Histology of Refractory Rejection

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REVIEW

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CURRENT OPINION

Distinctive morphological features of antibody-mediated and T-cell-mediated acute rejection in pancreas allograft biopsies

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Purpose of review

Two main histopathological types of acute rejection are recognized in solid organ transplantation: T-cell-mediated rejection (TCMR) and antibody-mediated rejection (AMR). In pancreas allografts the contrasting morphological features of these entities have only recently been described.

Recent findings

Acute TCMR is characterized by active septal infiltrates composed predominantly of T cells and often involving veins (venulitis) and ducts (ductitis). Inflammation of the arterial endothelium (intimal arteritis or endarteritis) may be present. Focal or diffuse acinar inflammation (acinitis) is also typical of TCMR. Acute AMR in contrast, is characterized by predominantly macrophagic (±neutrophilic) inflammation, concentrated in, and around the interacinar microvasculature (interacinar inflammation, capillaritis) and typically shows focal or diffuse C4d staining of the interacinar capillaries. Architectural preservation is common in milder forms of AMR, whereas severe or untreated forms lead to extensive vascular injury and secondary parenchymal hemorrhagic necrosis. These morphological features strongly correlate with the presence of circulating donor-specific antibody (DSA)+.

Table 1. Histological features in stereotypical acute T-cell-mediated rejection and antibody-mediated rejection

	ACMR	AMR
Septal infiltrates	+++	− to +
Eosinophils	+ to +++	− to +
Neutrophils	− to ++	+/− to +++
T-lymphocytes	++ to +++	+/− to +
Macrophages	++	++++
Venulitis	++	−
Ductitis	++	−
Acinar cell injury	+/− to ++	+++
Acinar inflammation	− to +++	+ to +++
Acinitis (mononuclear infiltrates within the basement membrane of individual acini)	+ to +++	− to +/−
Interacinar capillaritis	− to +/−	+ to +++
Intimal arteritis	+	+
Necrotizing vasculitis/ thrombosis	− to +	+++
Confluent hemorrhagic necrosis	− to ++	+++

ACMR, acute T-cell-mediated rejection. Adapted from [18▪▪].

Acute TCMR Banff Grading

(3) Acute TCMR
  (a) Grade I/mild acute TCMR
    (i) Active septal inflammation (activated, blastic lymphocytes, ±eosinophils) involving septal structures: venulitis (subendothelial accumulation of inflammatory cells and endothelial damage in septal veins), ductitis (epithelial inflammation and damage of ducts) and/or focal acinar inflammation. No more than two inflammatory foci per lobule with absent or minimal acinar cell injury.
  (b) Grade II/moderate–acute TCMR (requires differentiation from AMR)
    (i) Multifocal (but not confluent or diffuse) acinar inflammation (≥3 foci per lobule) with spotty (individual) acinar cell injury and drop-out and/or mild-intimal arteritis (with minimal, <25% luminal compromise).
  (c) Grade III/severe–acute TCMR (requires differentiation from AMR)
    (i) Diffuse, (widespread, extensive) acinar inflammation with focal or diffuse multicellular/confluent acinar cell necrosis;
    (ii) And/or moderate or severe intimal arteritis, more than 25% luminal compromise;
    (iii) And/or transmural inflammation: necrotizing arteritis.

Septal

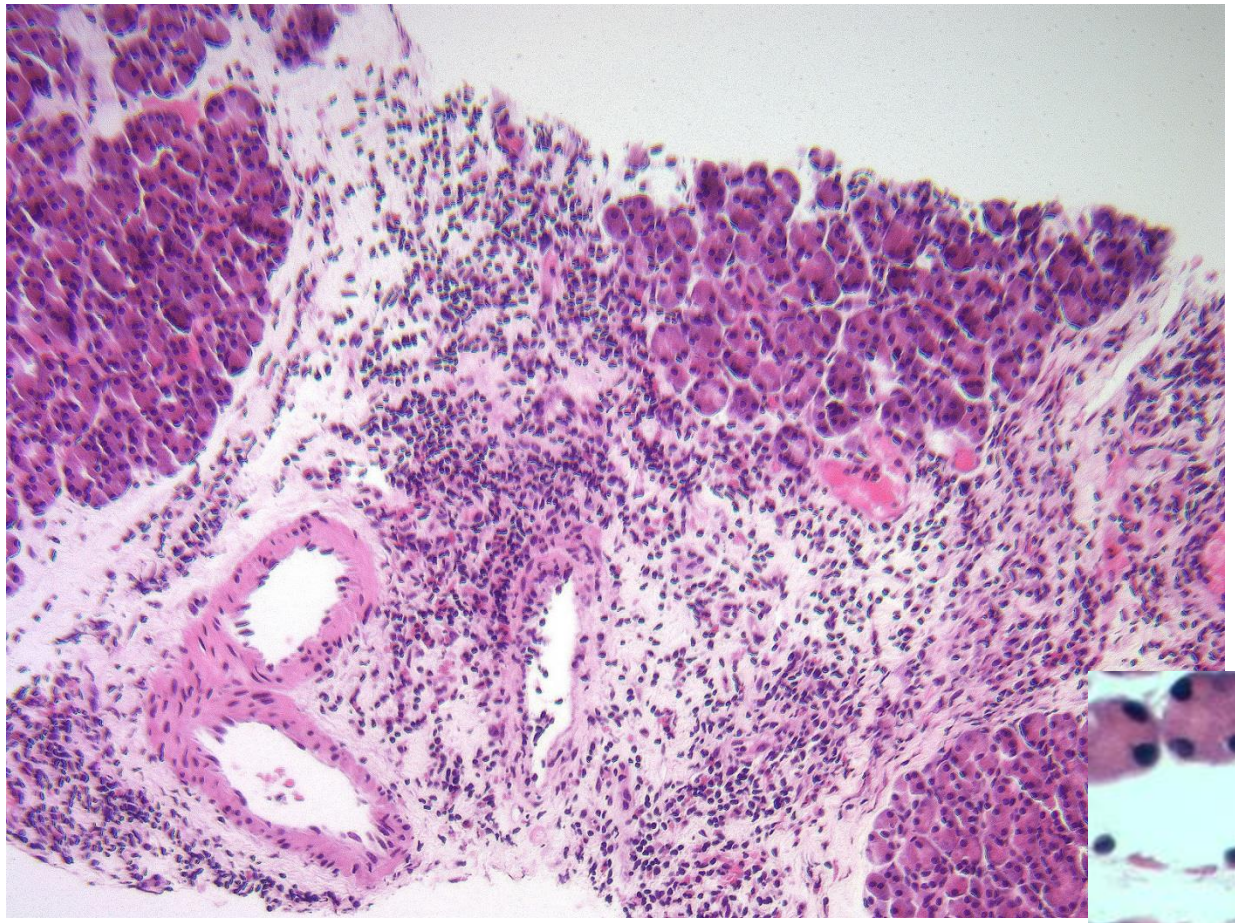
Acinar +/- vascular

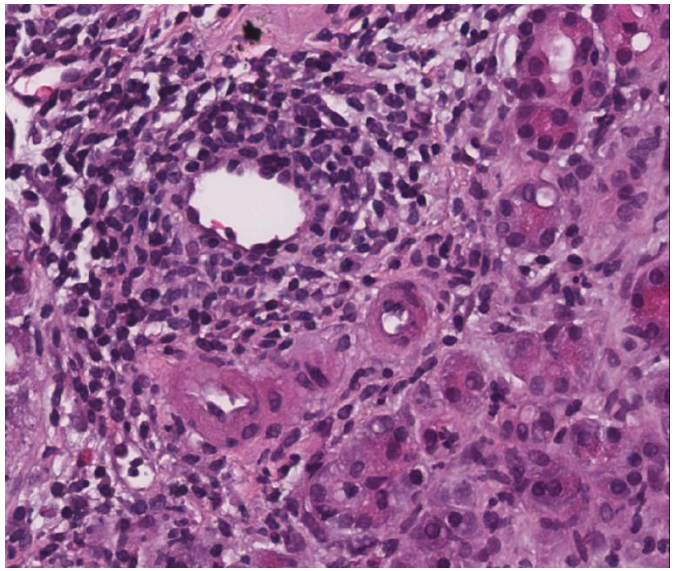
Targets of T-cell mediated rejection

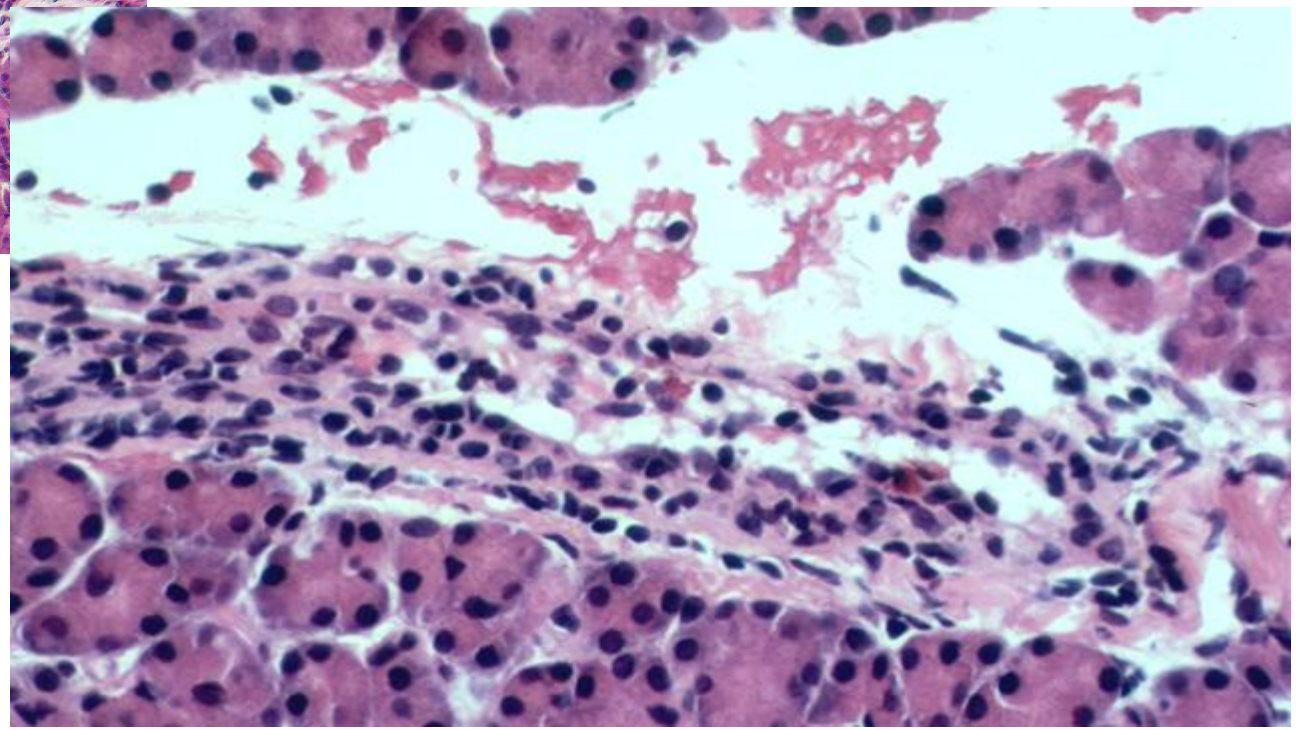
- **Ducts**
  - **Ductitis**
- **Veins**
  - **Venulitis**

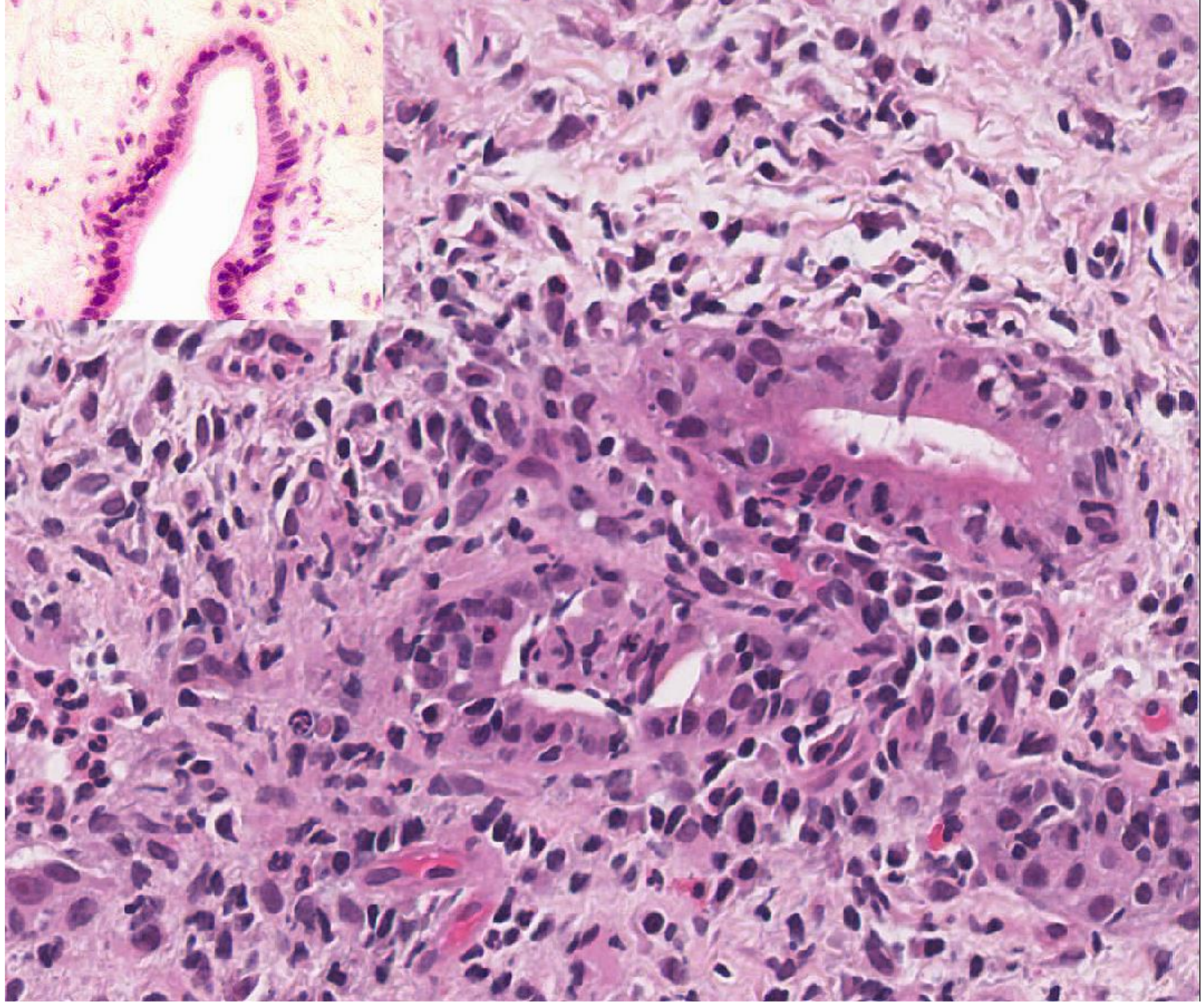
- **Arteries**
  - **Intimal arteritis, transmural arteritis**

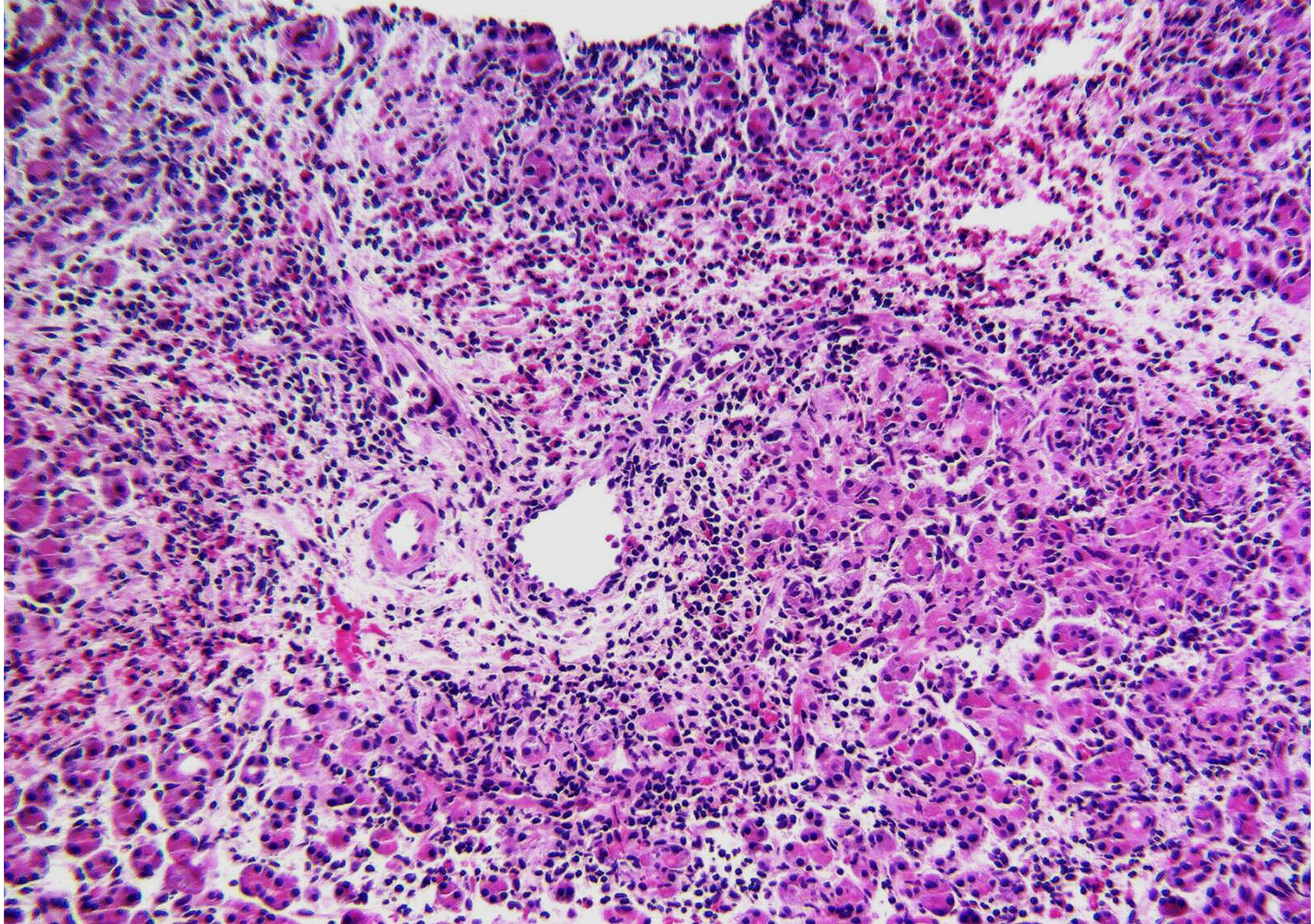
- **Exocrine acini**
  - **Acinitis**
  - **Acinar cell damage / death**

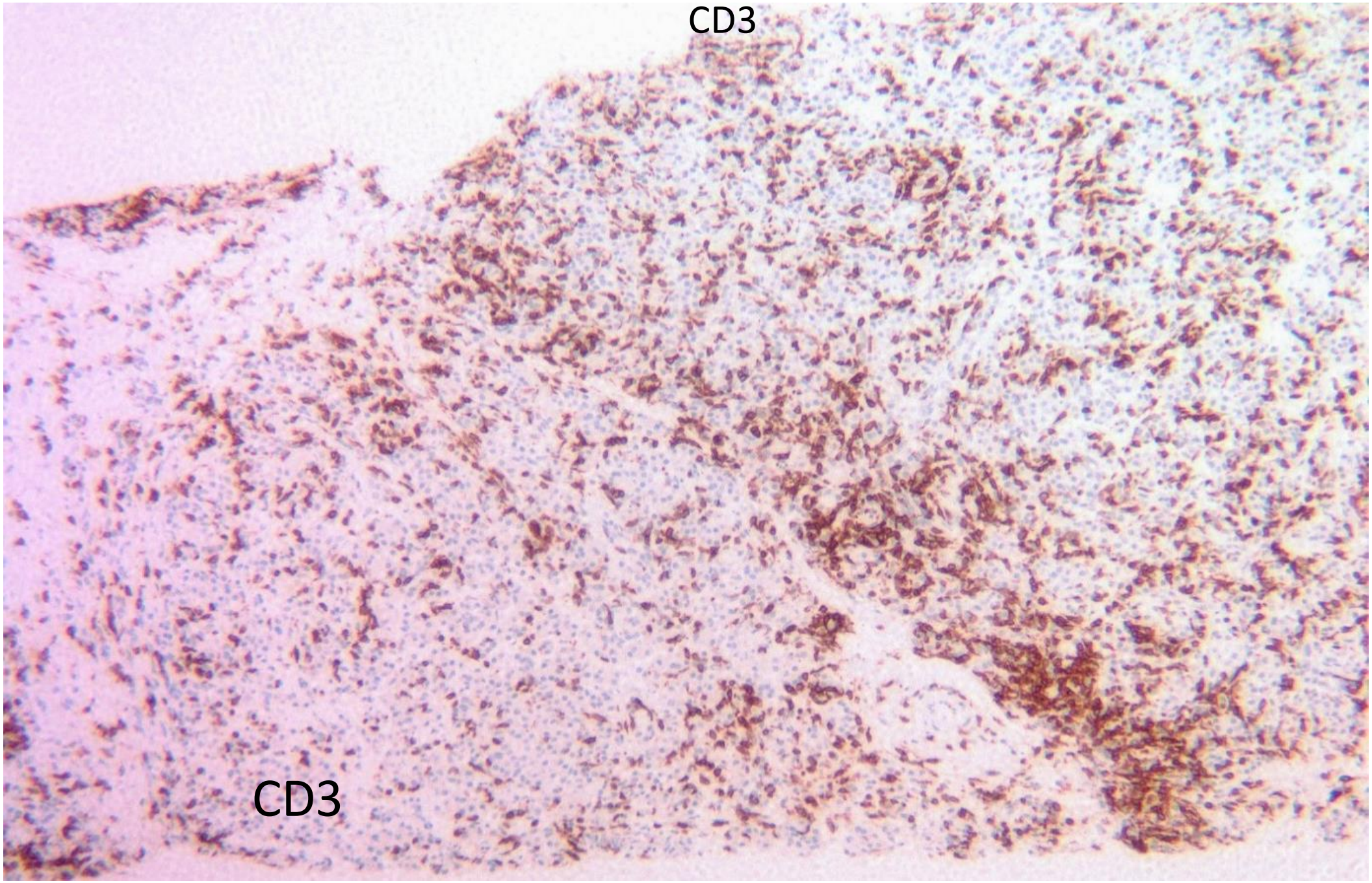


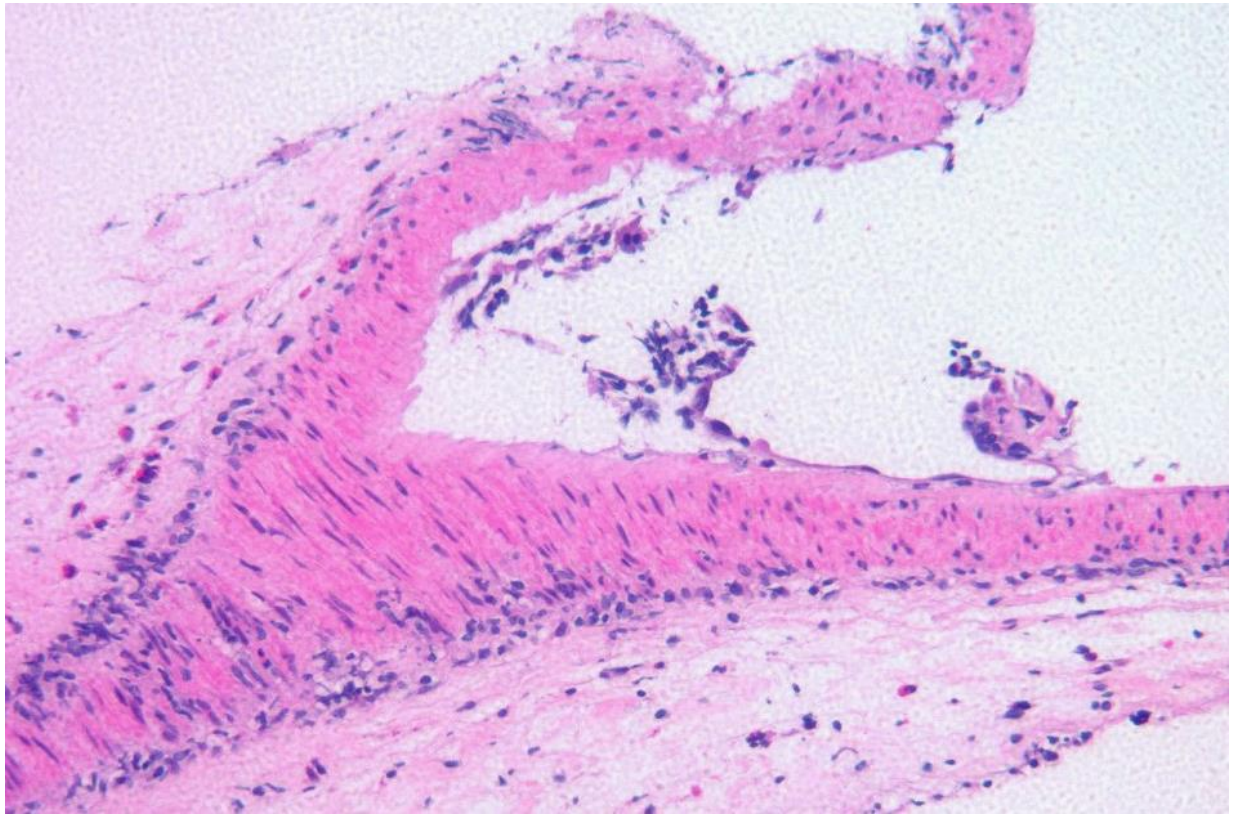


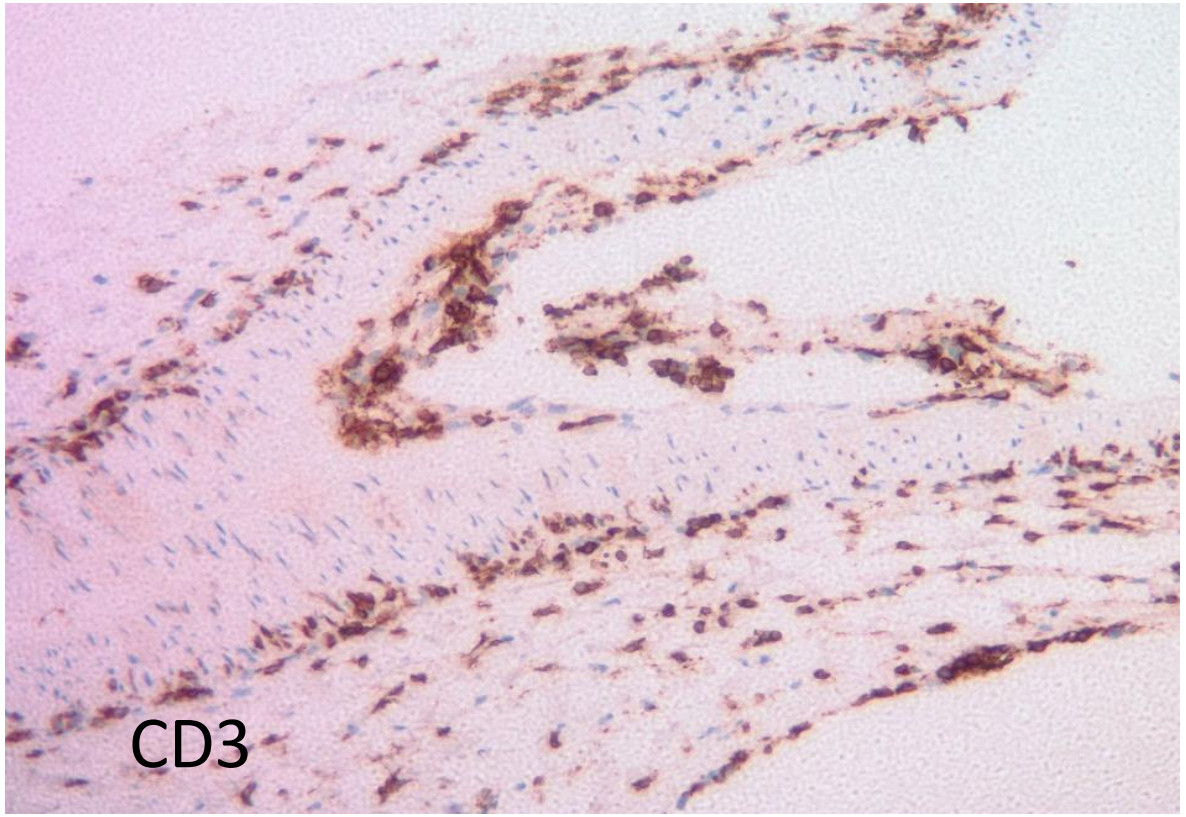







CD3
CD3

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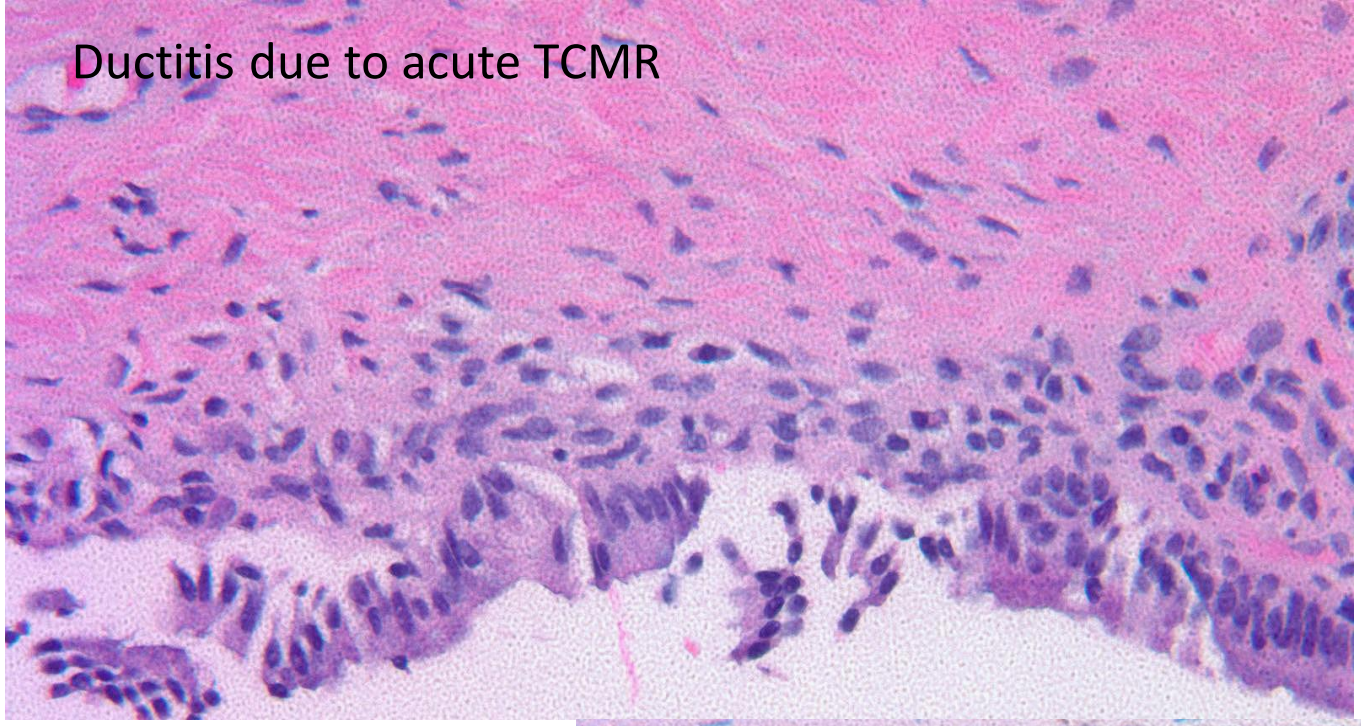
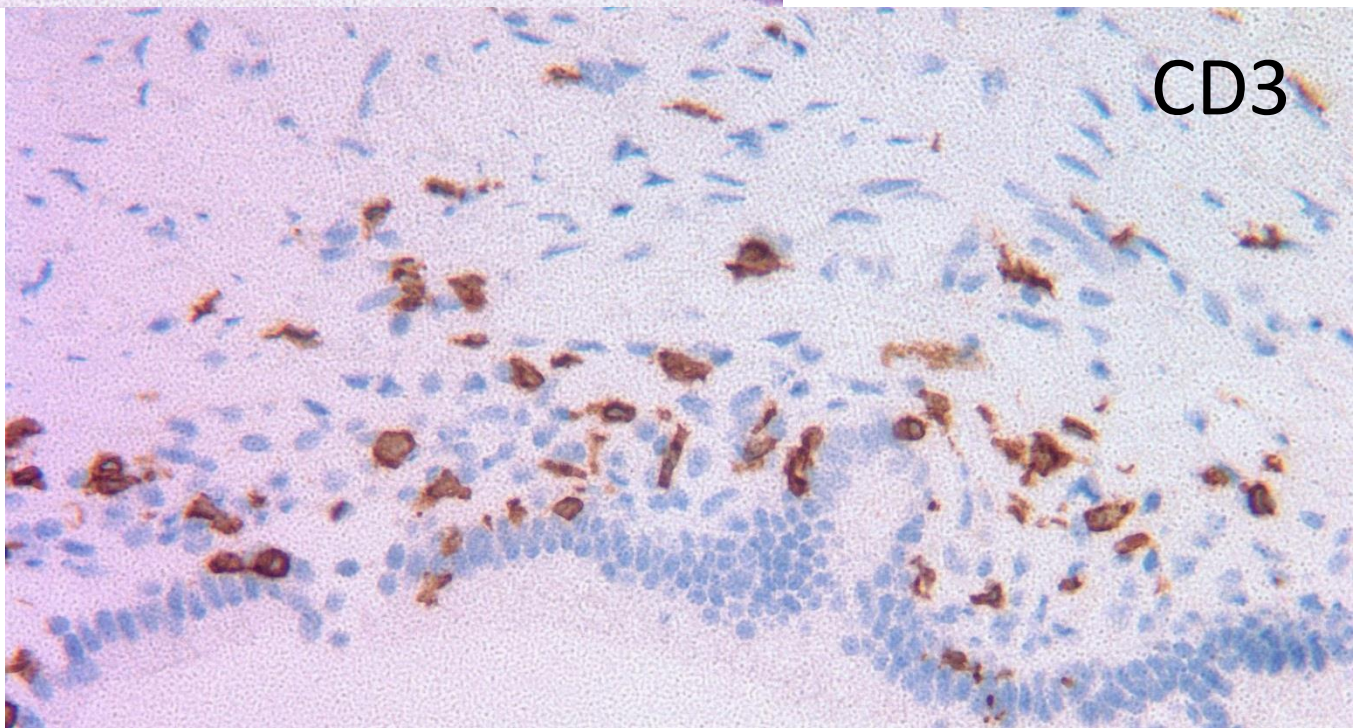
Persistent/refractory rejection

- Features of active rejection
- Features of evolving, chronic tissue damage


Ductitis due to acute TCMR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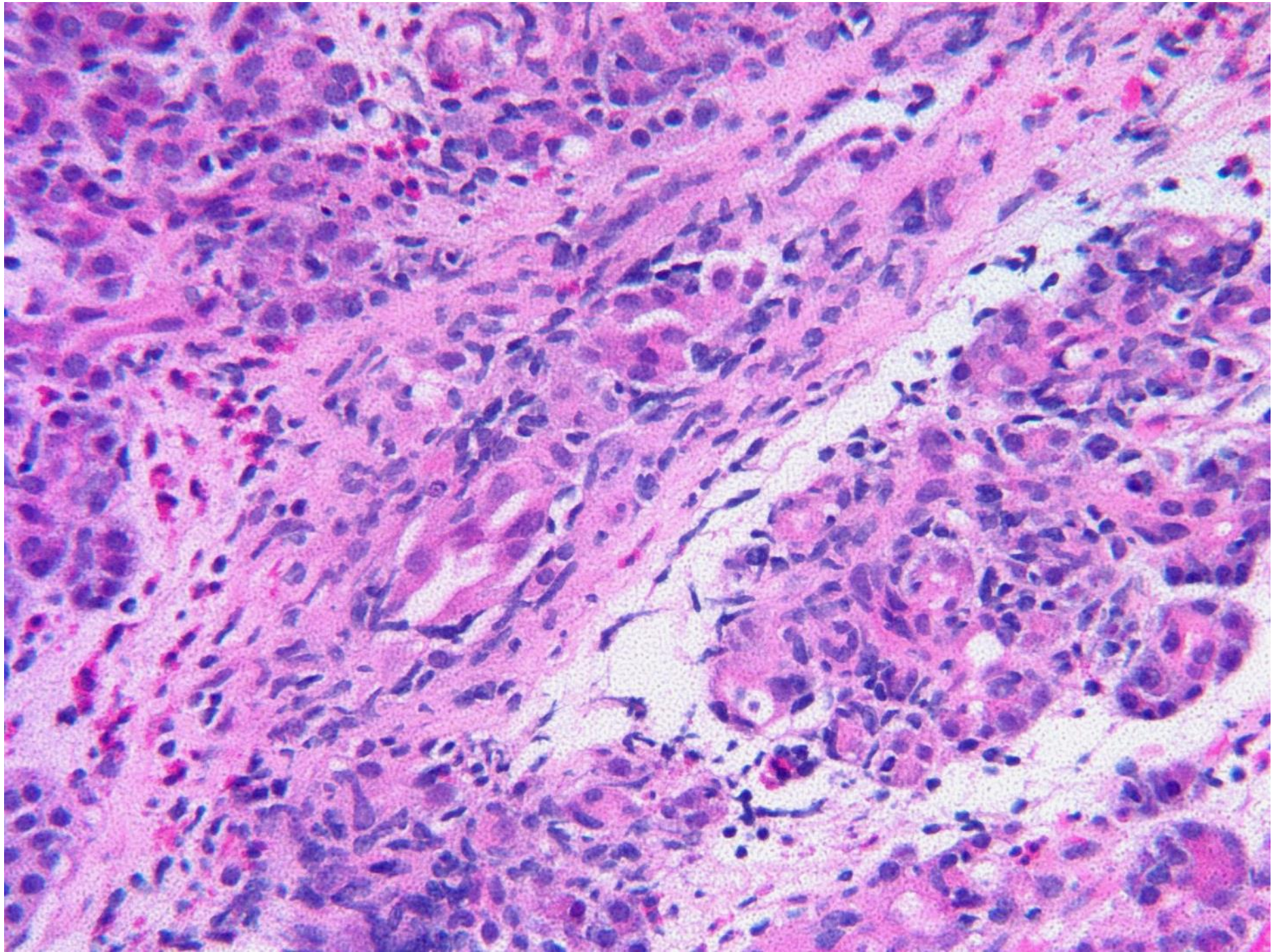
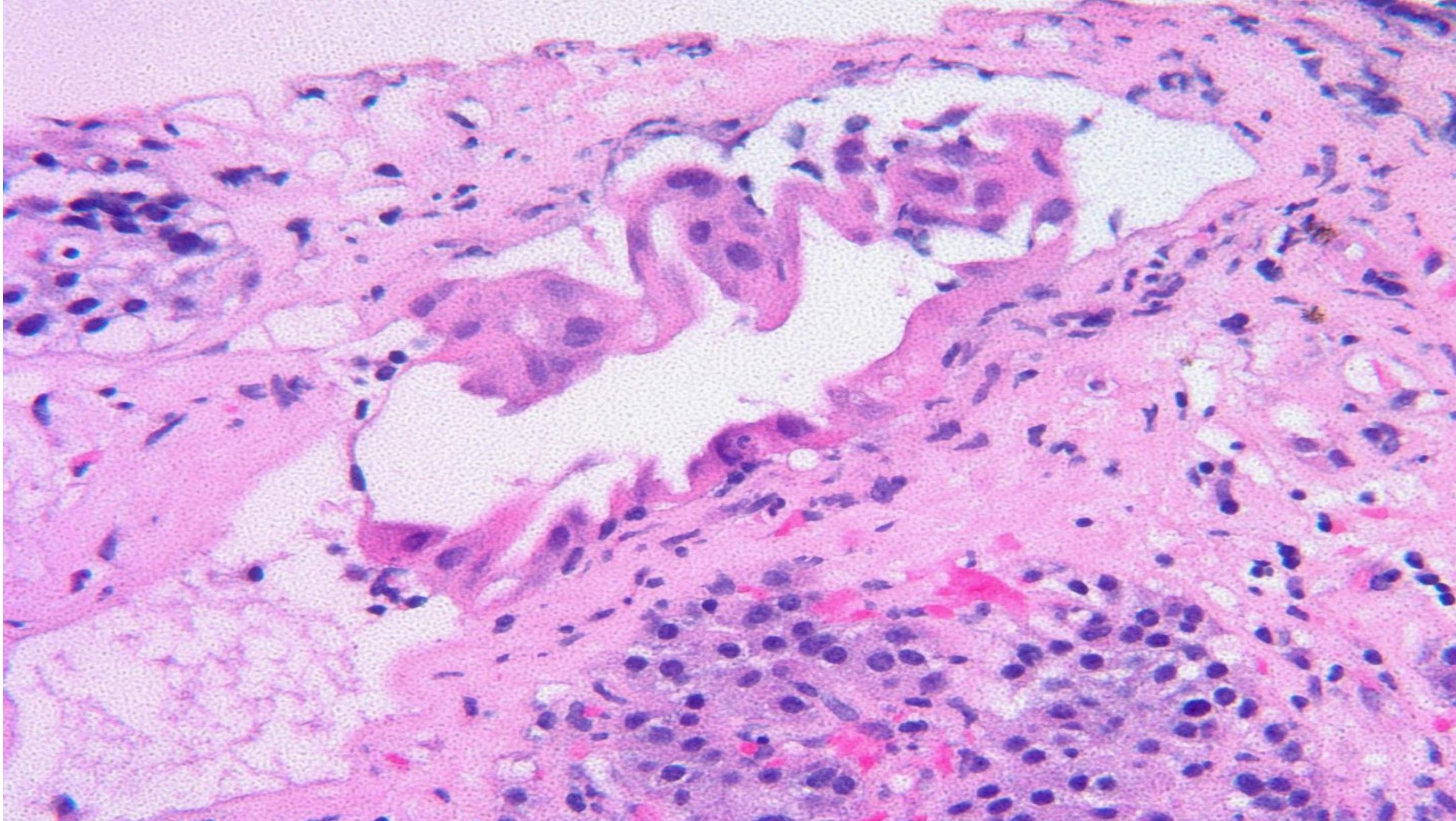
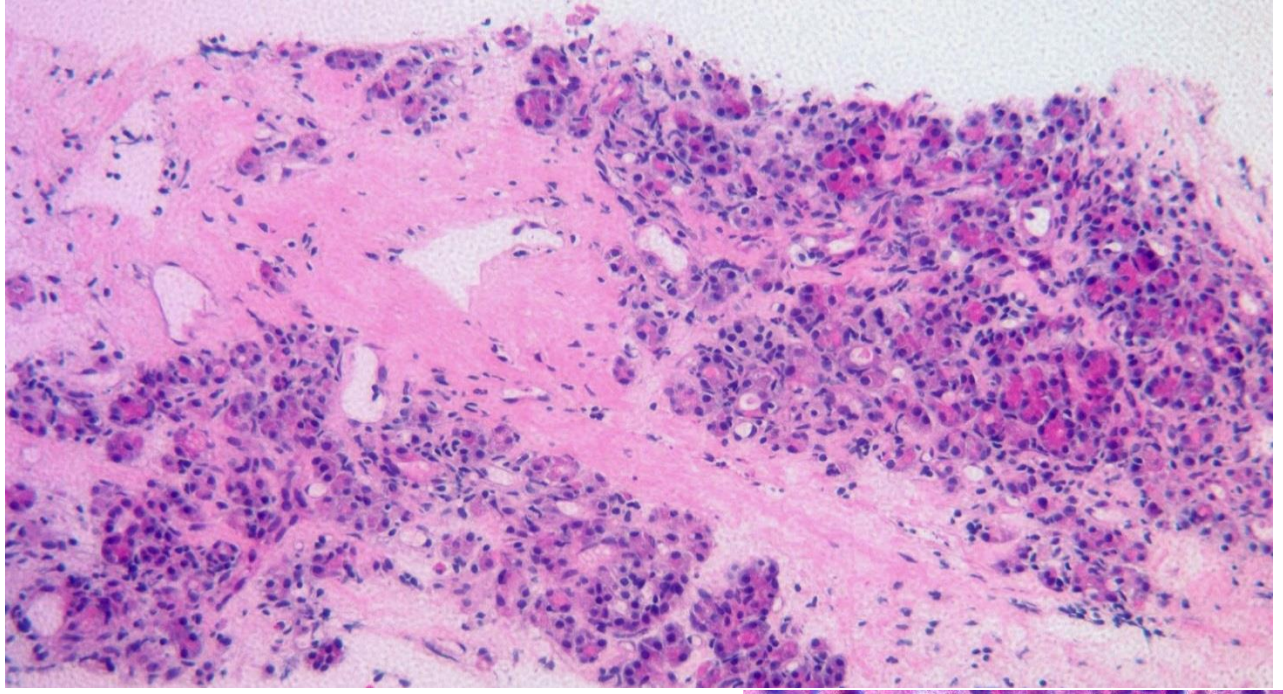
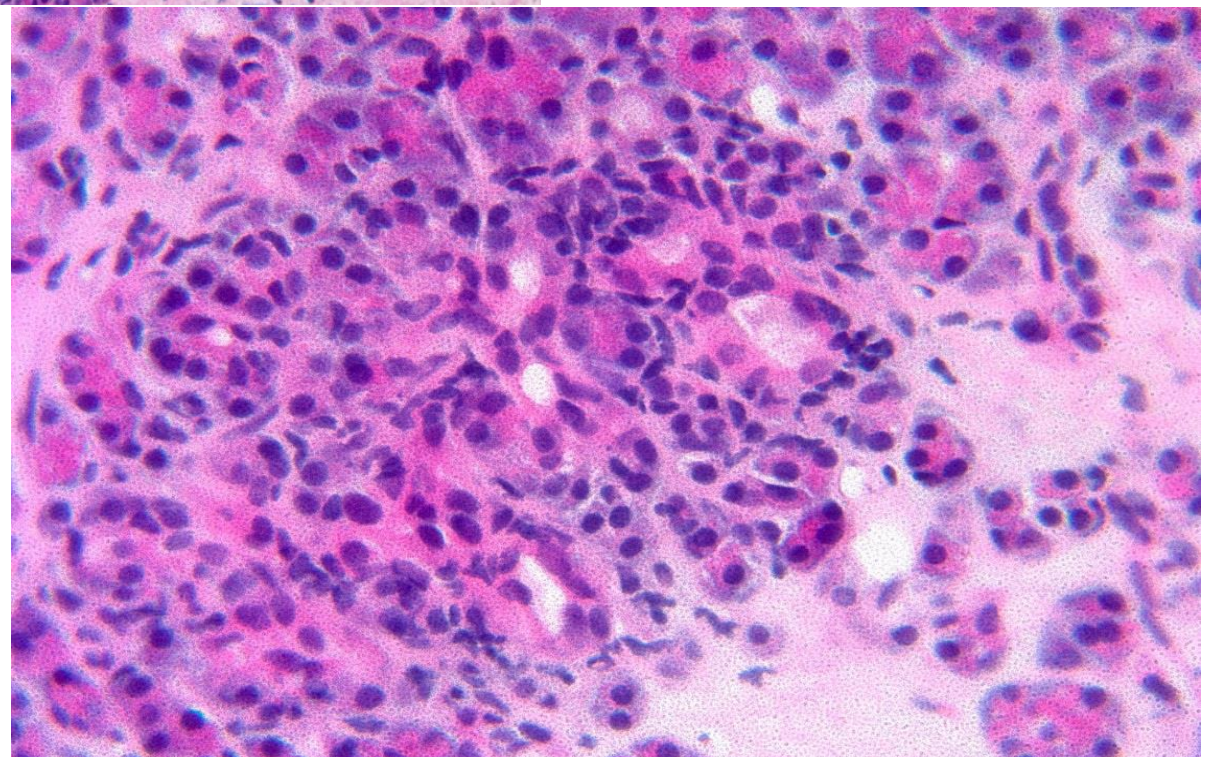
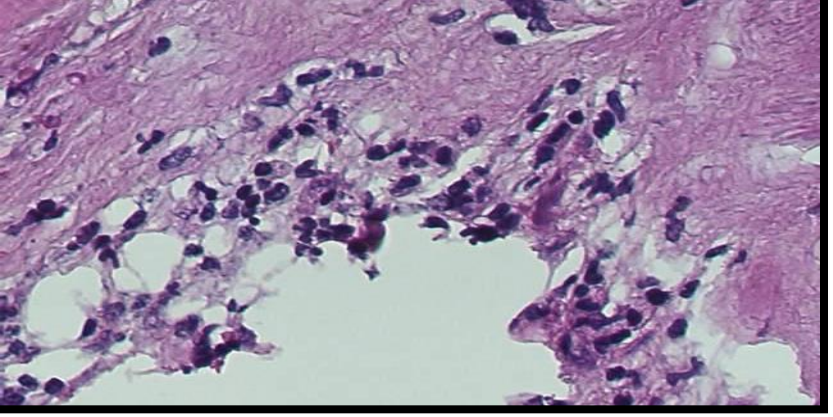
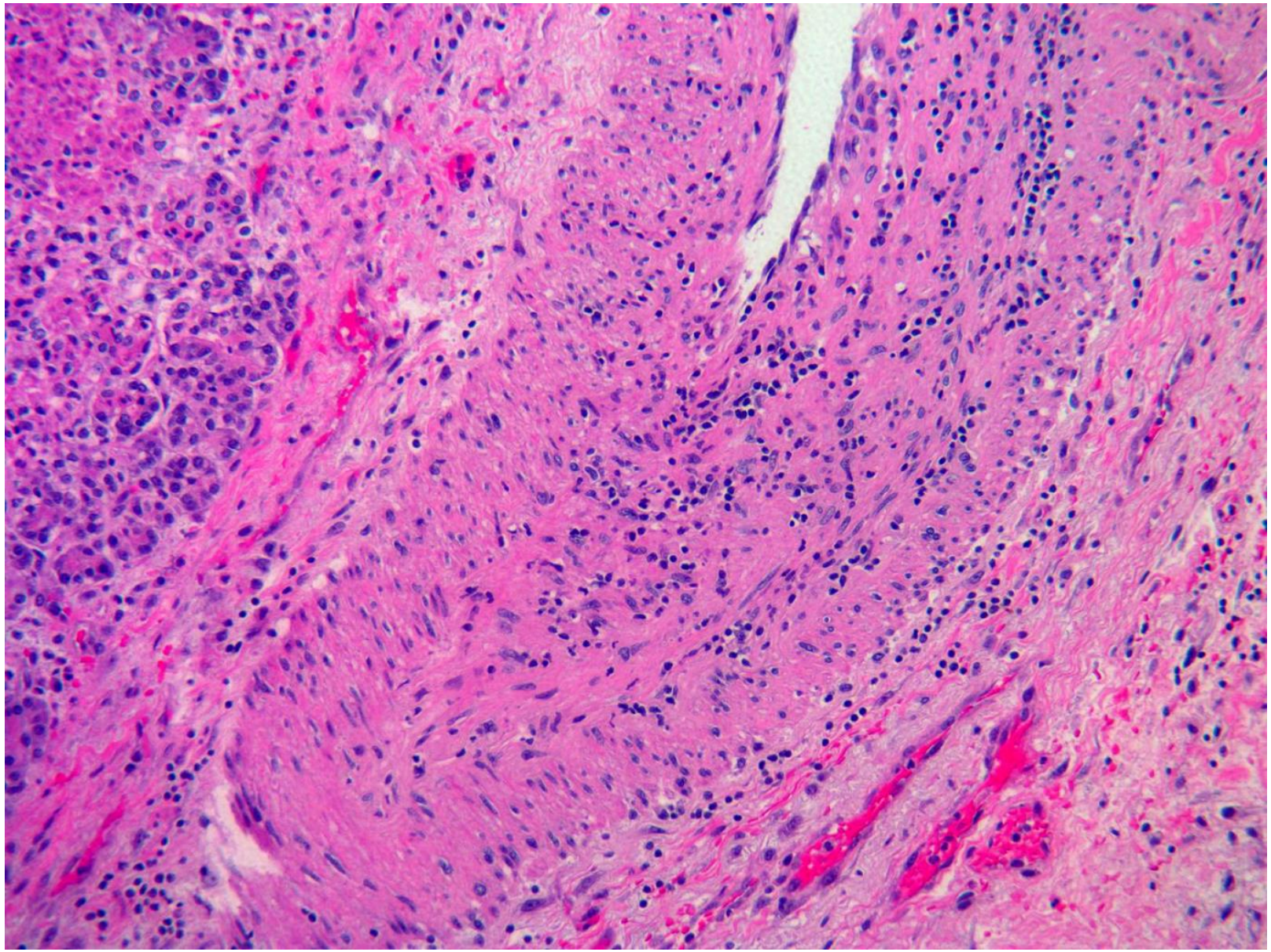


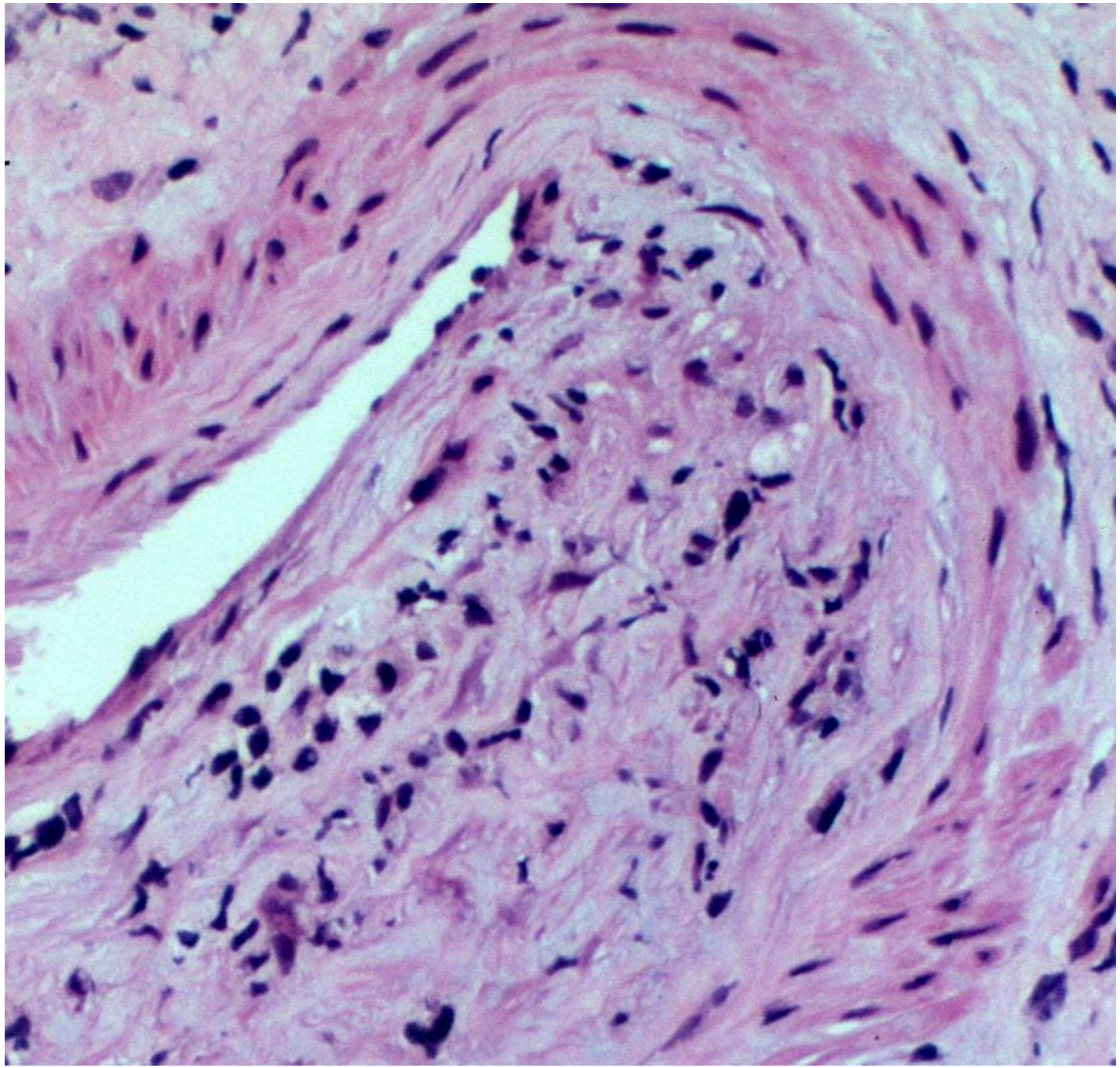


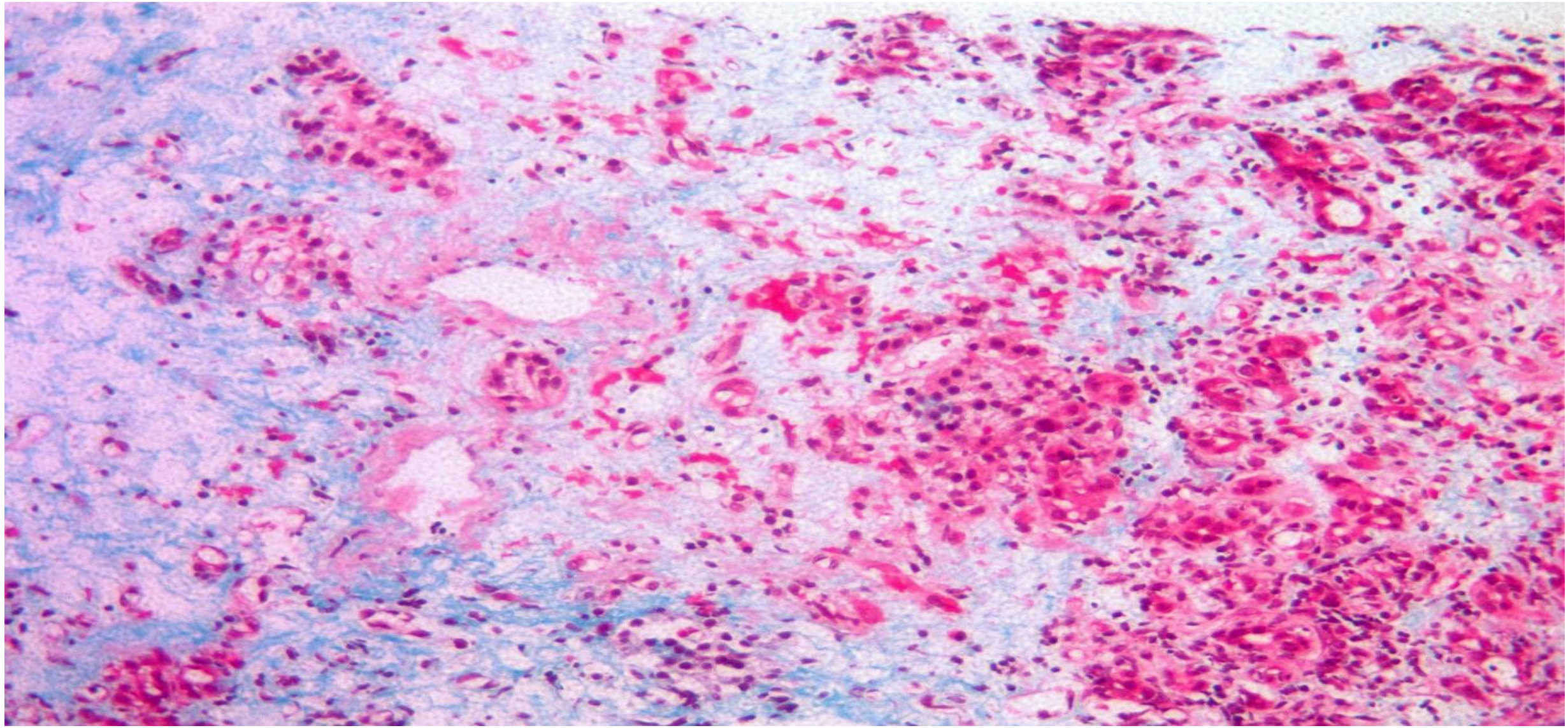


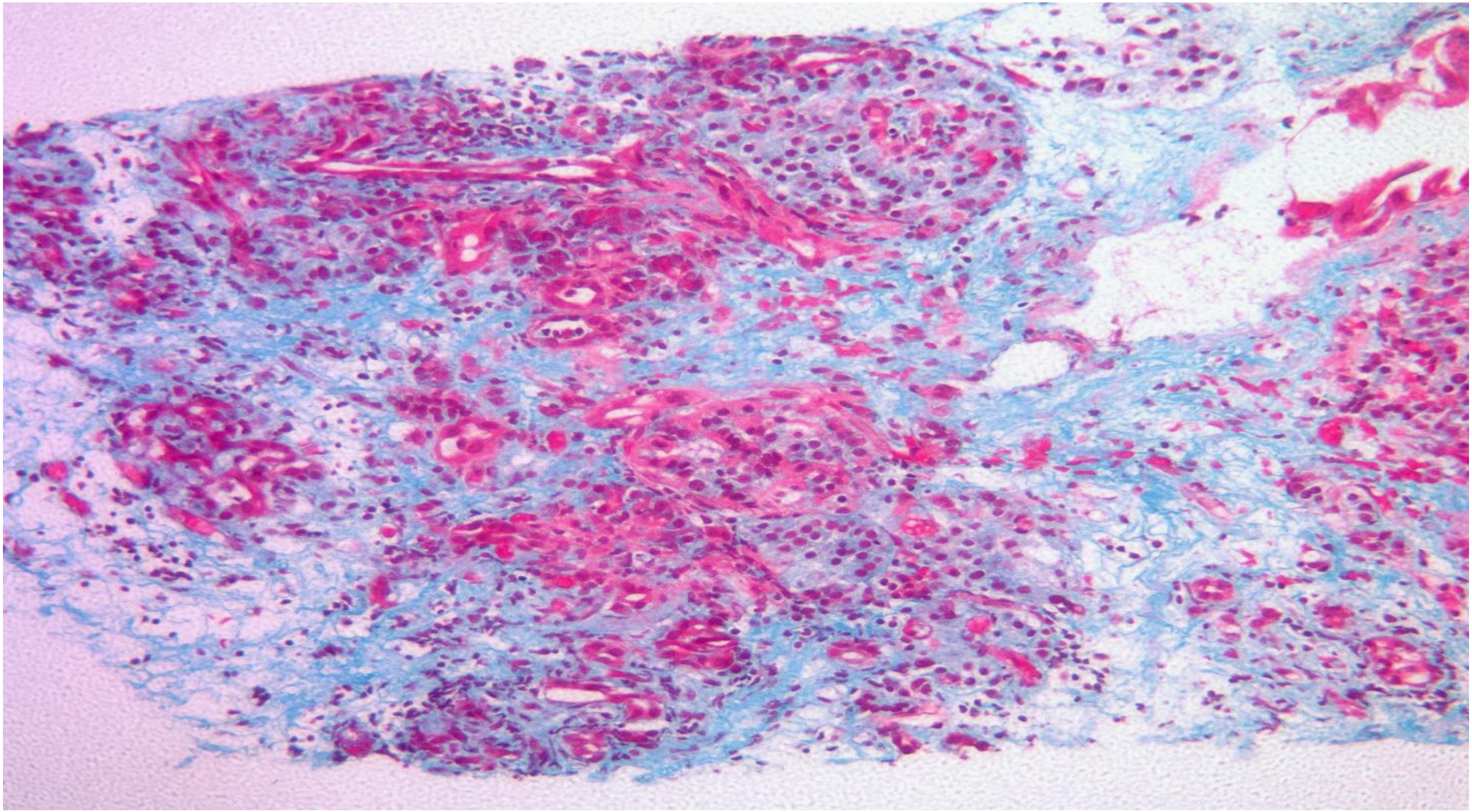


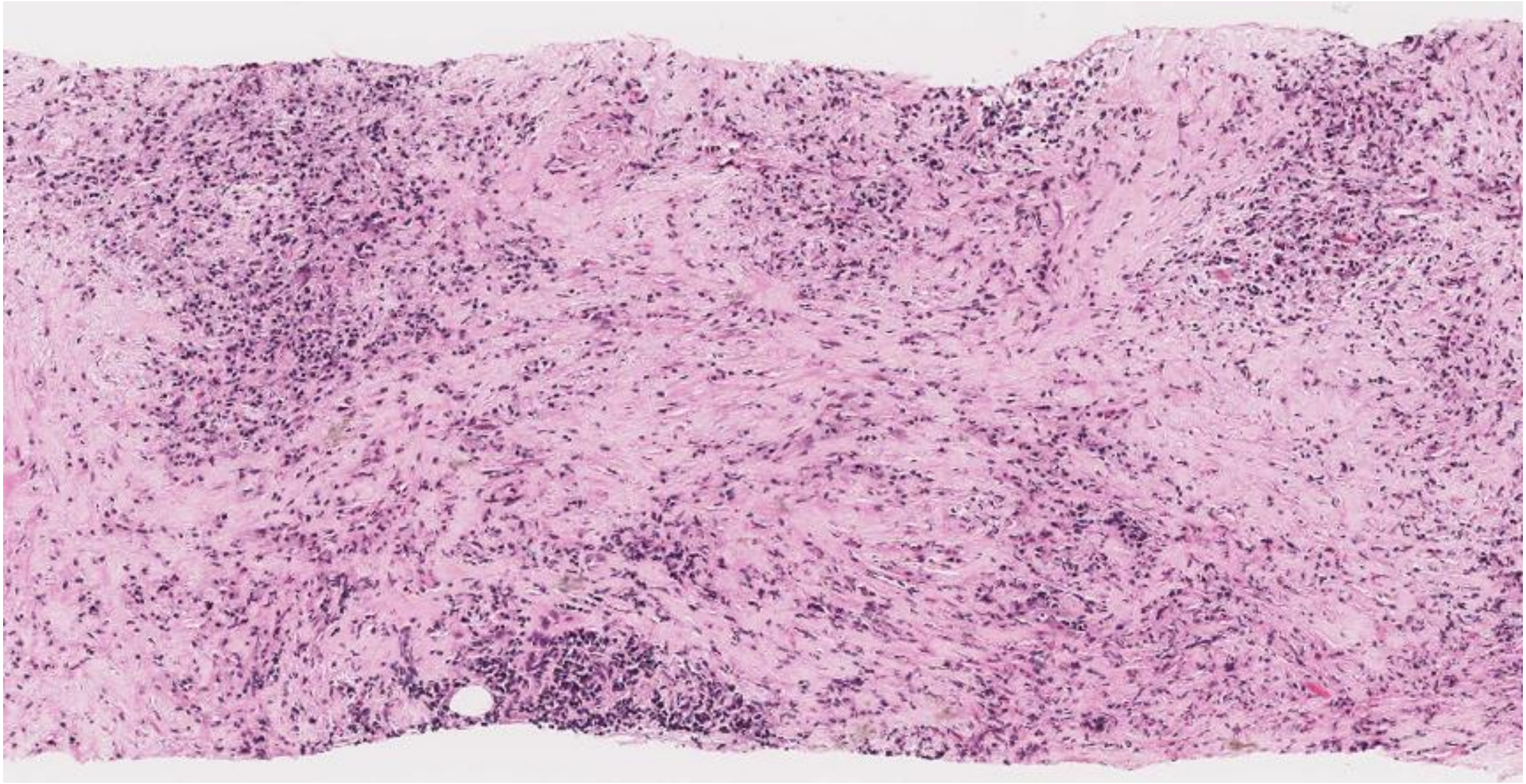




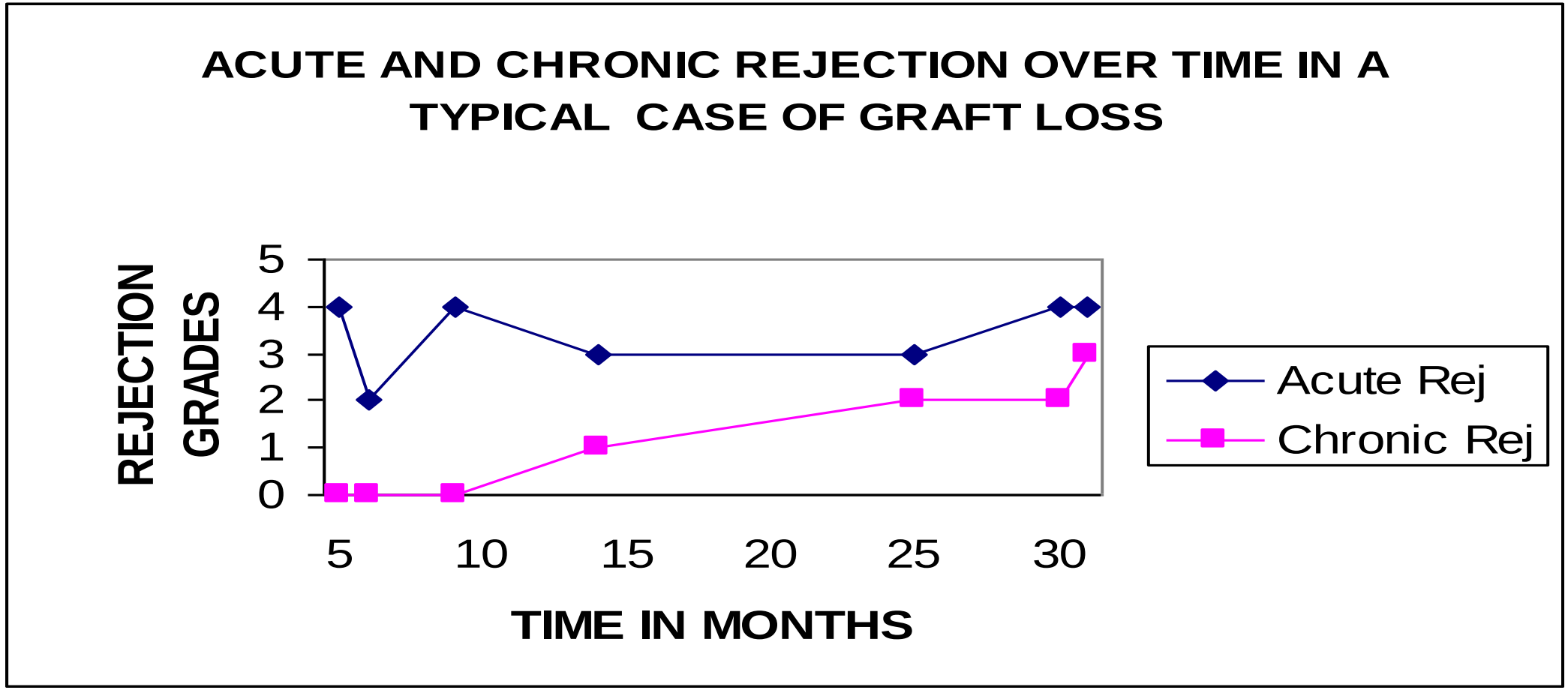




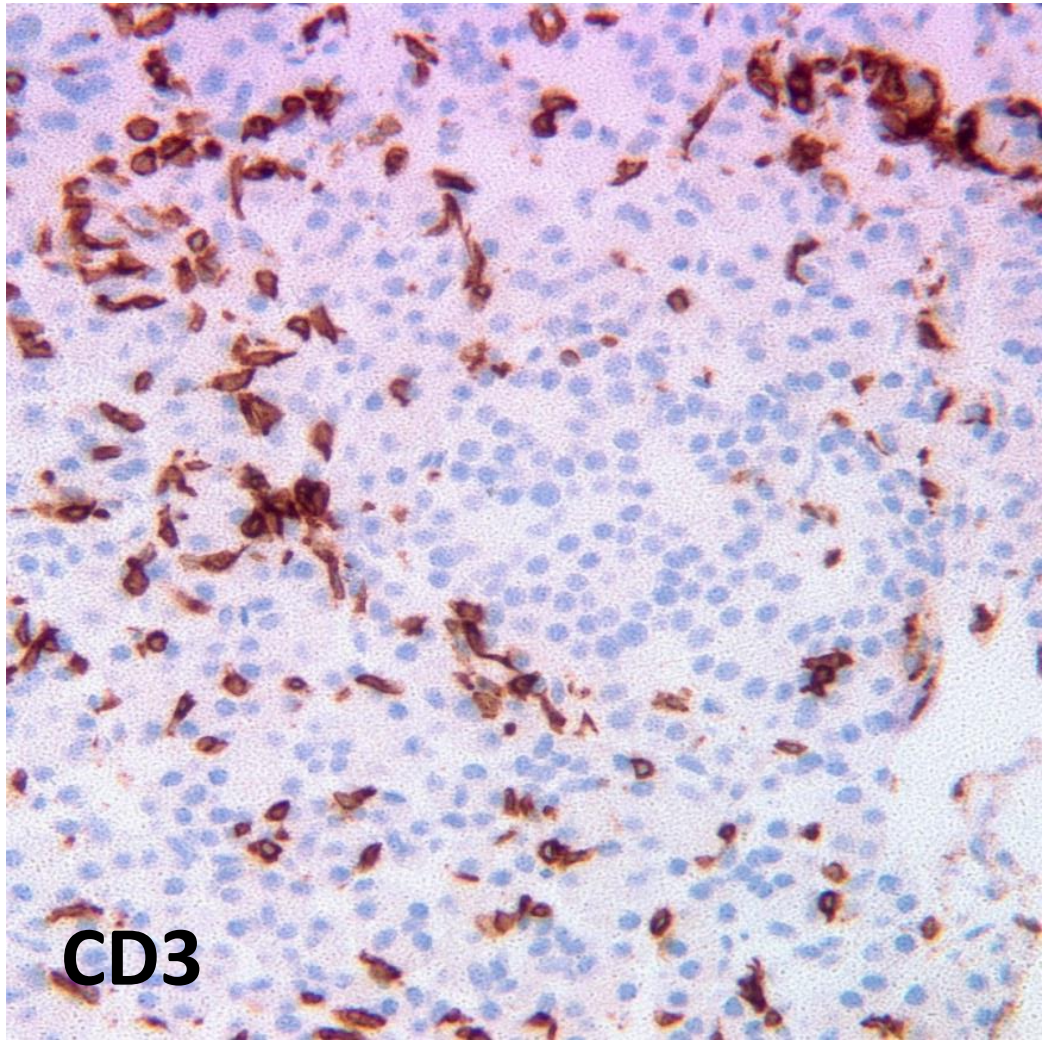


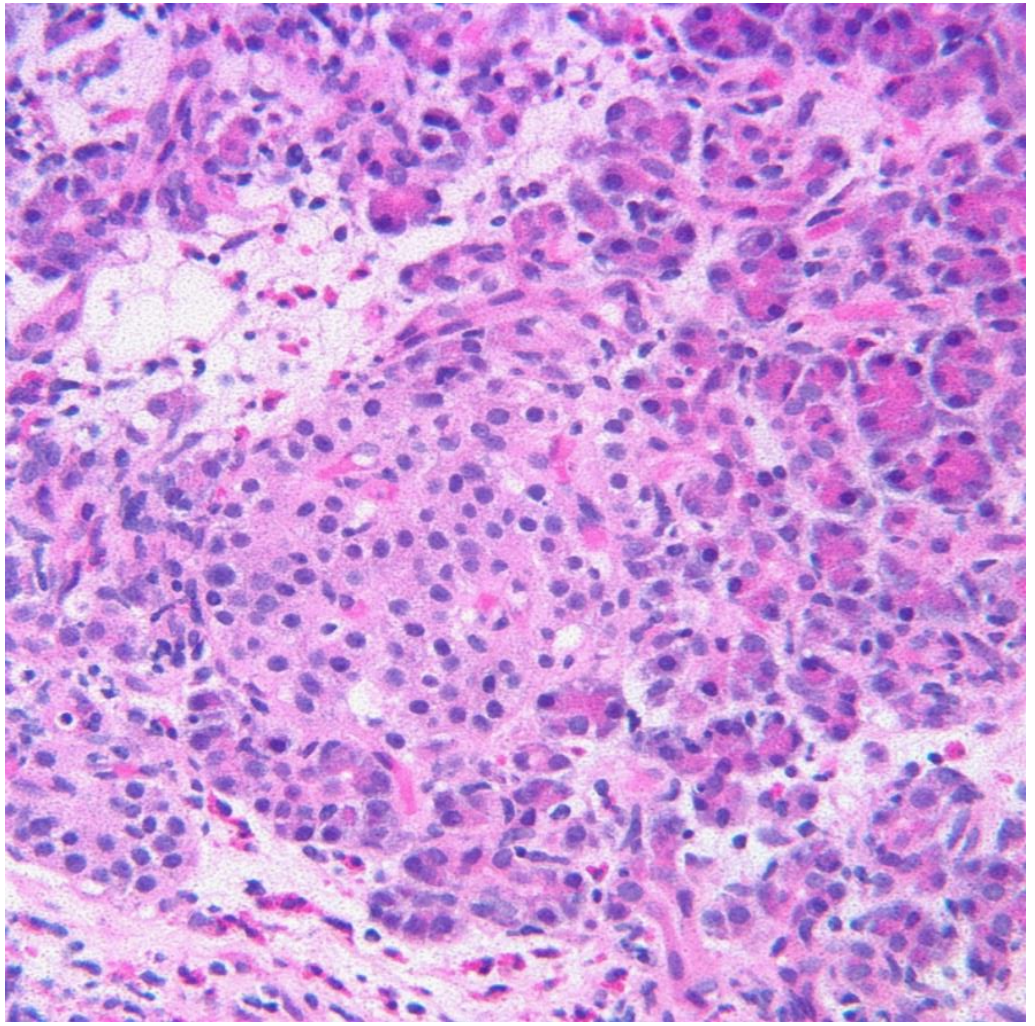


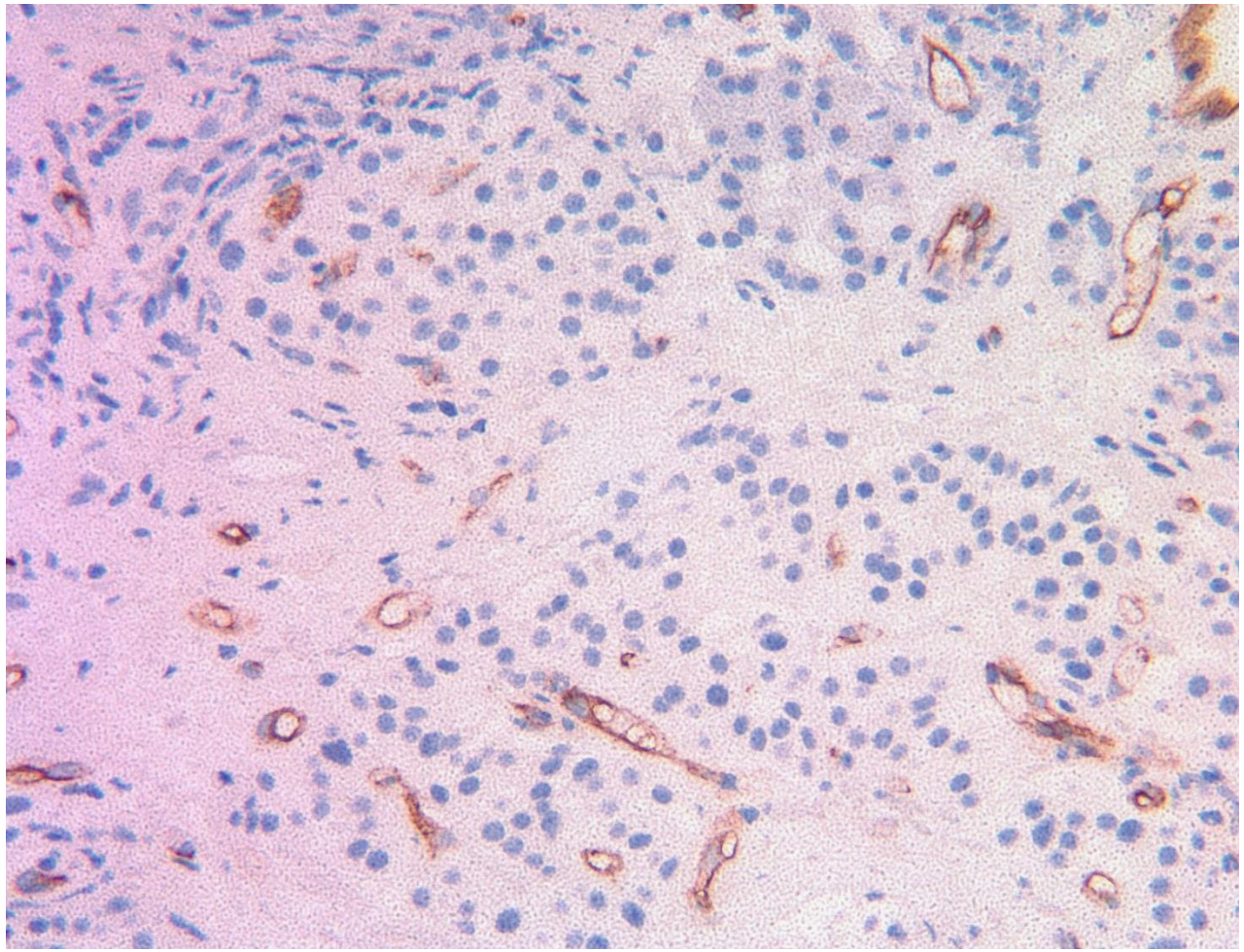
Chronic active TCMR



(Papadimitriou et al.: AJT May 2003)

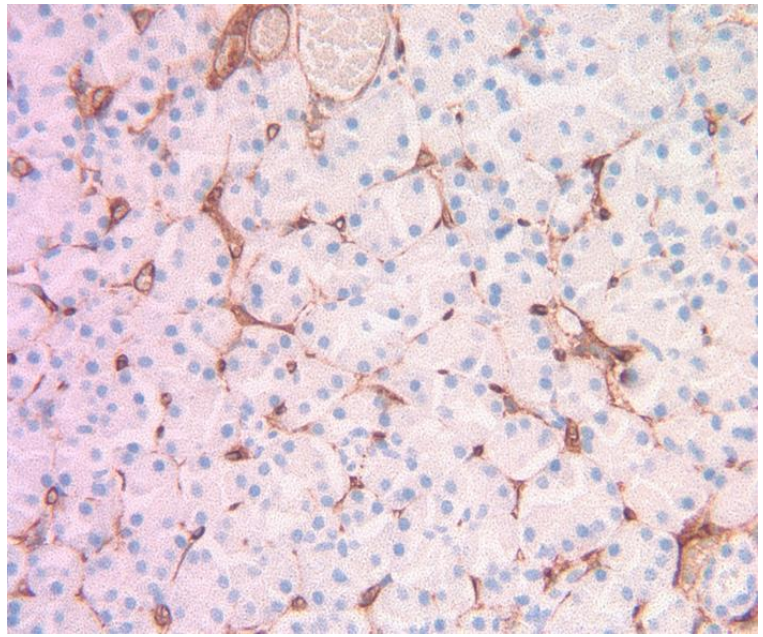

CD3

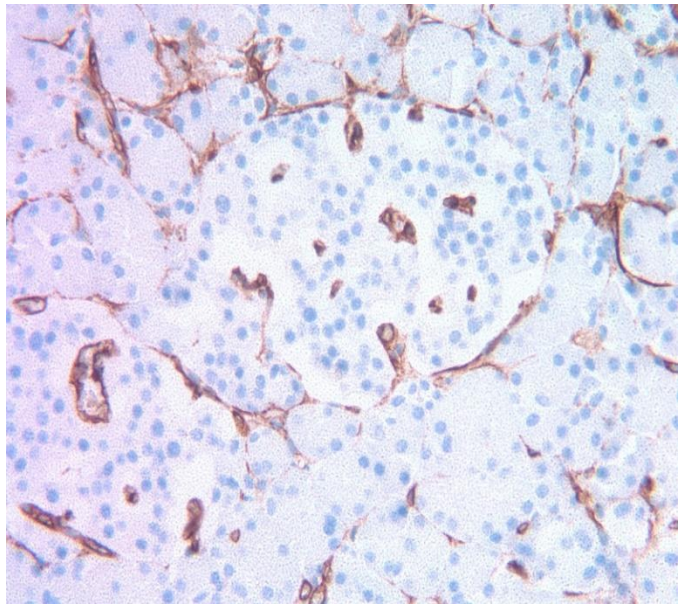




CD34 Vascular network in chronic T-cell mediated rej.

ISLET/GRAFT FAILURE





Normal vascular network

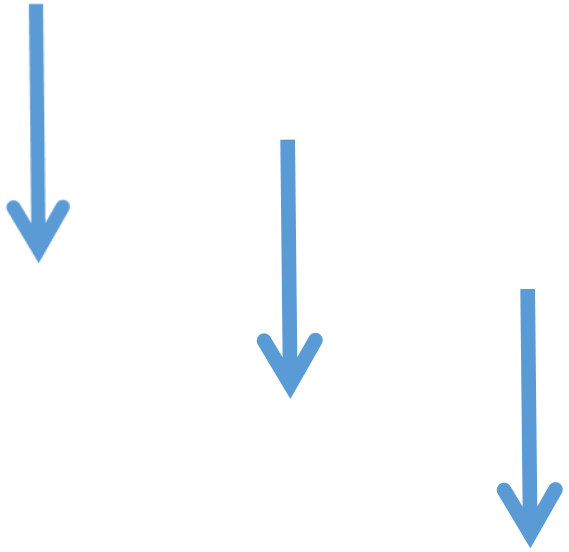
Targets of Antibody Mediated Rejection

- Vessels
  - Microvasculature
  - Arteries (veins)

Acute AMR Grading

(g) Grading of acute AMR:
  (i) Grade I/mild acute AMR: well preserved architecture, mild monocytic–macrophagic or mixed (monocytic–macrophagic/neutrophilic) infiltrates with rare acinar cell damage.
  (ii) Grade II/moderate acute AMR: overall preservation of the architecture with interacinar monocytic–macrophagic or mixed (monocytic–macrophagic/neutrophilic) infiltrates, capillary dilatation, capillaritis, congestion, multicellular acinar cell drop-out, extravasation of red blood cells.
  (iii) Grade III/severe acute AMR: architectural disarray, scattered inflammatory infiltrates in a background of interstitial hemorrhage, multifocal and confluent parenchymal necrosis, arterial and venous wall necrosis and thrombosis.

Microvasculature injury/inflammation and progressive tissue destruction

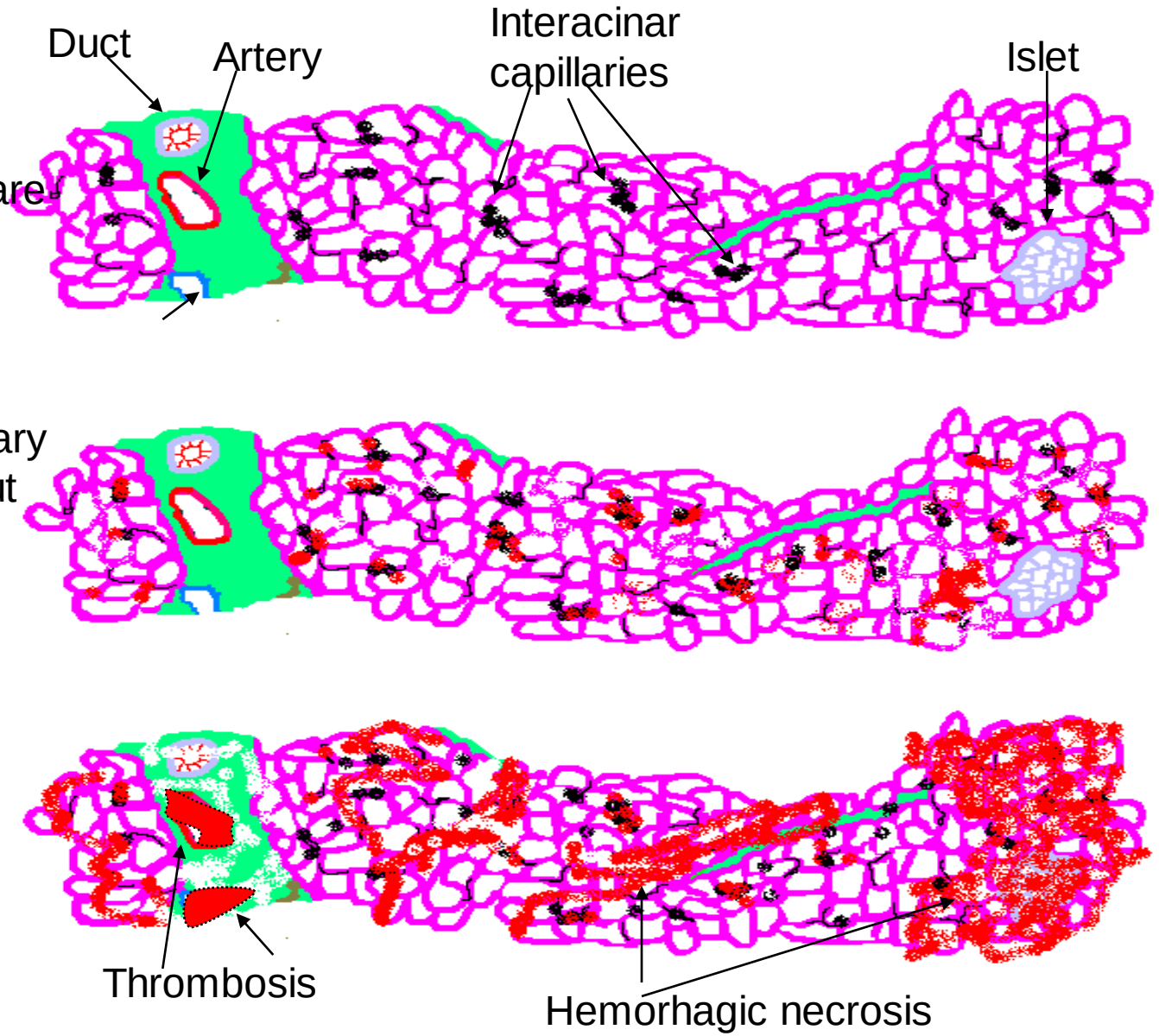


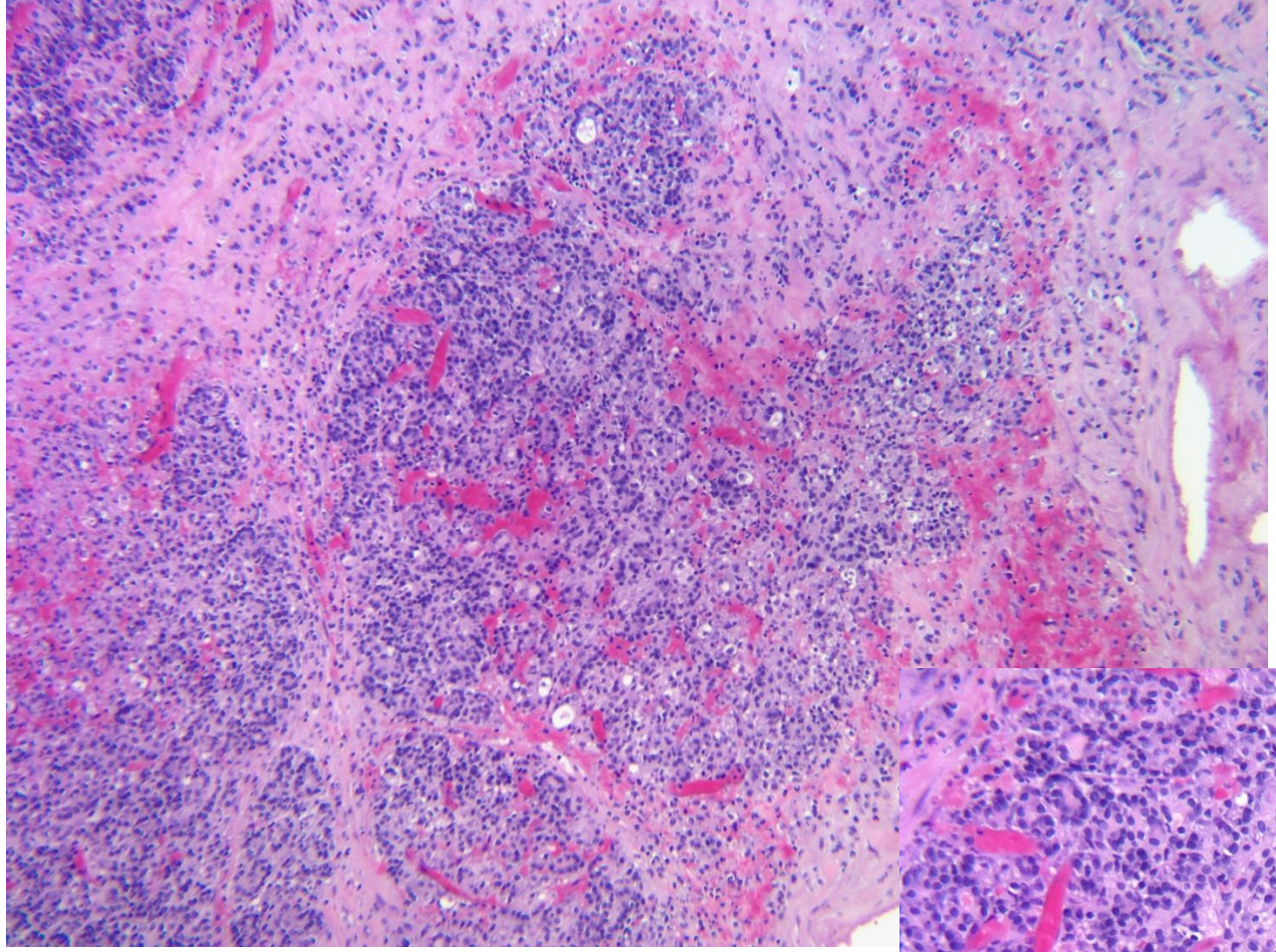
Morphology and grading of acute AMR

Grade I/Mild Normal architecture, mild interacinar monocytic/macrophagic-neutrophilic infiltrates with rare acinar cell damage.

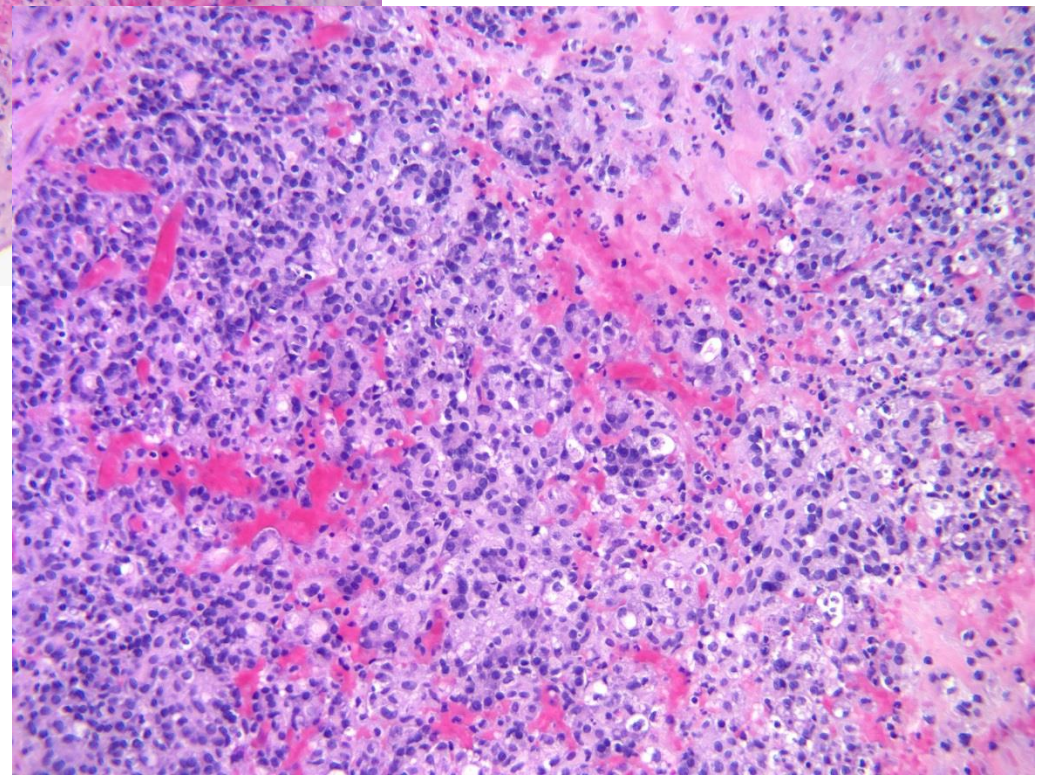
Grade II/Moderate
Preserved architecture with interacinar monocytic/macrophagic-neutrophilic infiltrates, capillary dilatation, congestion, multicellular acinar cell dropout and extravasation of red blood cells.

Grade III/Severe Architectural disarray, scattered inflammatory infiltrates in a background of interstitial hemorrhage, multifocal and confluent parenchymal necrosis, arterial and venous wall necrosis and thrombosis.

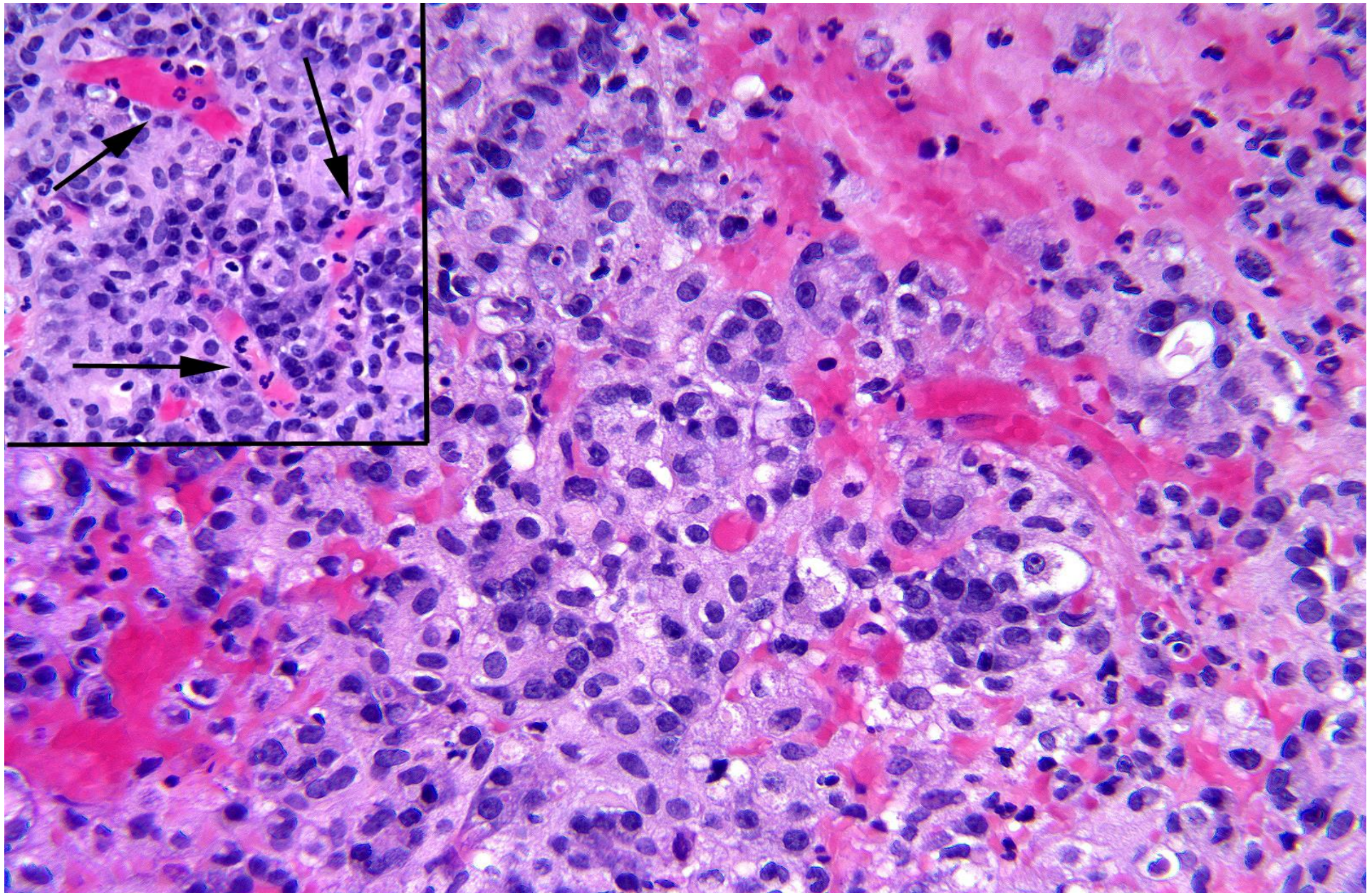


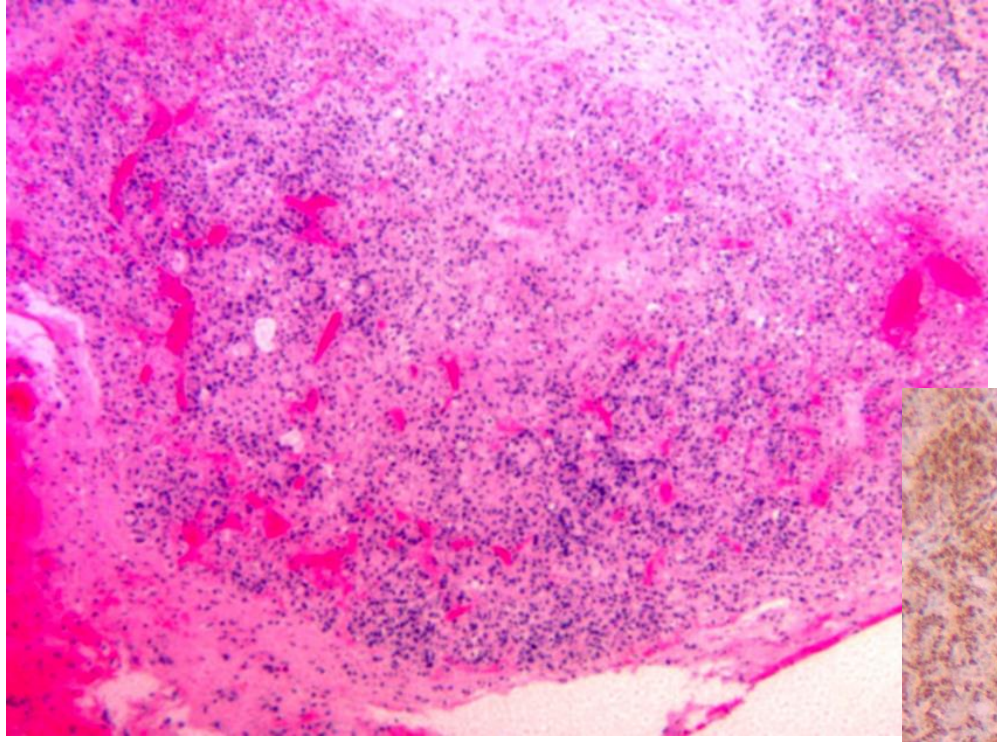


Moderate Acute AMR

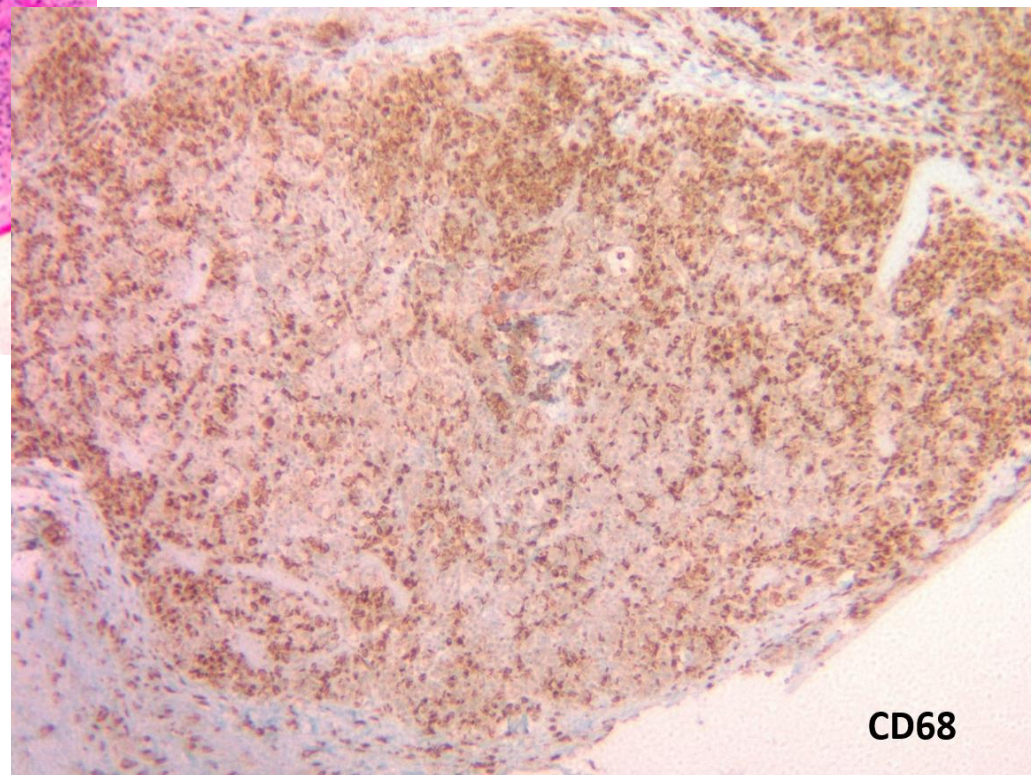


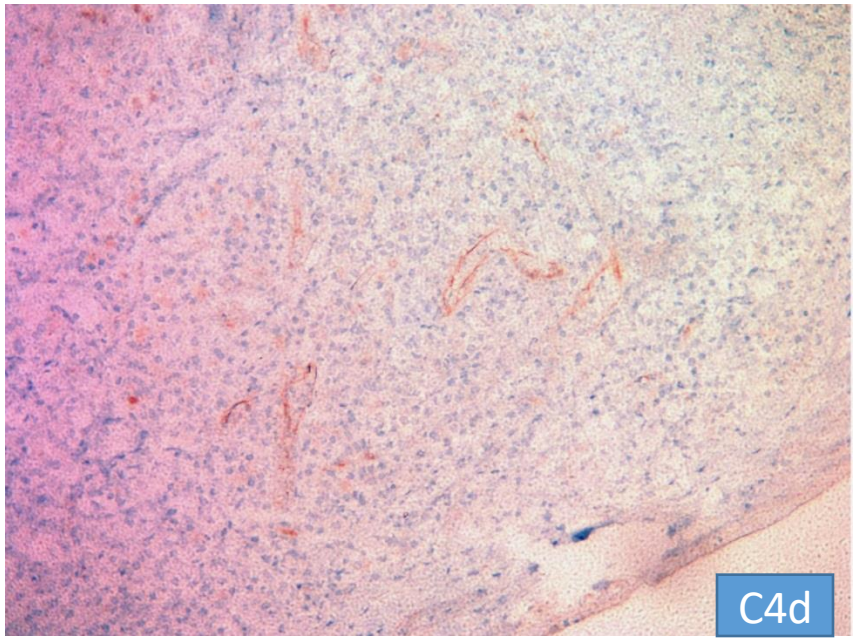
WPTx Acute Antibody Mediated Rejection



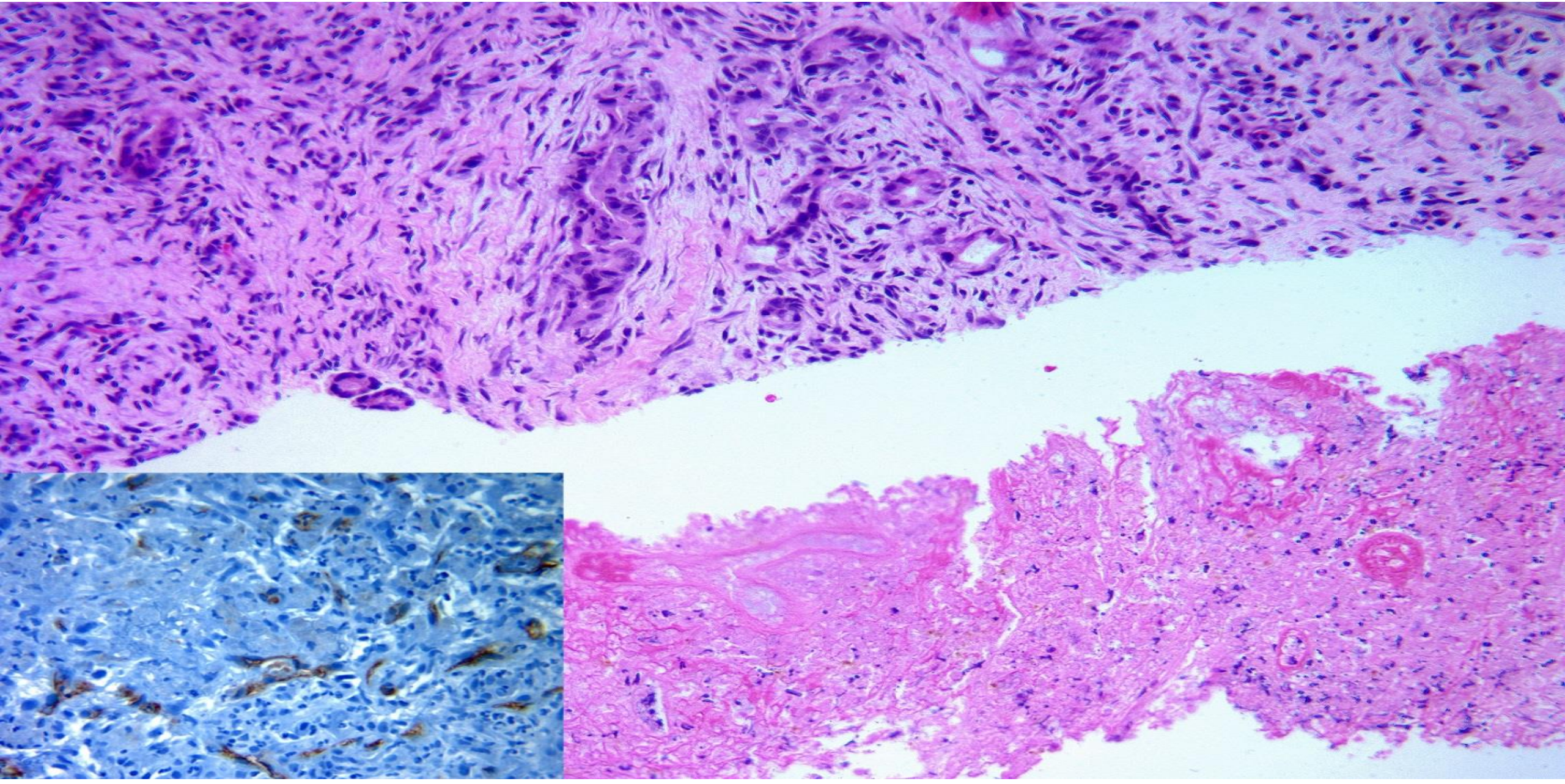


Moderate to severe acute AMR

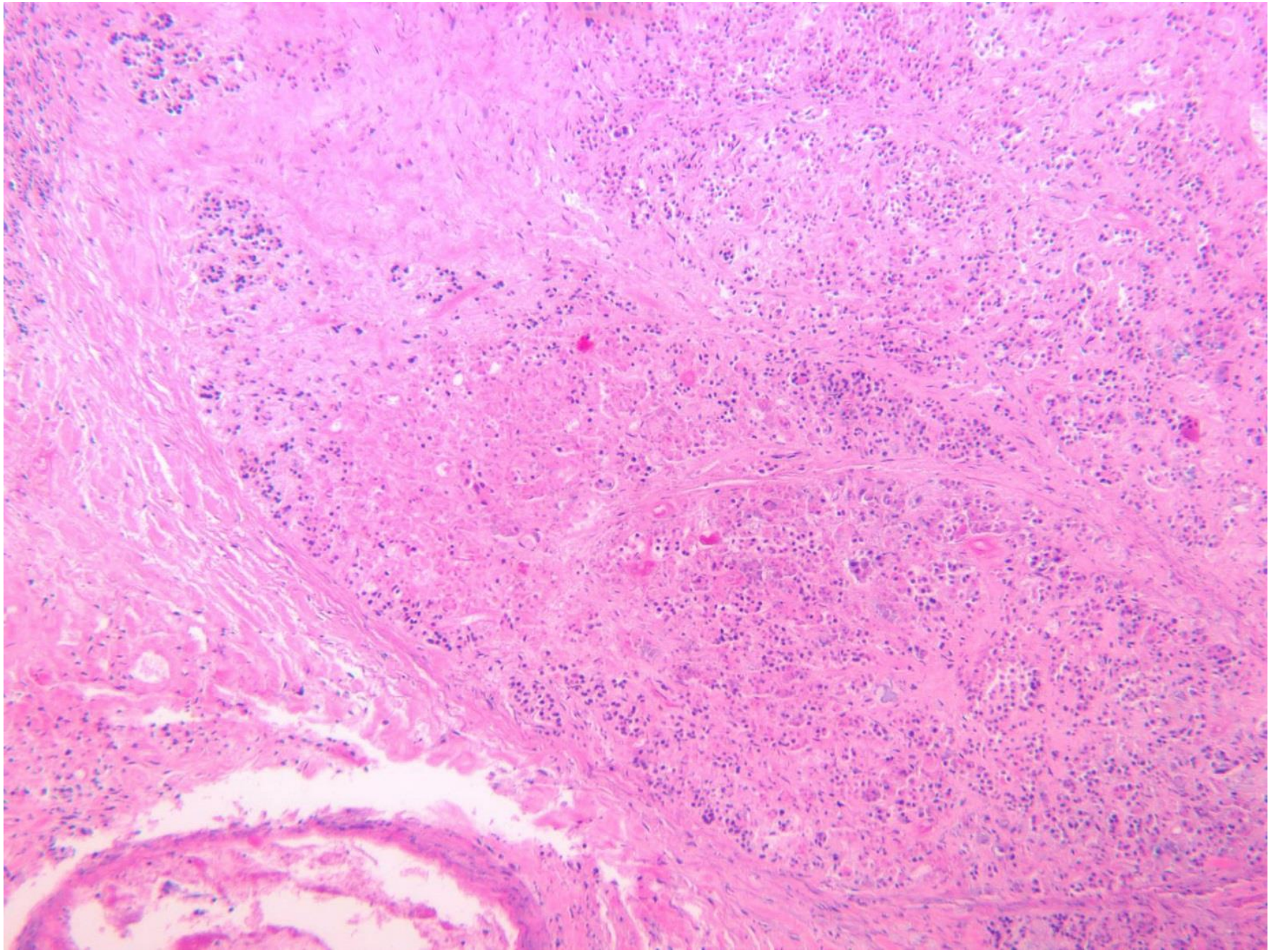


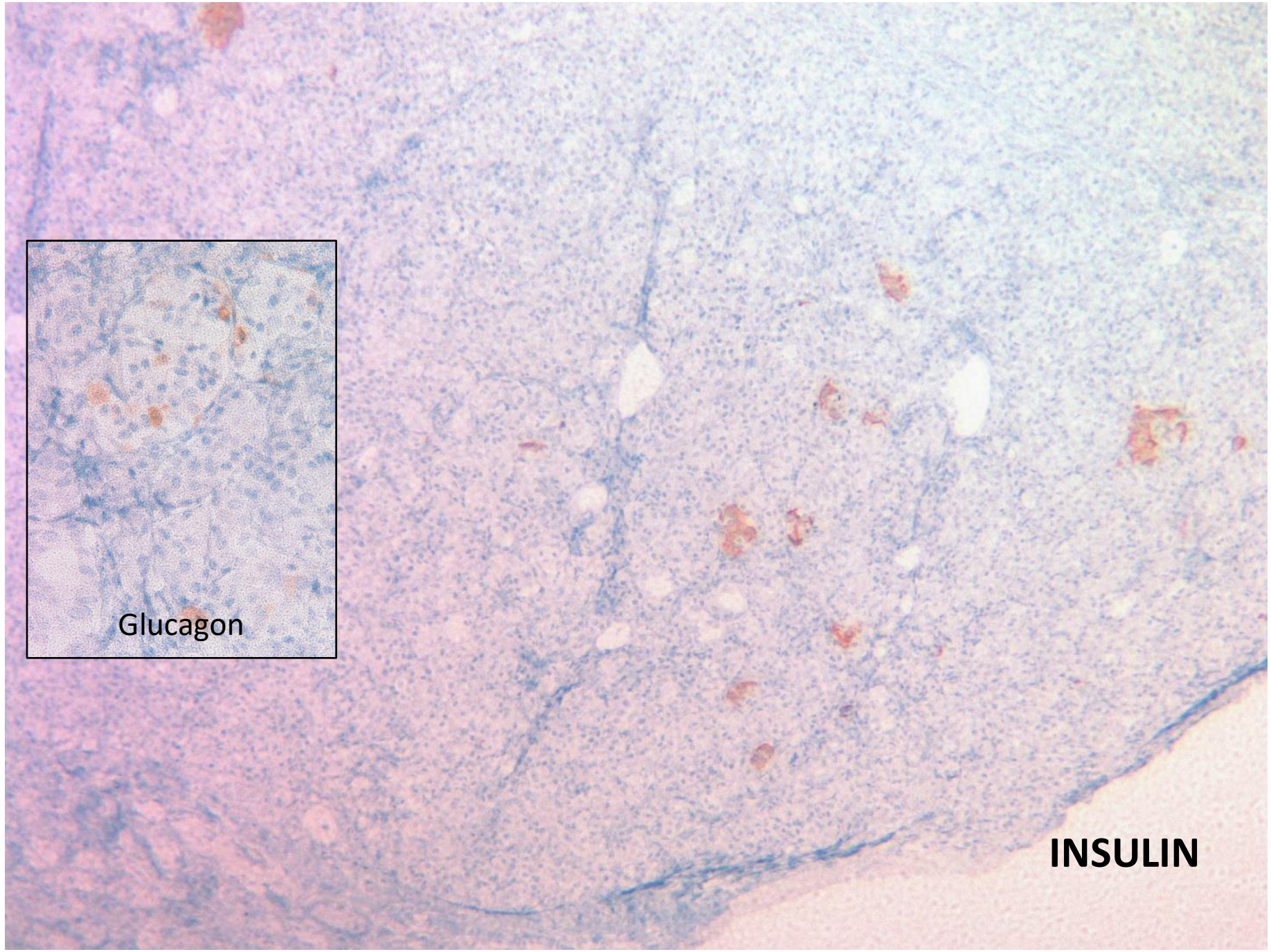


Severe, ongoing AMR with alternating necrosis and organization

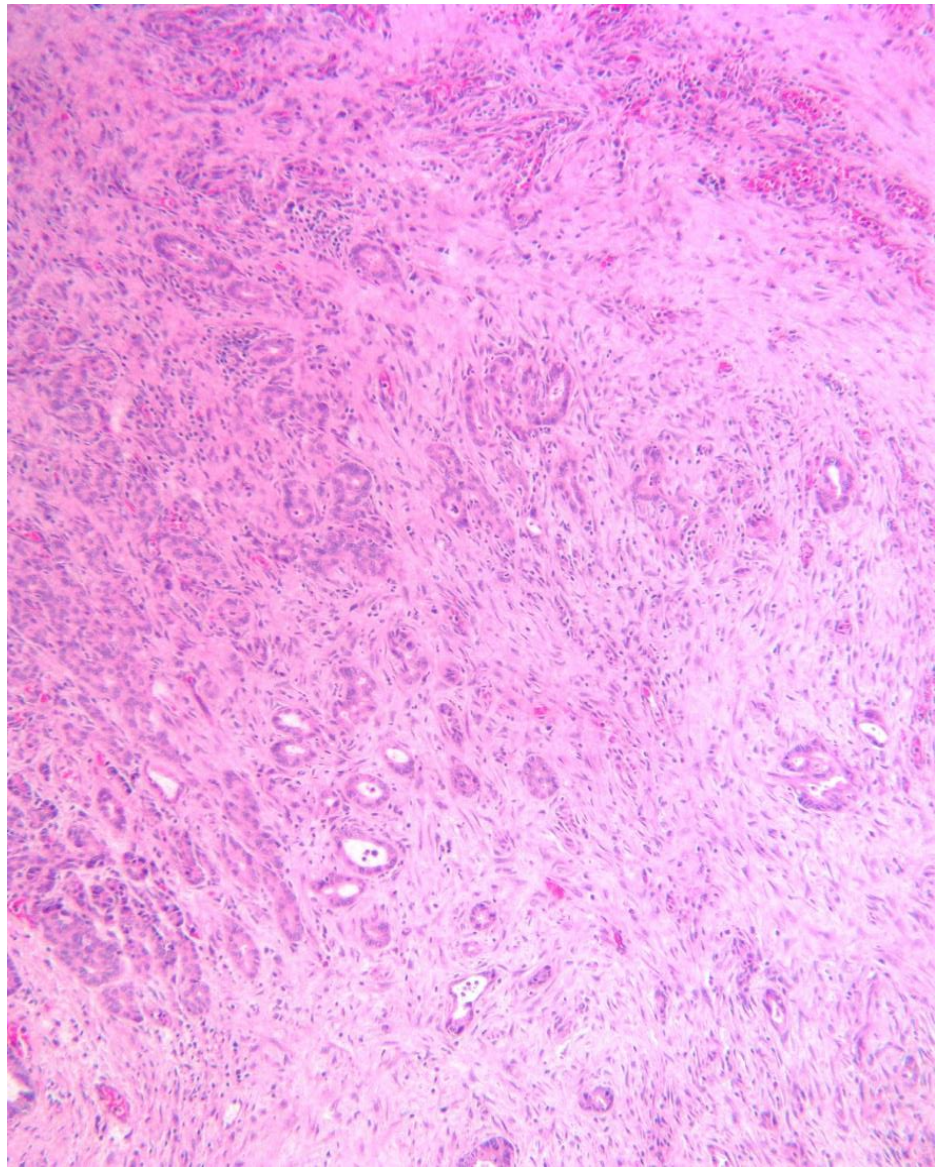


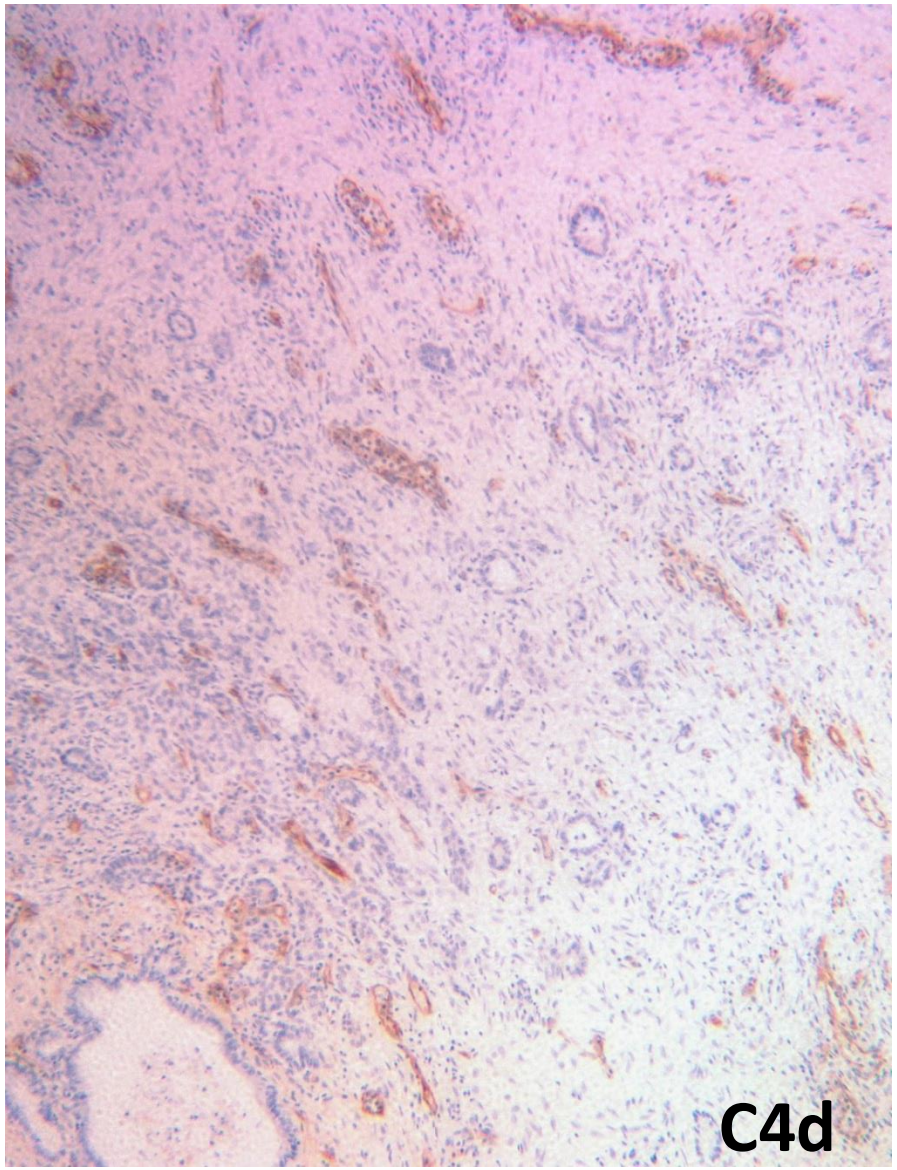
Severe AMR with extensive necrosis and fibrosis

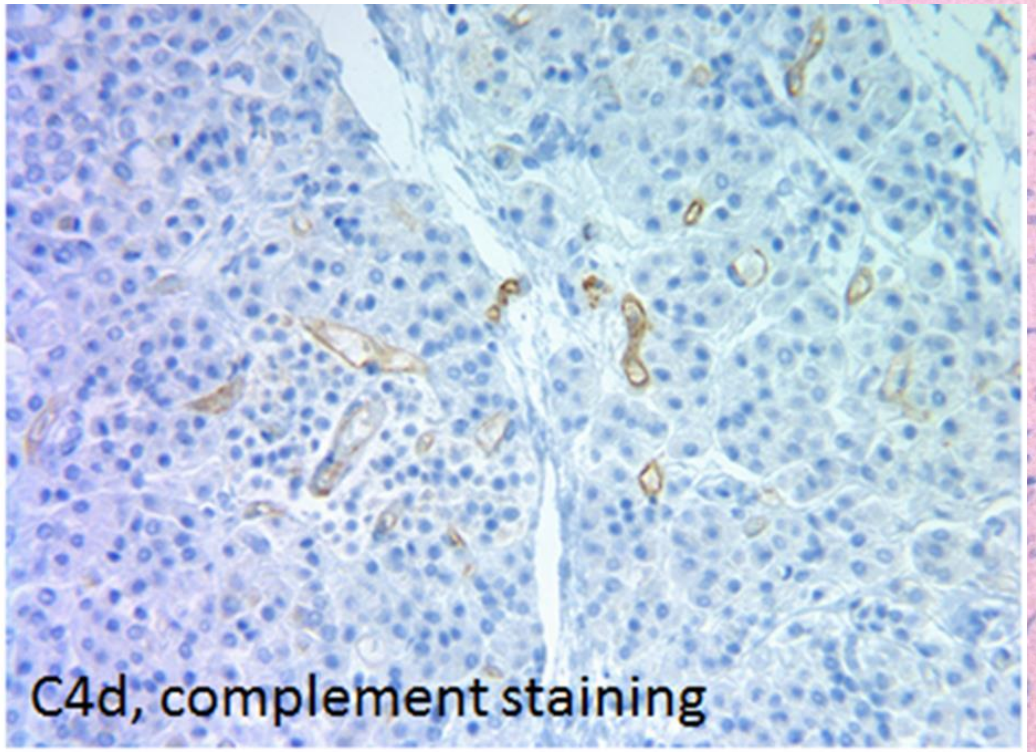



Glucagon
INSULIN

Acute and chronic AMR





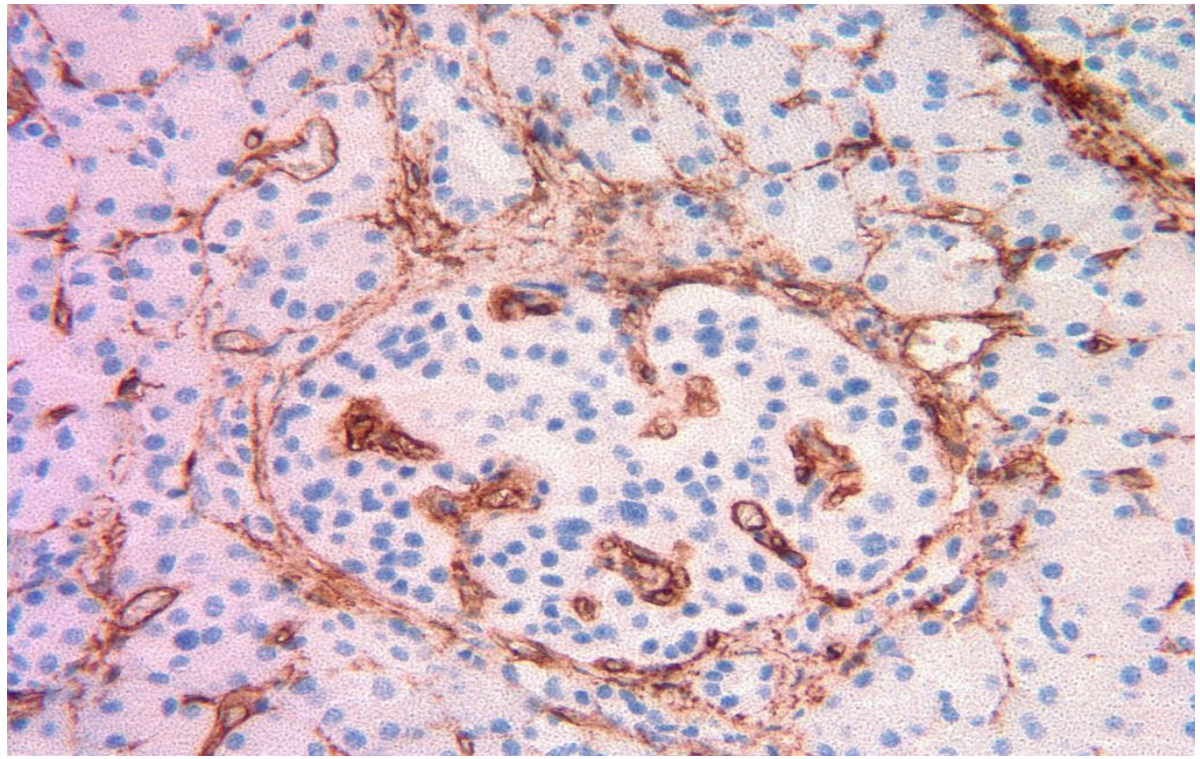


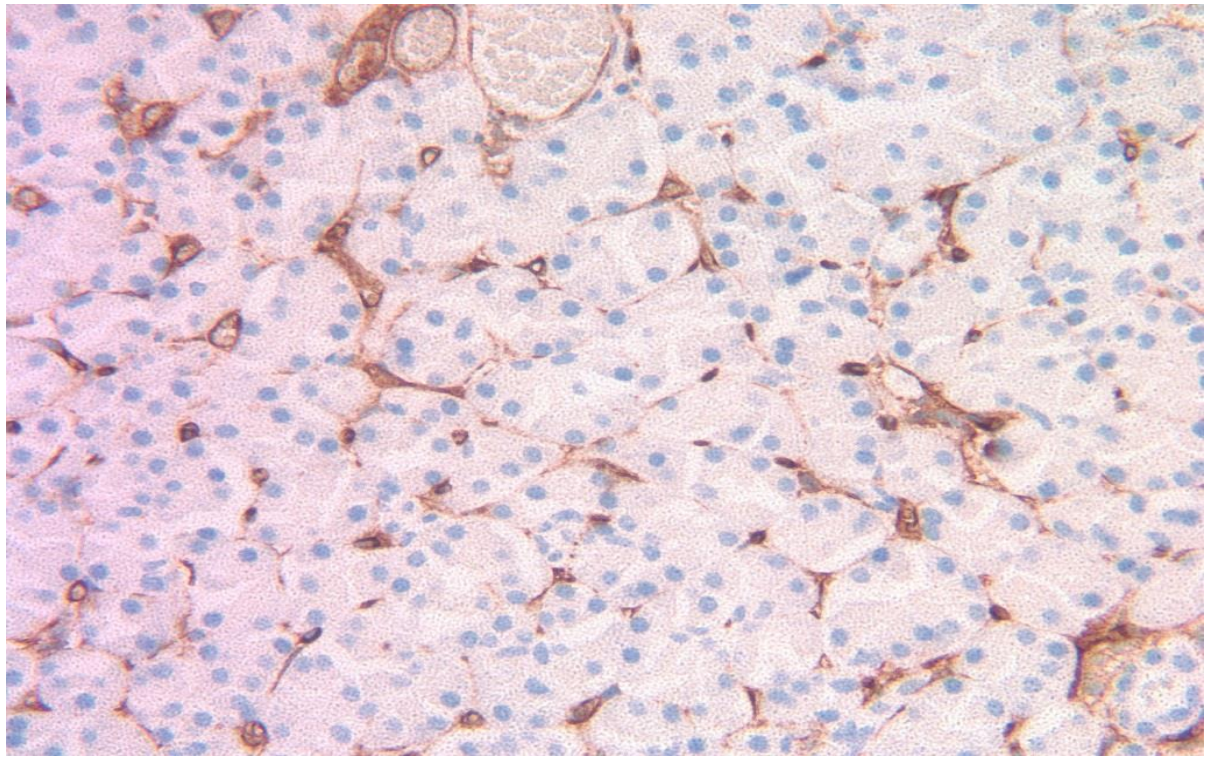
CD34 Residual Vascular Network – chronic AMR

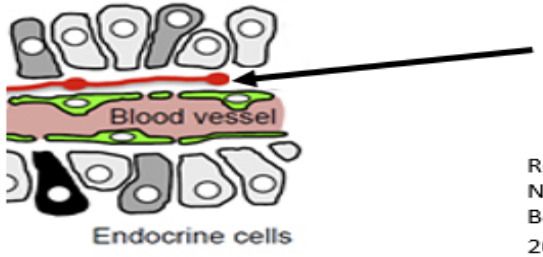
ISLET LOSS/GRAFT FAILURE

Organizational and Structural Integrity in WPTx

CD34 stain for endothelial cells







Sympathetic nerves innervate smooth muscle cells in islet vasculature

Rodriguez-Diaz R, Caicedo A.
Neural control of the endocrine pancreas.
Best Pract Res Clin Endocrinol Metab.
2014 Oct;28(5):745-56.

RESPONSE TO TREATMENT

HISTOLOGIC GRADING OF ACUTE ALLOGRAFT REJECTION IN PANCREAS NEEDLE BIOPSY: Correlation to Serum Enzymes, Glycemia, and Response to Immunosuppressive Treatment1

Papadimitriou, John C.; Drachenberg, Cinthia B.; Wiland, Anne; Klassen, David K.; Fink, Jeffrey; Weir, Matthew R.; Cangro, Charles; Schweitzer, Eugene J.; Bartlett, Stephen T.

Transplantation. 66(12):1741-1745, December 27, 1998.

Biopsy specimen grade	Total number of biopsies	Bx ↗ Ez[a]	Treated[b]	CS[c]	CS/AL	Overall response	% Response CS	% Response CS/AL
0	23	7 (30%)	4	3	1	1 (25%)	1 (33%)	0 (0%)
I	32	16 (50%)	15	11	4	6 (40%)	4 (36%)	2 (50%)
II	30	25 (83%)	25	7	18	22 (88%)	6 (86%)	16 (89%)
III	48	46 (96%)	46	19	27	36 (78%)	13 (68%)	23 (85%)
IV	11	11 (100%)	10	3	7	5 (50%)	0 (0%)	5 (71%)
V	7	7 (100%)	6	0	6	1 (17%)	—	1 (17%)

[a] Bx ↗ Ez = number of biopsies with increased serum enzymes.
[b] From the number with increased enzymes.
[c] Abbreviations used in table: CS, pulse corticosteroids; CS/AL, pulse corticosteroids/antilymphocyte regimen.

Table 1. Histological grade and response to treatment

The University of Wisconsin Diagnosis and Treatment Algorithm *

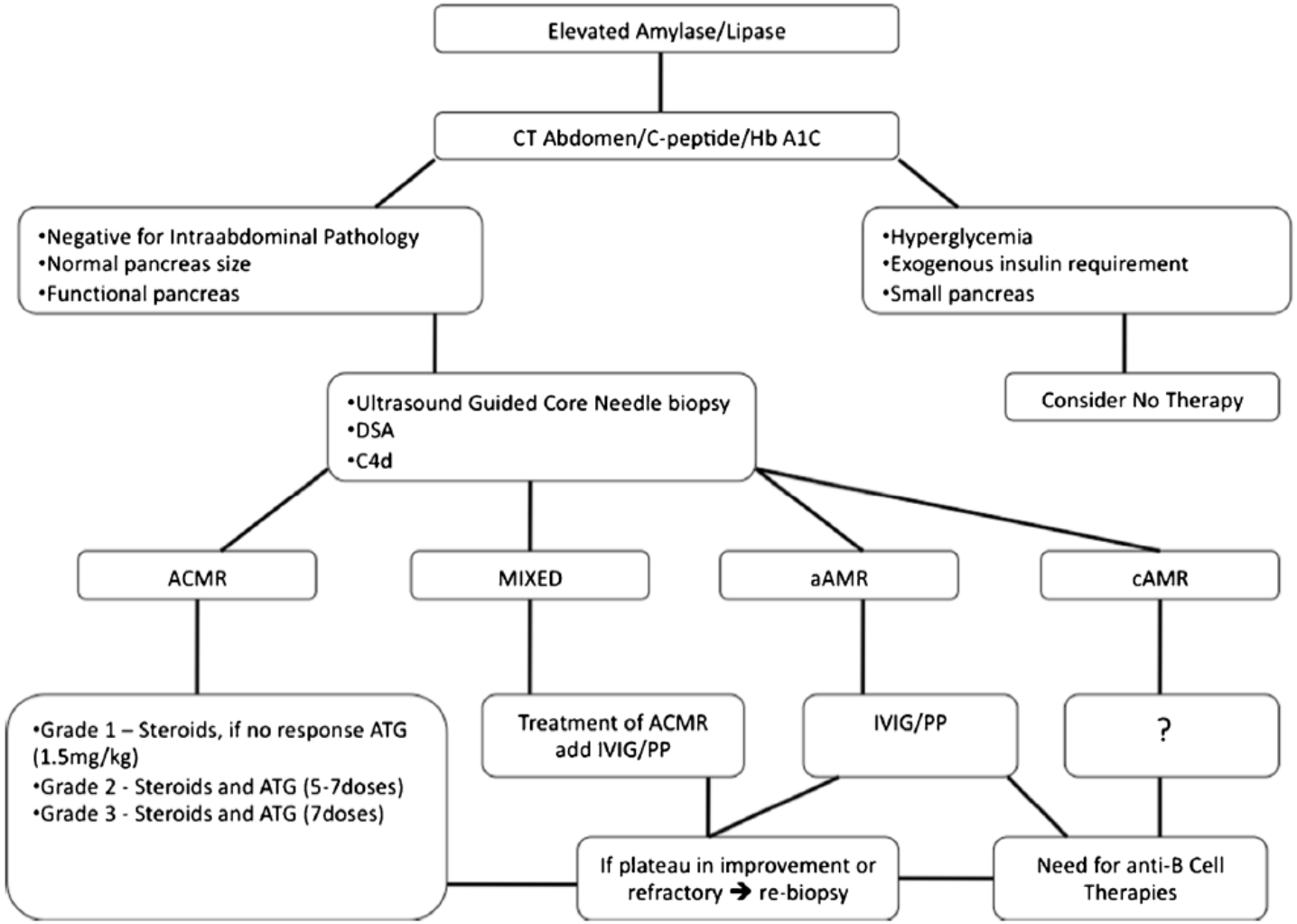


Fig. 2 The University of Wisconsin Diagnosis and Treatment Algorithm Abbreviations: *DSA* donor-specific antibody, *ACMR* acute cell-mediated rejection, *aAMR* acute antibody-mediated rejection, *cAMR* chronic antibody-mediated rejection, *ATG* anti-thymocyte globulin, *IVIg* intravenous immunoglobulin, *PP* plasmapheresis. [(Published in Trends in Transplantation, © Permanyer Publications) 2].

Redfield RR, Kaufman DB and Odorico JS Curr Transpl Rep 2015 2:169-75

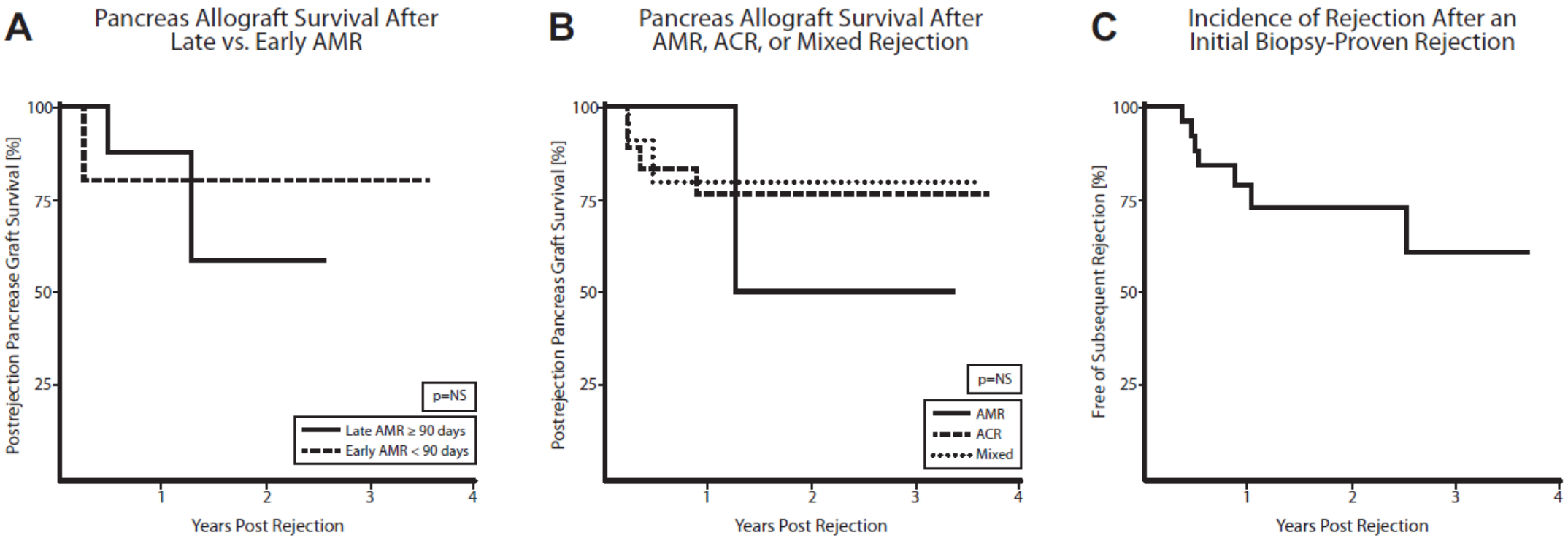
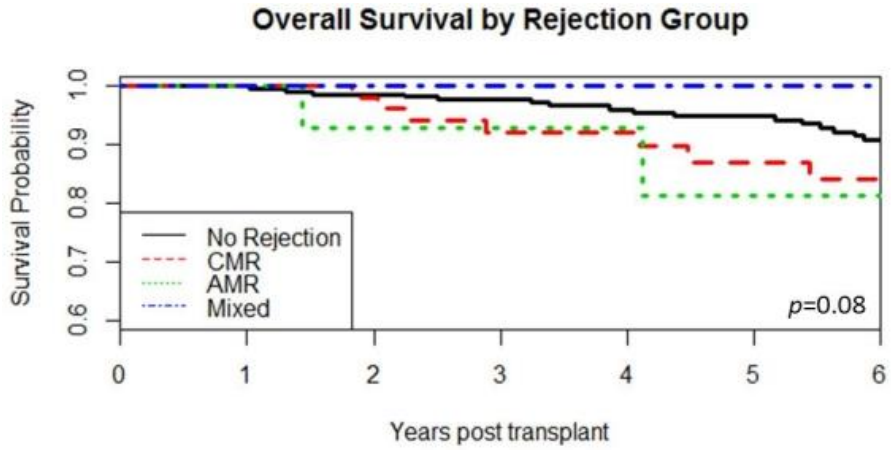


Figure 8: (A) Pancreas transplant allograft survival after pancreas graft antibody-mediated rejection (AMR) stratified by early (<90 days) or late (≥90 days) AMR. (B) Pancreas transplant allograft survival after rejection stratified by type of rejection, including biopsy-proven acute cellular rejection (ACR), AMR and mixed rejection. (C) Incidence of recurrent rejection after an initial biopsy-proven pancreas rejection episode.

S. V. Niederhaus et al., American Journal of Transplantation 2013; 13: 2945–2955



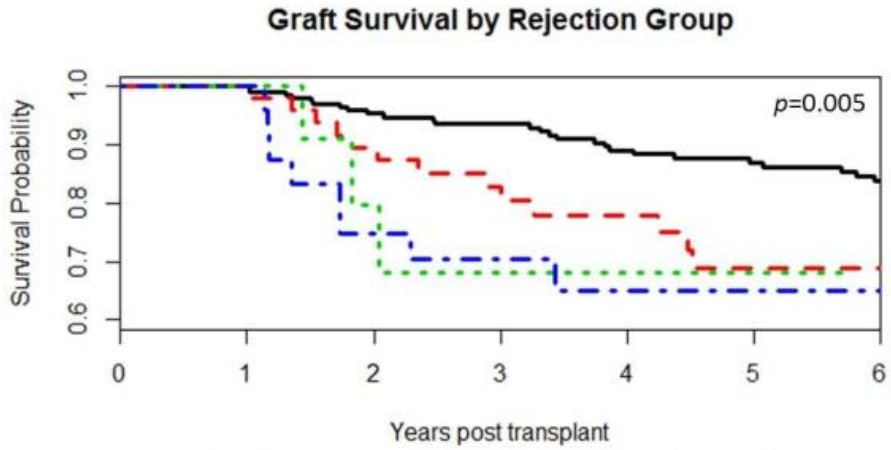


Figure 1. Overall Patient (A) and Graft (B) Survival for Patients with AMR, CMR, Mixed Rejection, or No Rejection.

Antibody-Mediated Rejection in Pancreas Transplantation.

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A Single-center Experience on the Value of Pancreas Graft Biopsies and HLA Antibody Monitoring After Simultaneous Pancreas-Kidney Transplantation

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ABSTRACT

Background. In simultaneous pancreas-kidney transplantation (SPKT), monitoring of the pancreas allograft is more complex than the kidney allograft due to difficulties in obtaining pancreas histology and weak clinical evidence supporting the role of donor-specific antibodies (DSA).

Methods. We performed a single-center retrospective analysis of all 17 SPKT recipients who underwent a total of 22 pancreas allograft indication biopsies from October 2009 to September 2012. Fifteen patients had at least 2 DSA measurements: pretransplantation and at the time of biopsy.

Results. All 7 patients (100%) with post-transplantation DSA-positivity (de novo: n = 6; persistent: n = 1) at biopsy had at least 1 rejection episode either of the pancreas (n = 4) or the kidney (n = 3), with 3 antibody-mediated rejections (AMR). In contrast, only 4 of 8 patients (50%) without post-transplantation DSA had evidence of rejection, with 1 AMR. Findings during pancreas allograft biopsy procedures led to a change of immunosuppressive therapy in 11 of 15 (73%) patients. Patient survival, graft survival, and function were not adversely affected by the presence of post-transplantation DSA. One major and 2 minor procedure-related complications occurred during the pancreas biopsies.

Conclusions. In this small retrospective analysis, pancreas allograft histology provided the most therapeutically relevant information, rather than the kidney histology or DSA monitoring.

http://dx.doi.org/10.1016/j.transproceed.2015.09.013

Conclusions

- Despite available antirejection, a minority of pancreas transplants are lost to refractory rejection.
- Refractory TCMR is characterized by ongoing cellular inflammation progressively destroying acinar parenchyma and the overall vasculature.
- Refractory AMR presents with predominantly microvascular injury in both exocrine and endocrine parenchyma.
- The islets are not specifically targeted by either type of rejection but

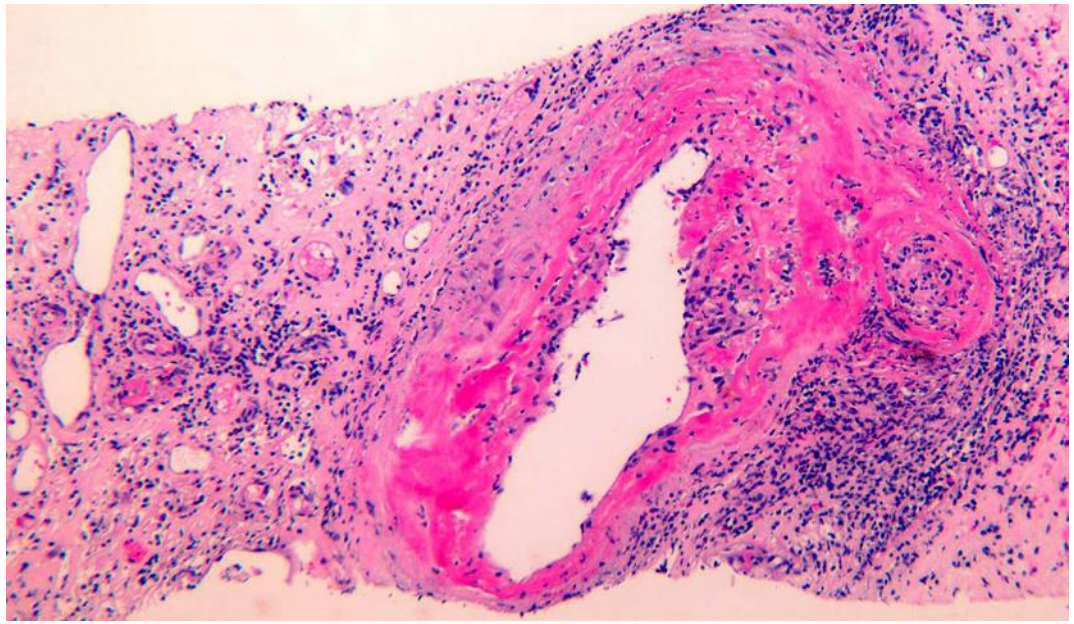
are eventually unable to function in this distorted milieu.

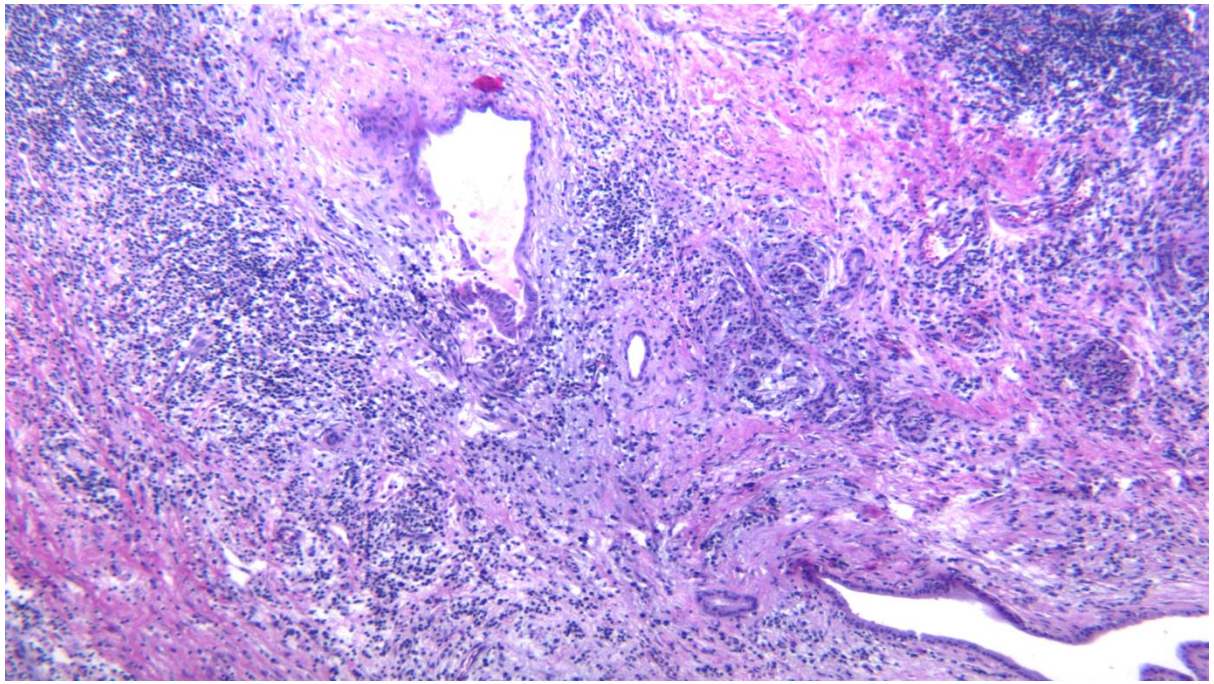
Remaining questions

- Chronic active TCMR and AMR , that have been defined in the kidney

need to be better characterized in the pancreas.

- Characterization of AMR has been limited up to now due to fewer cases (e.g. early versus late, de novo DSA, etc) .
- To examine the response to antirejection treatment according to the grade of AMR.





MIXED ACTIVE CHRONIC TCMR AND AMR