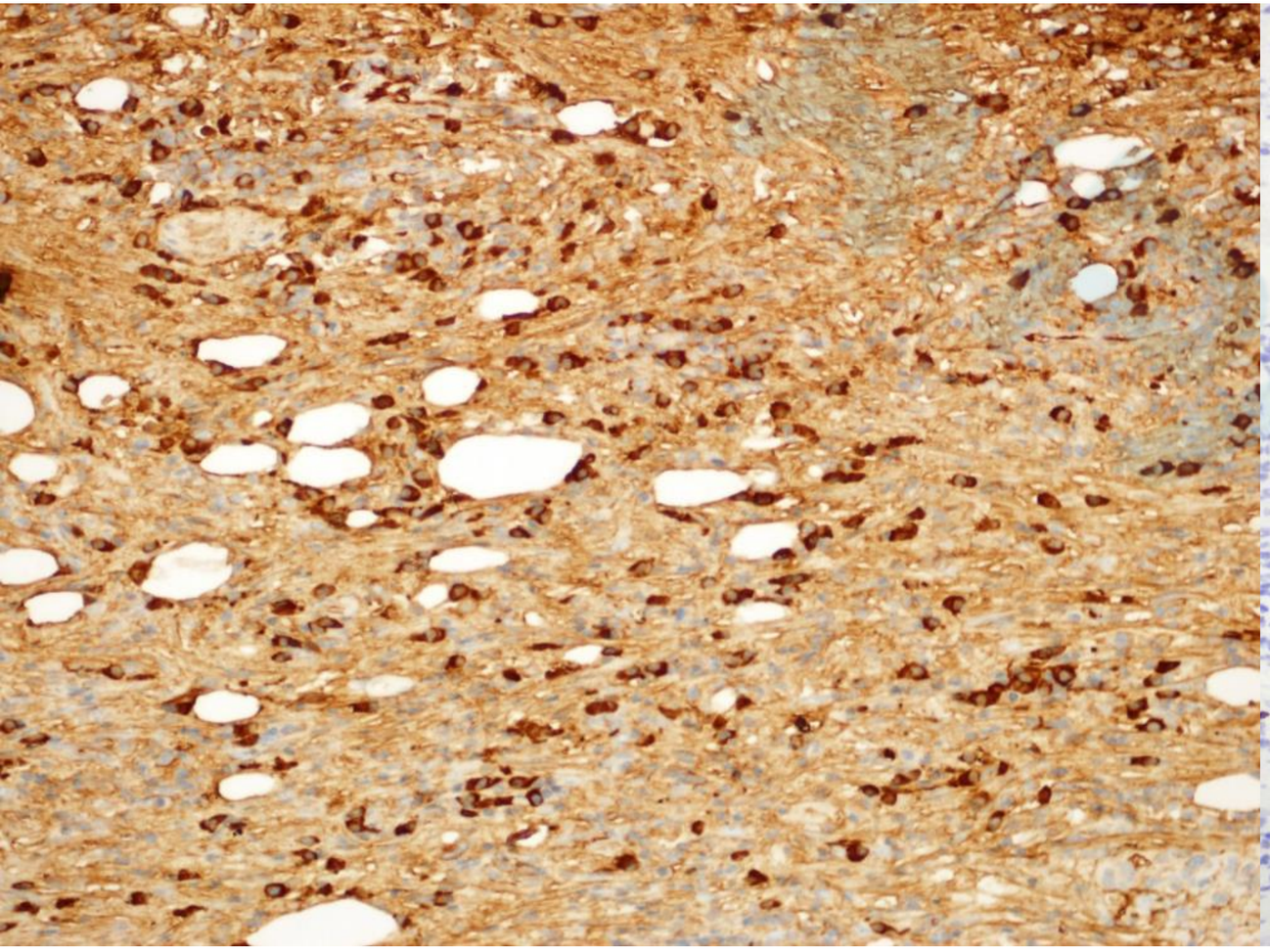




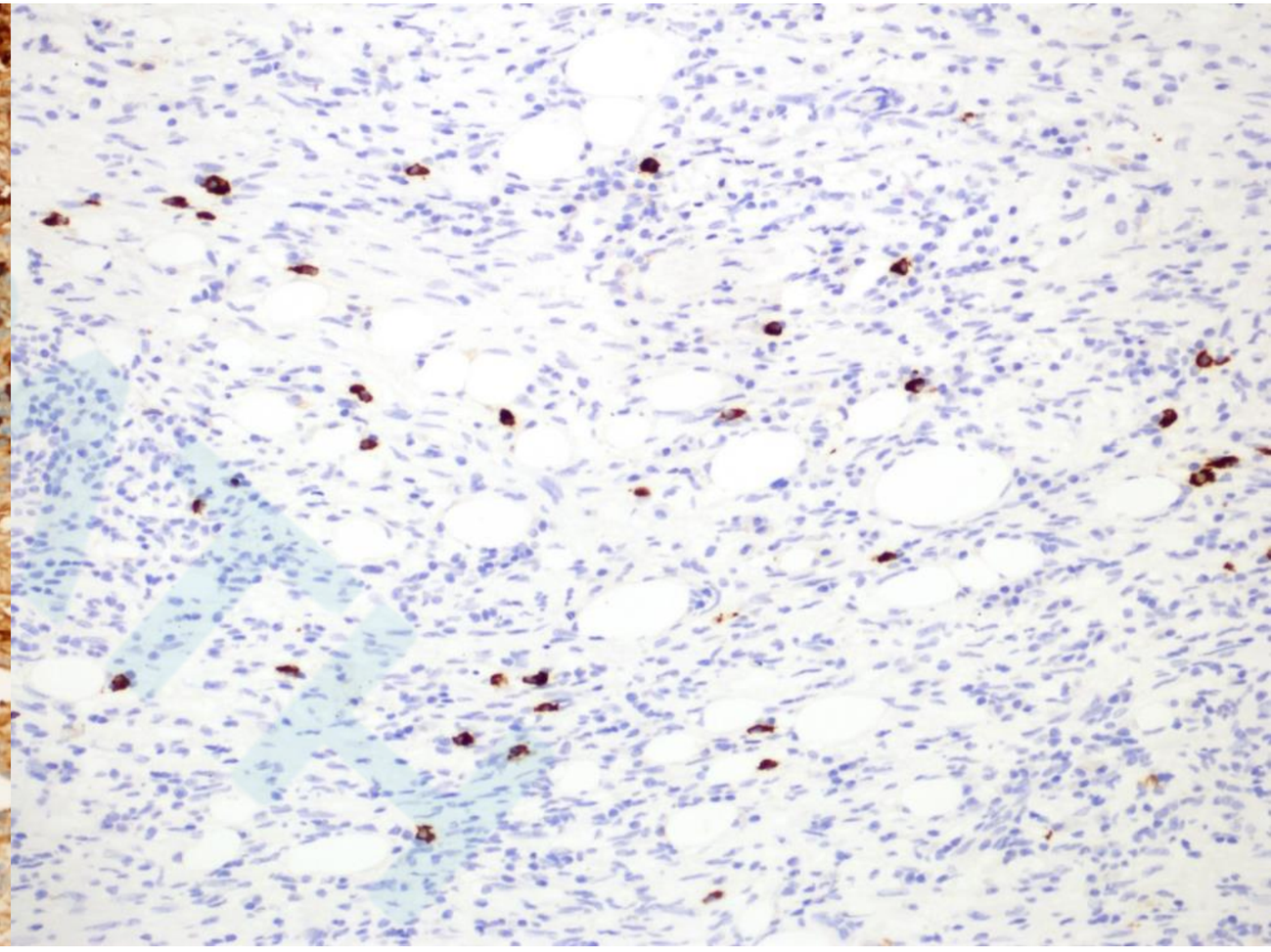




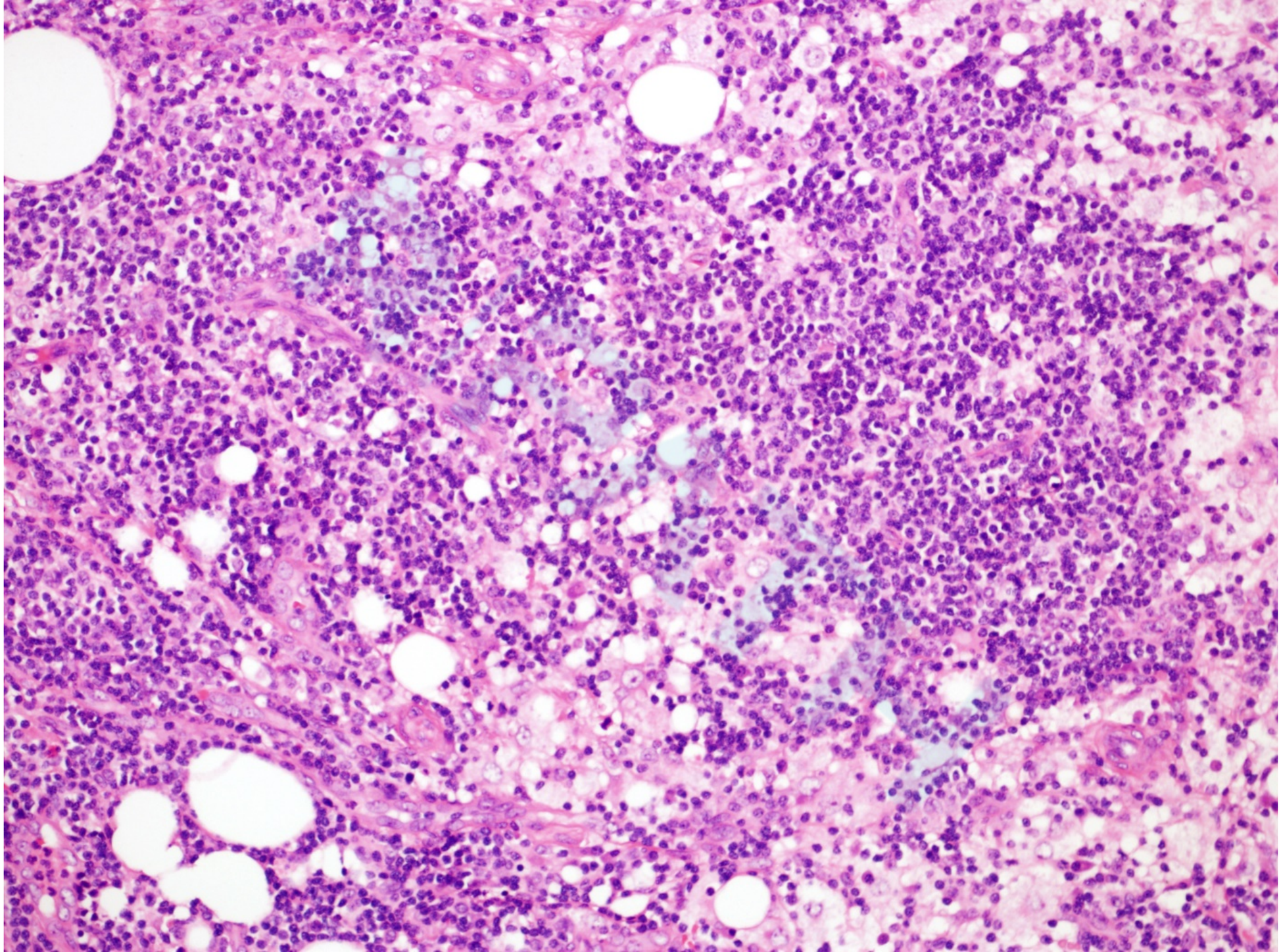


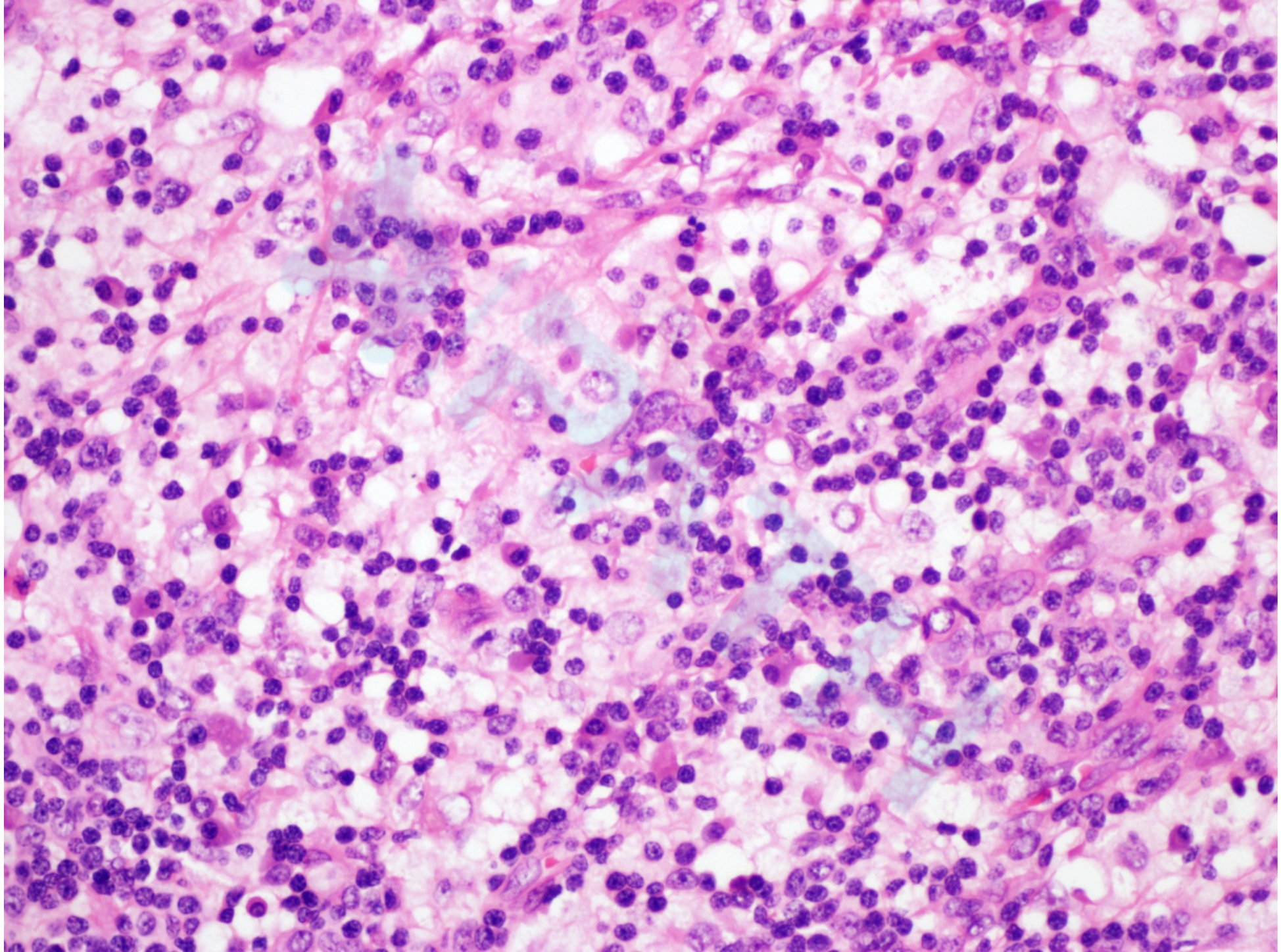


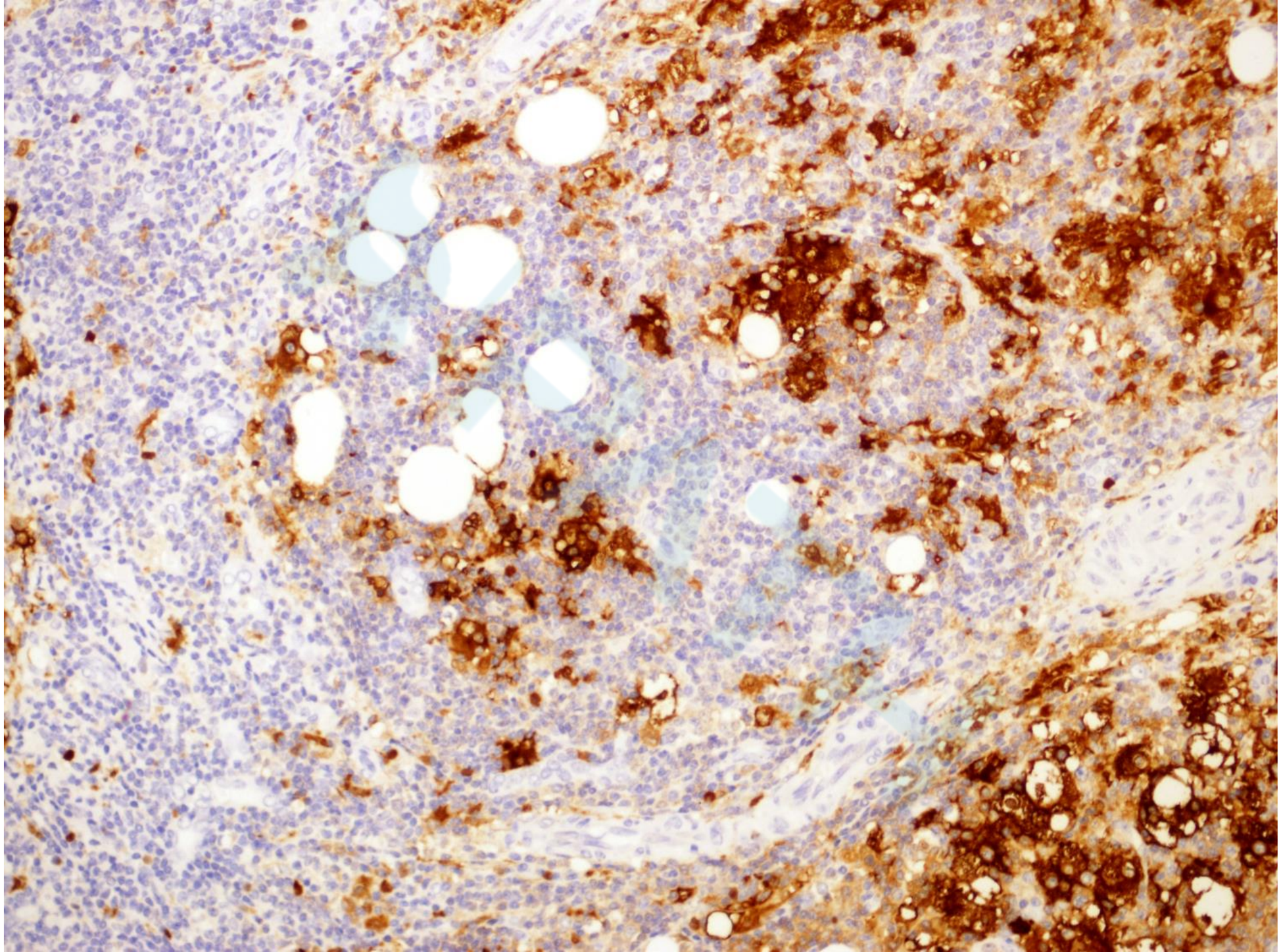
IgG



IgG4

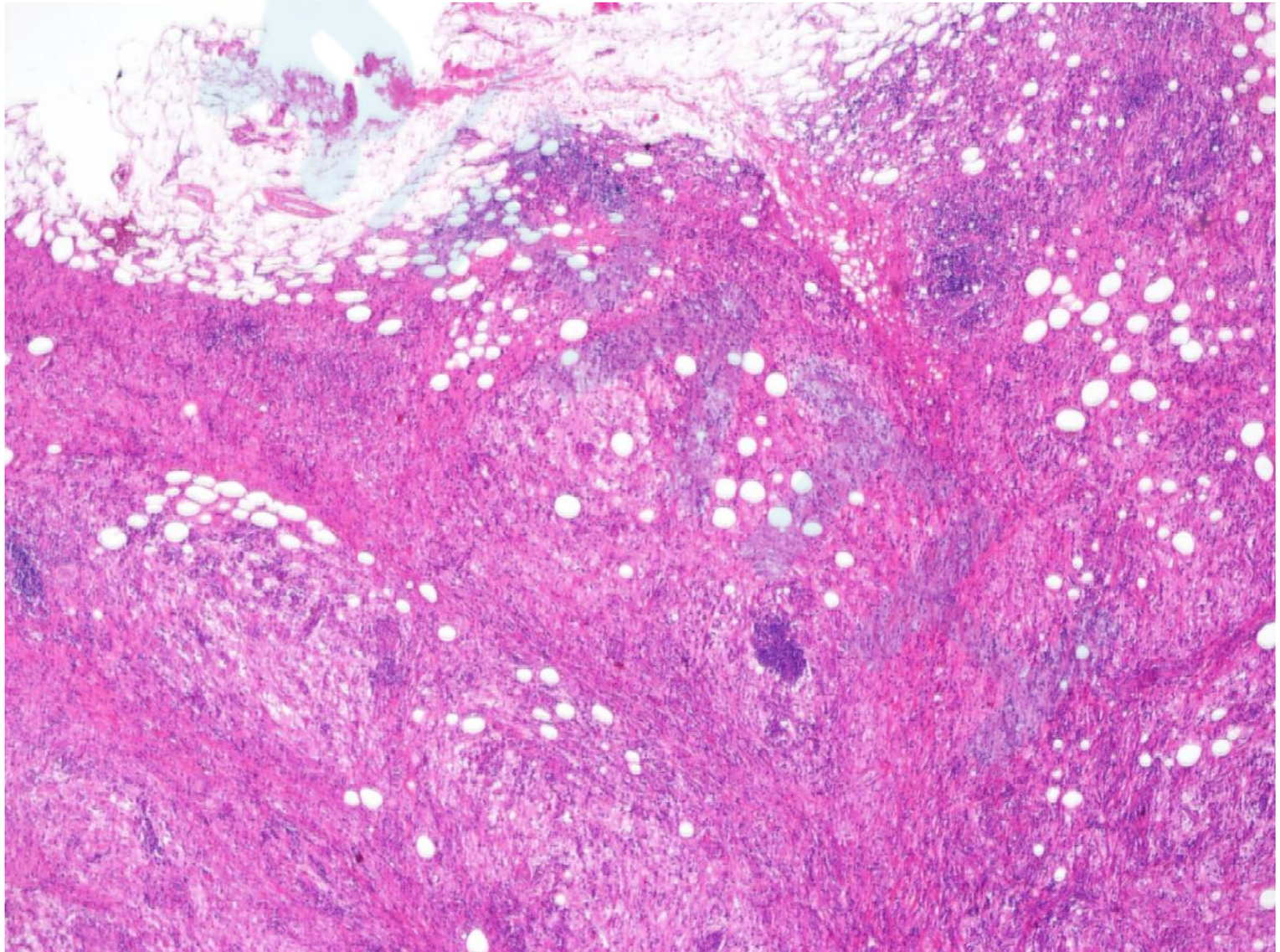


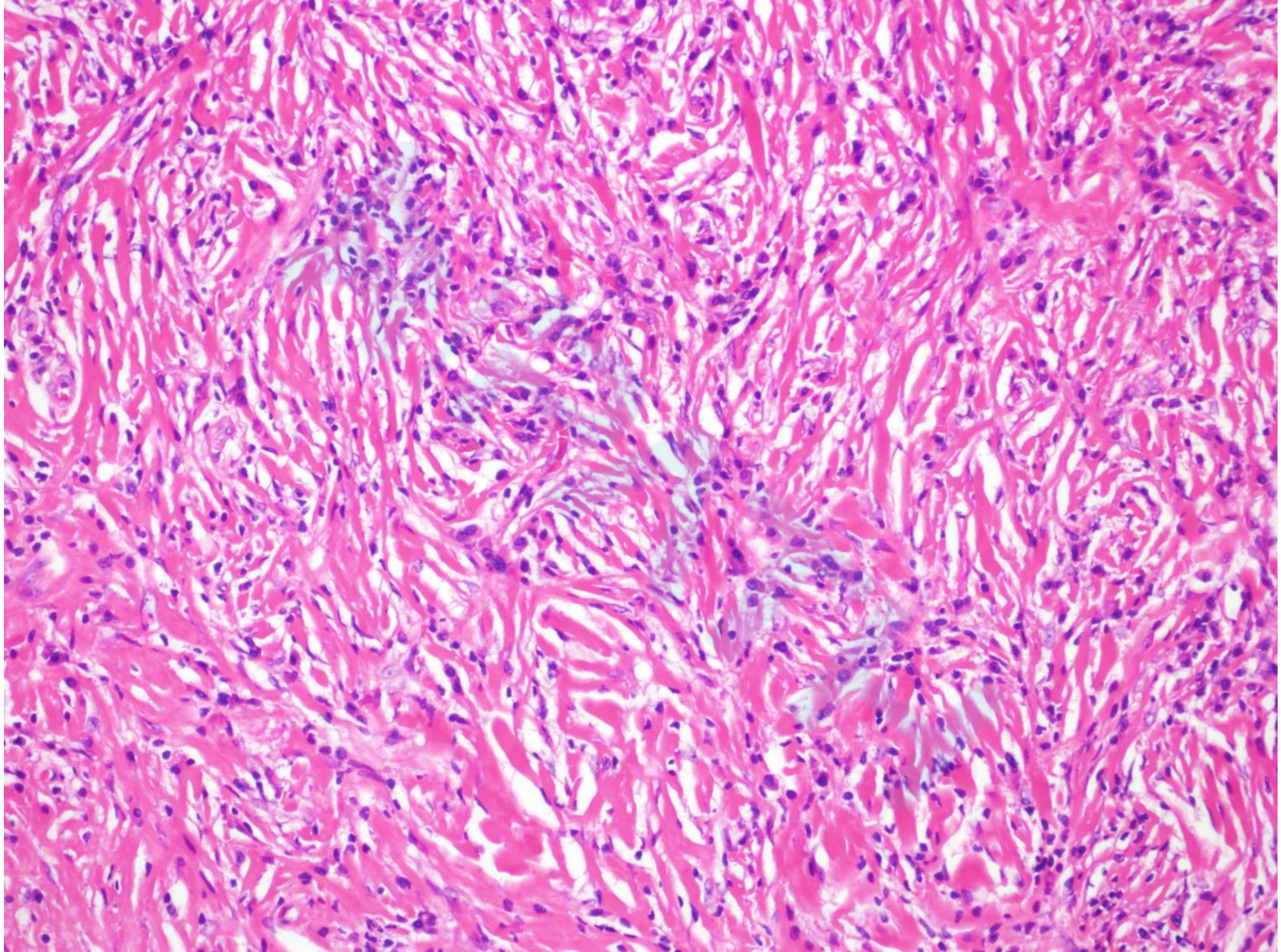


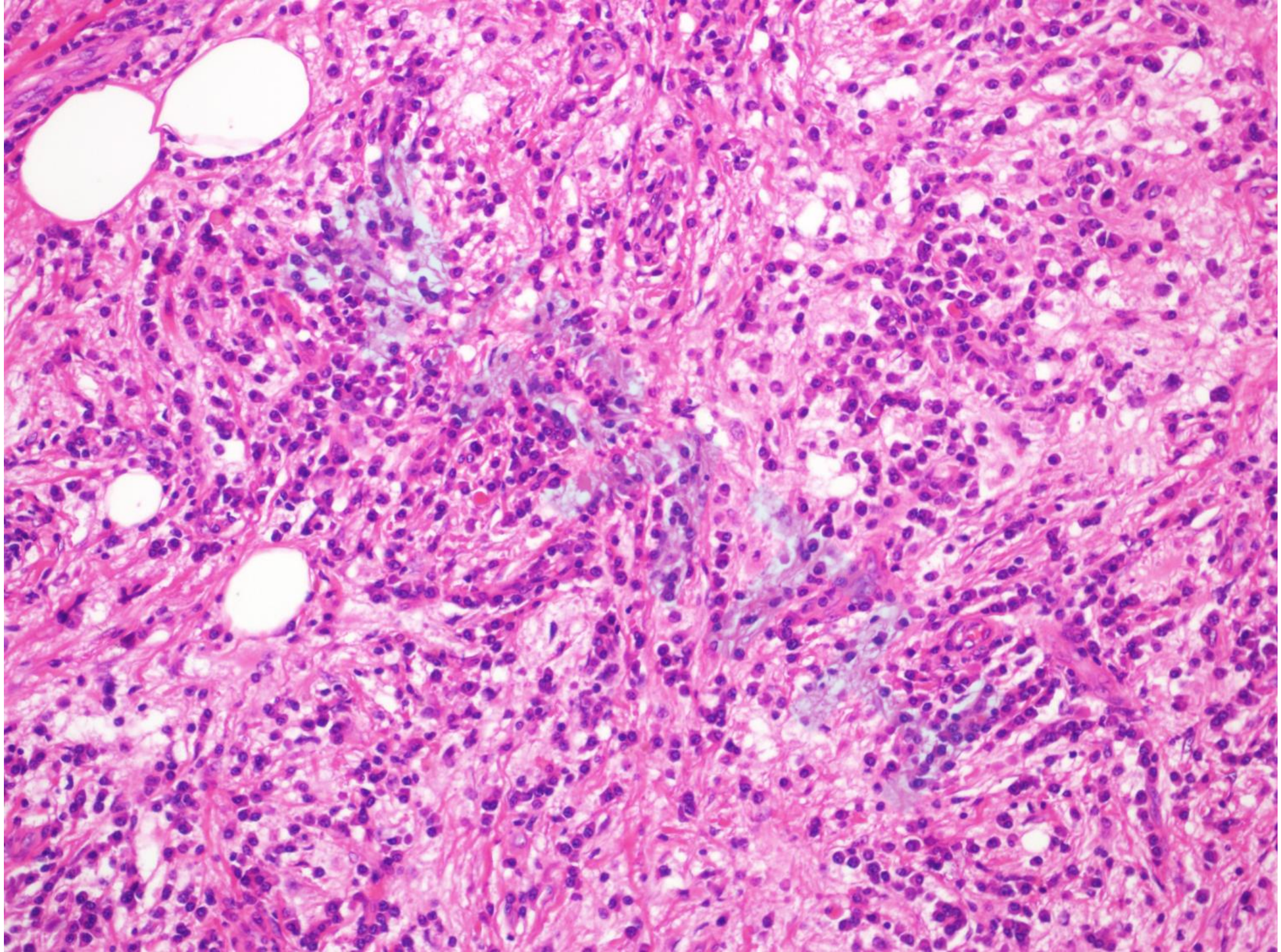


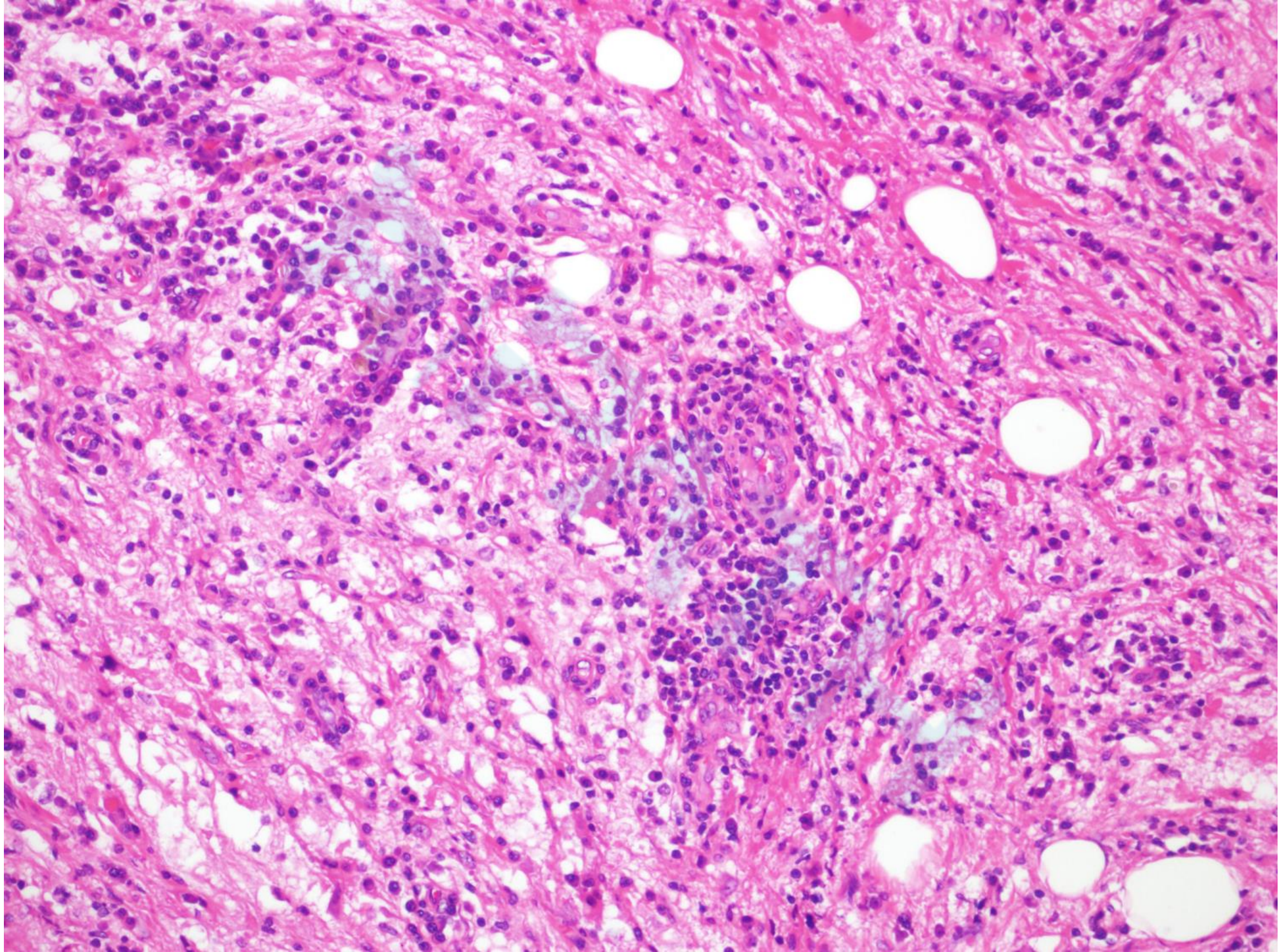
S100

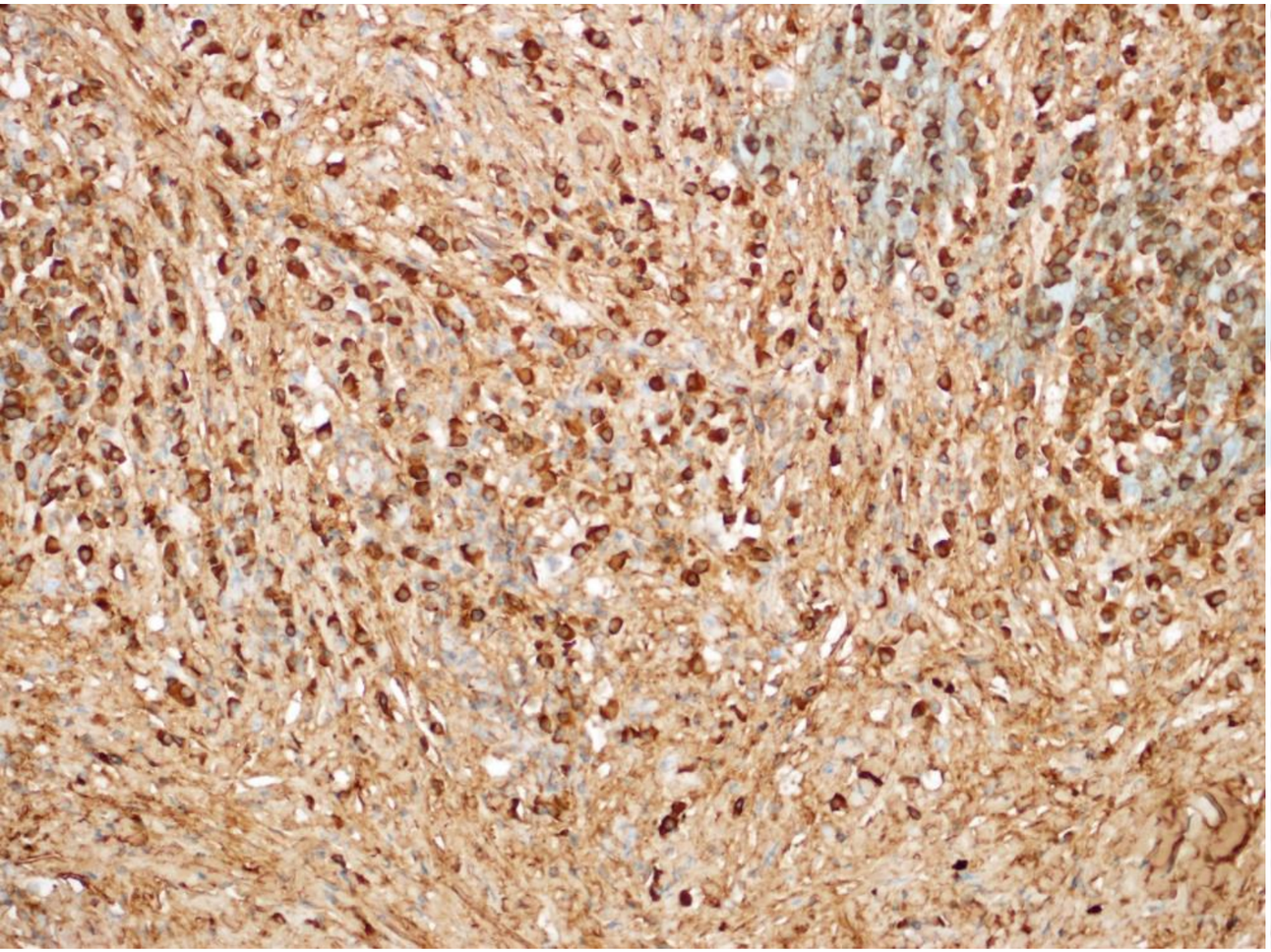
Case 2 M 31 Multiple mass



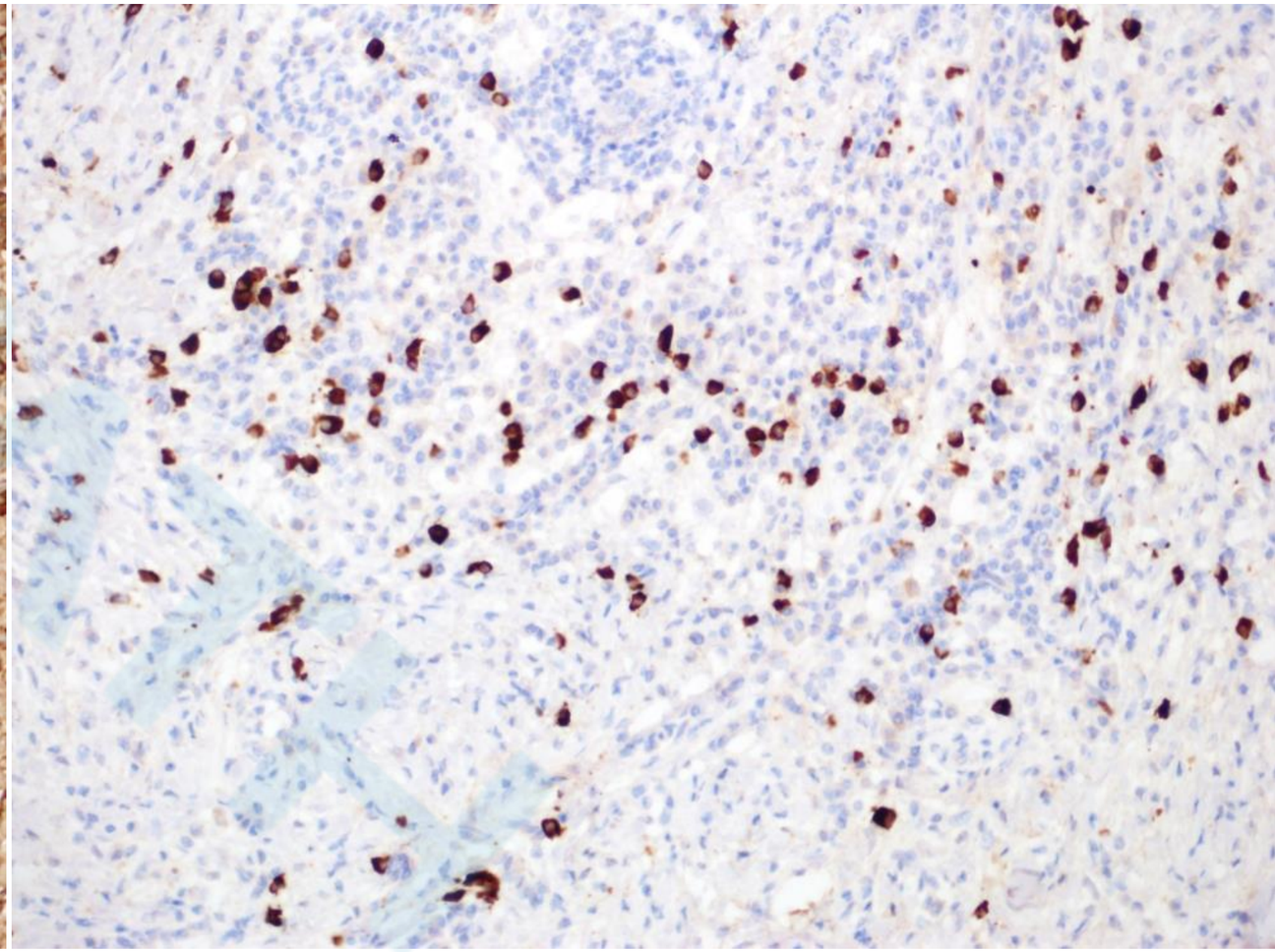




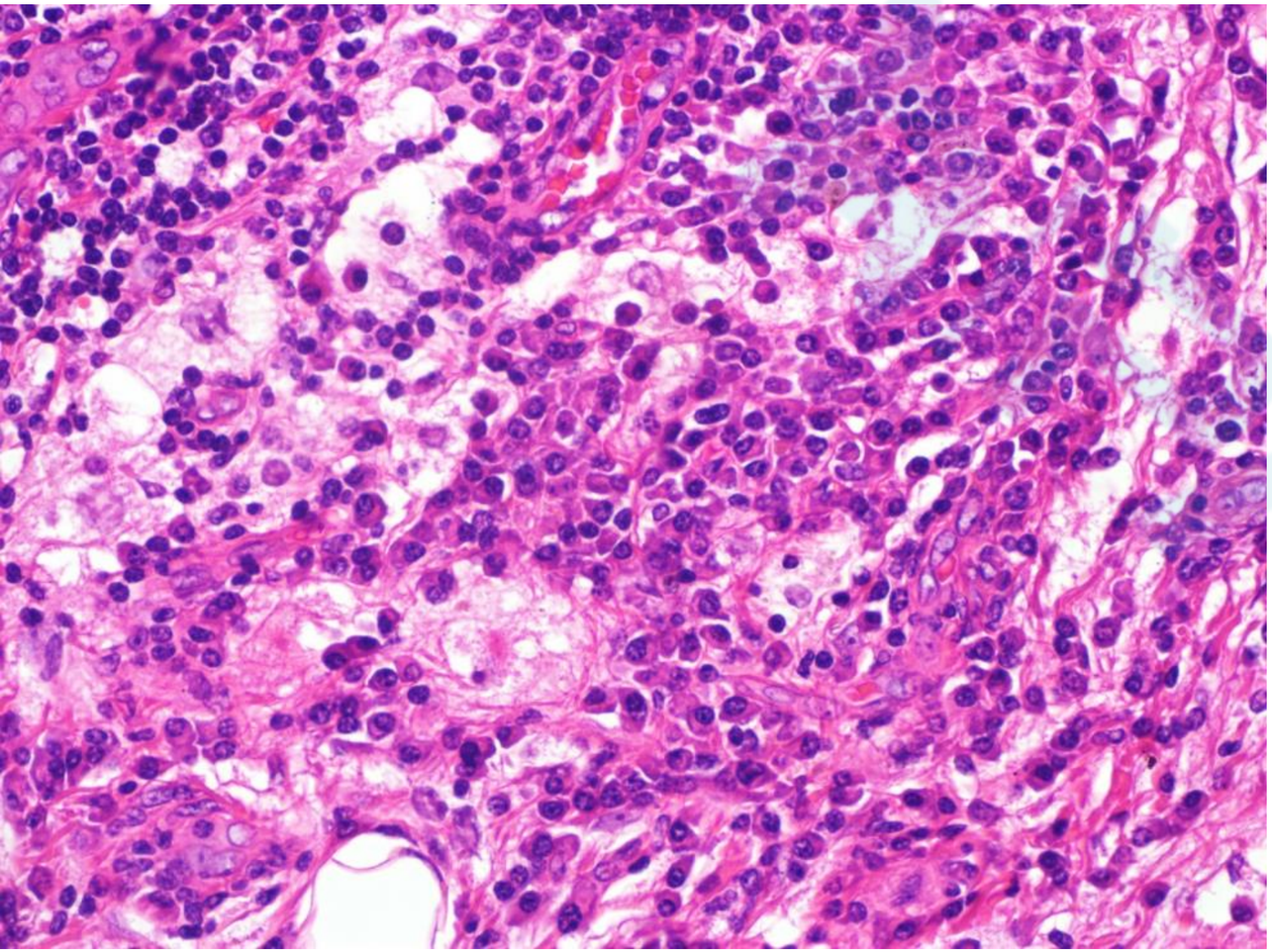


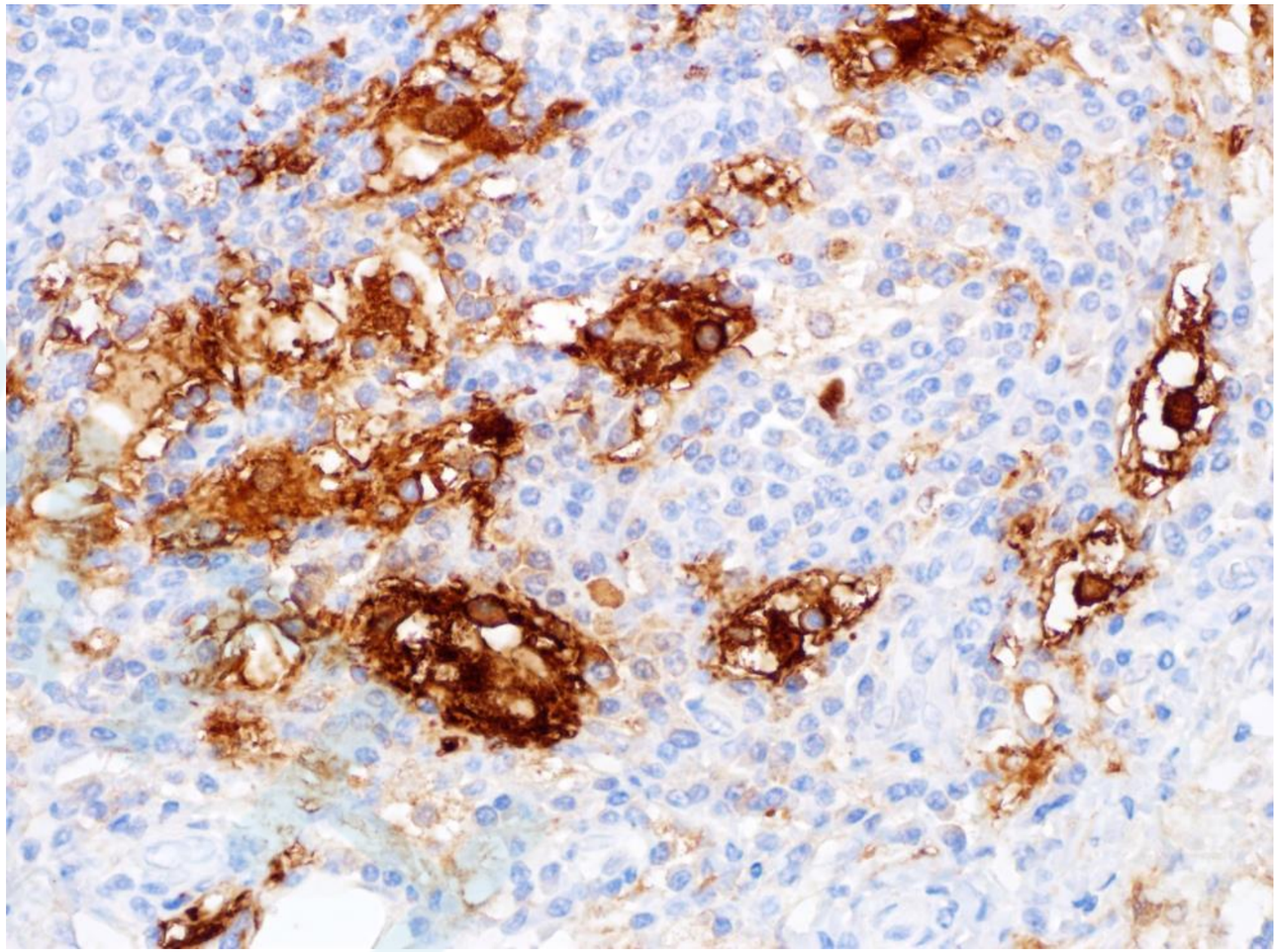


IgG



IgG4





S100