NKM Laboratório
Patologia e Citopatologia

SBP
Sociedade Brasileira de Patologia

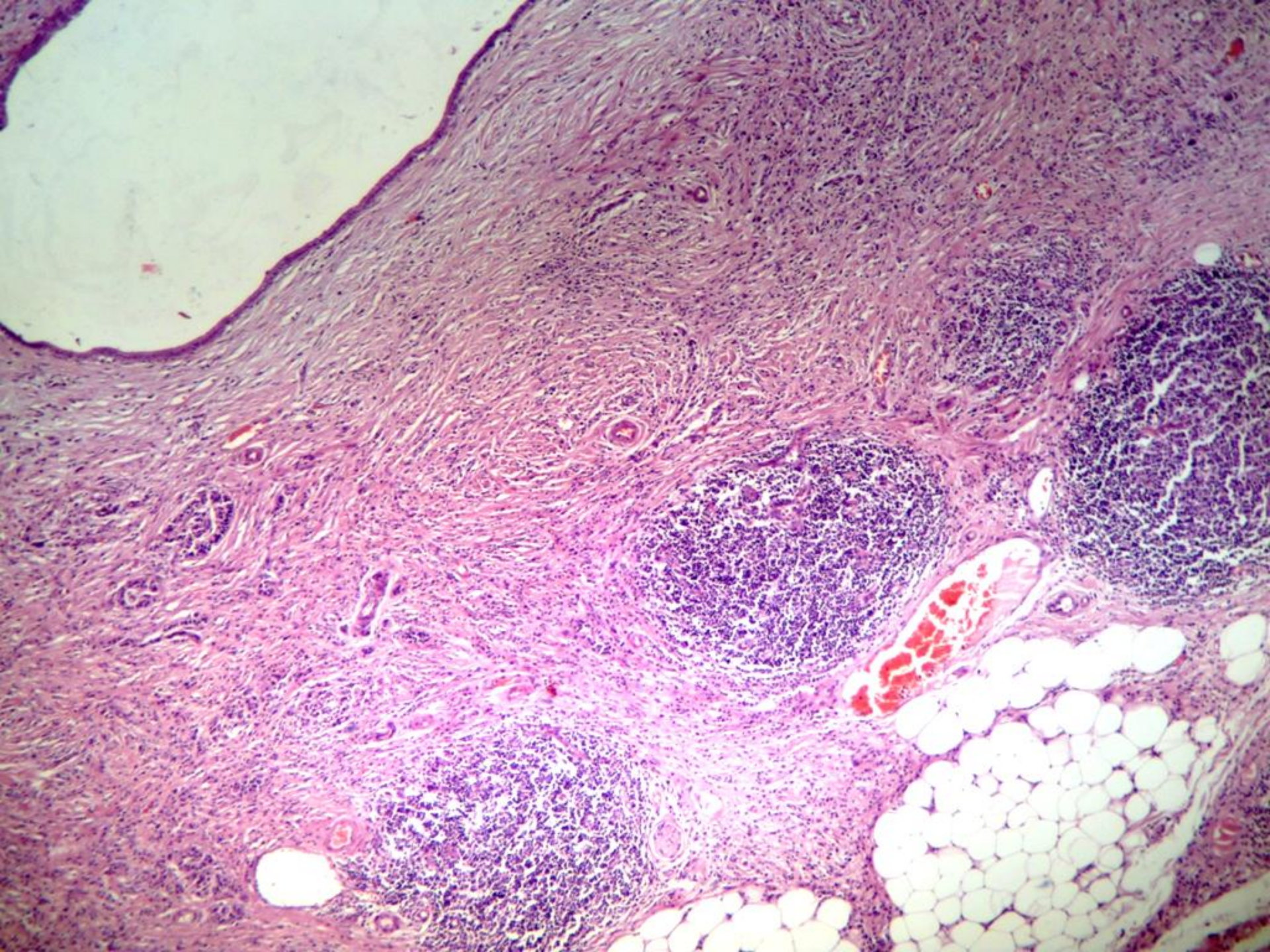
Caso do mês – Agosto/2016 - 2

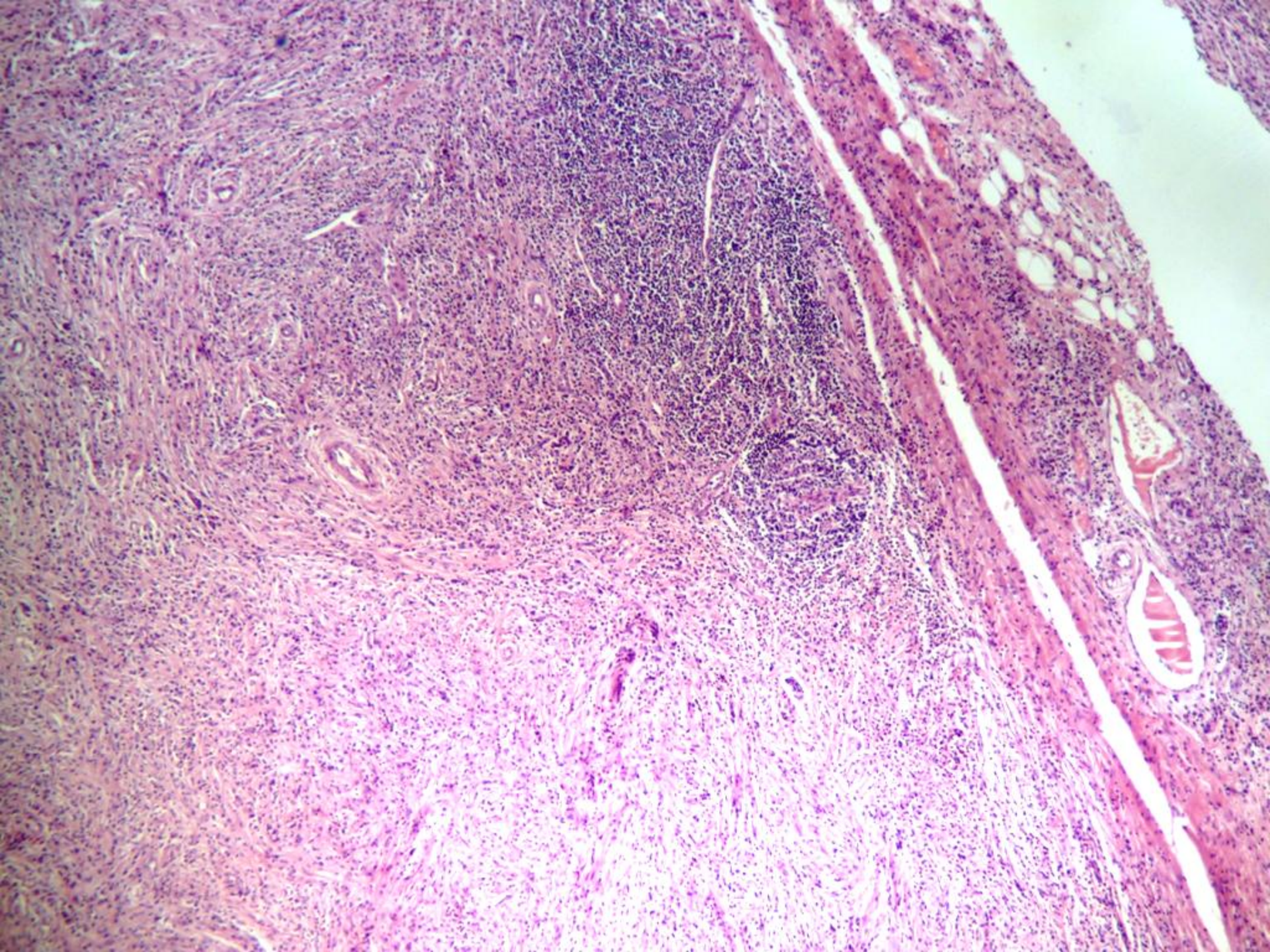
Carlos Camilo Neto

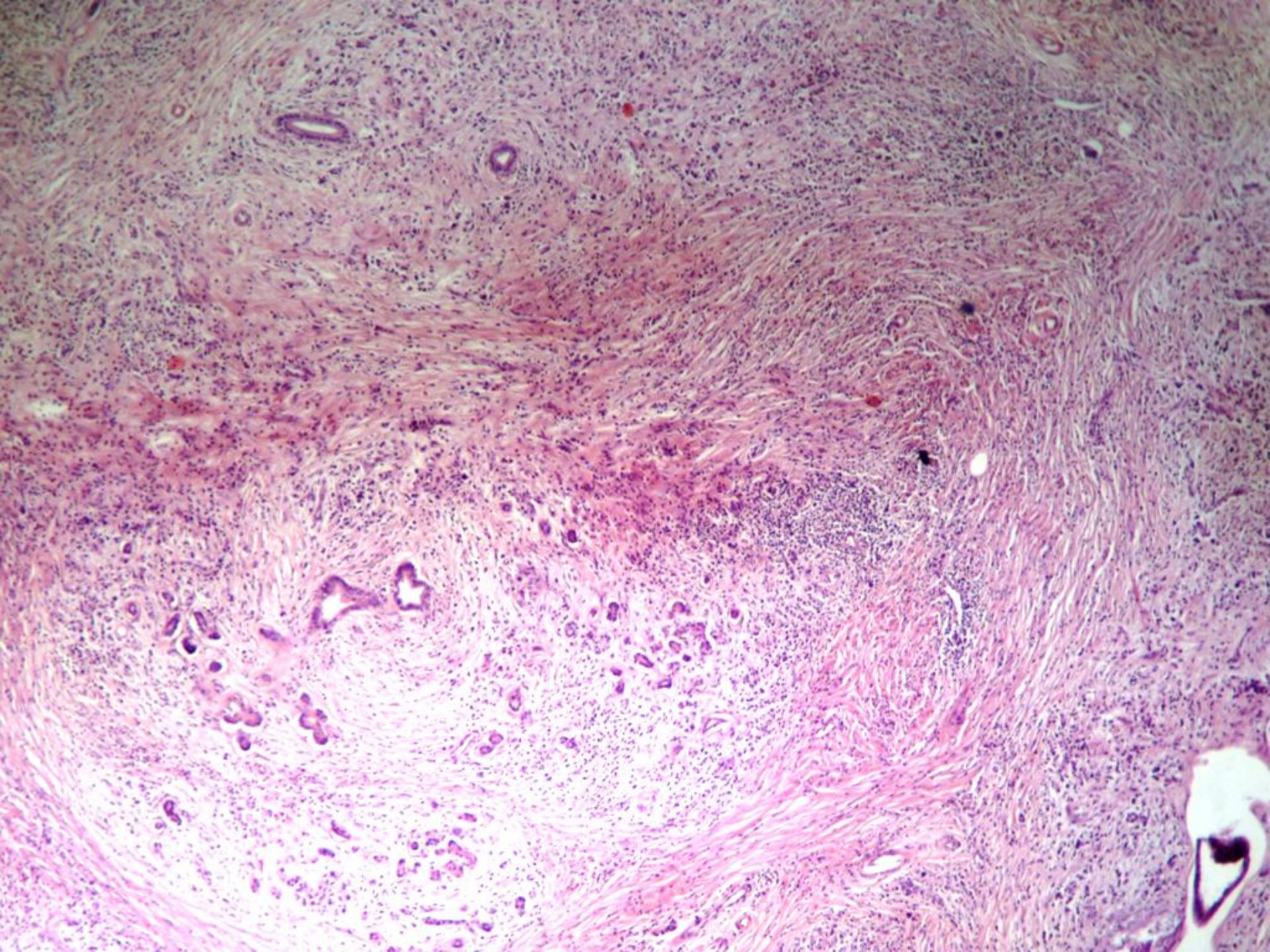
. CCR, feminino, 63 anos

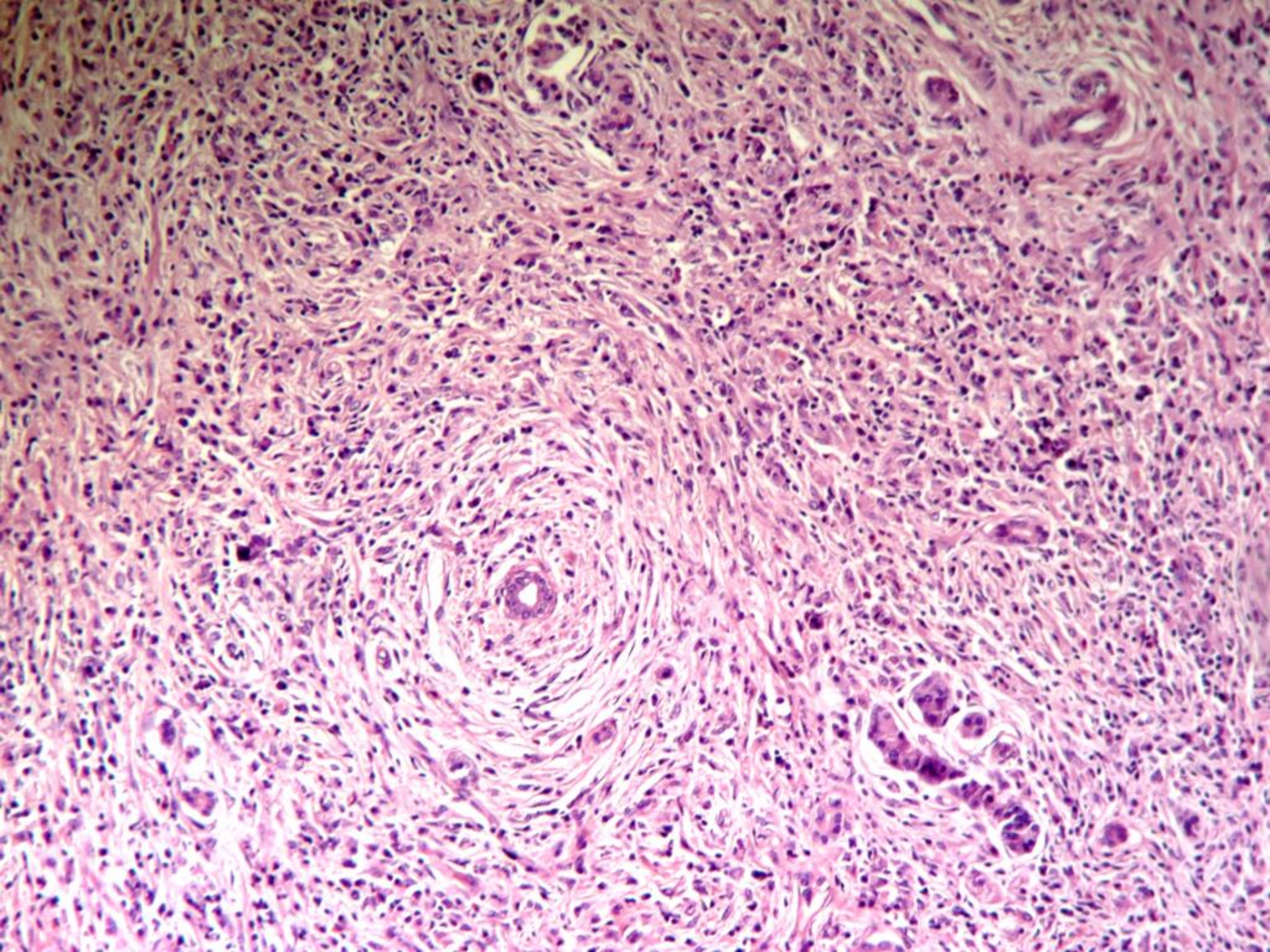
. Massa em cabeça de pâncreas a/e e icterícia obstrutiva

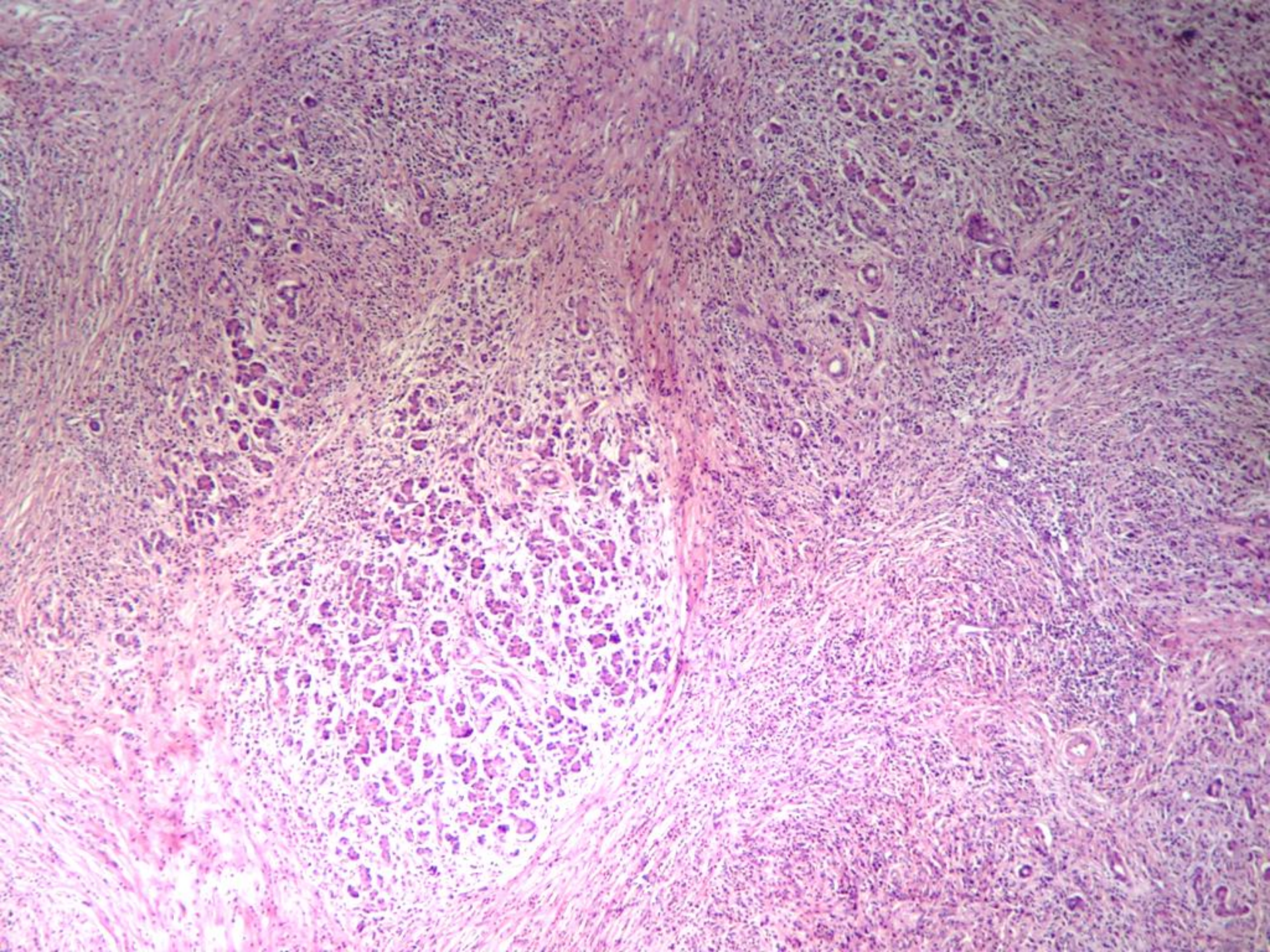
. Material enviado: GDP e vesícula biliar

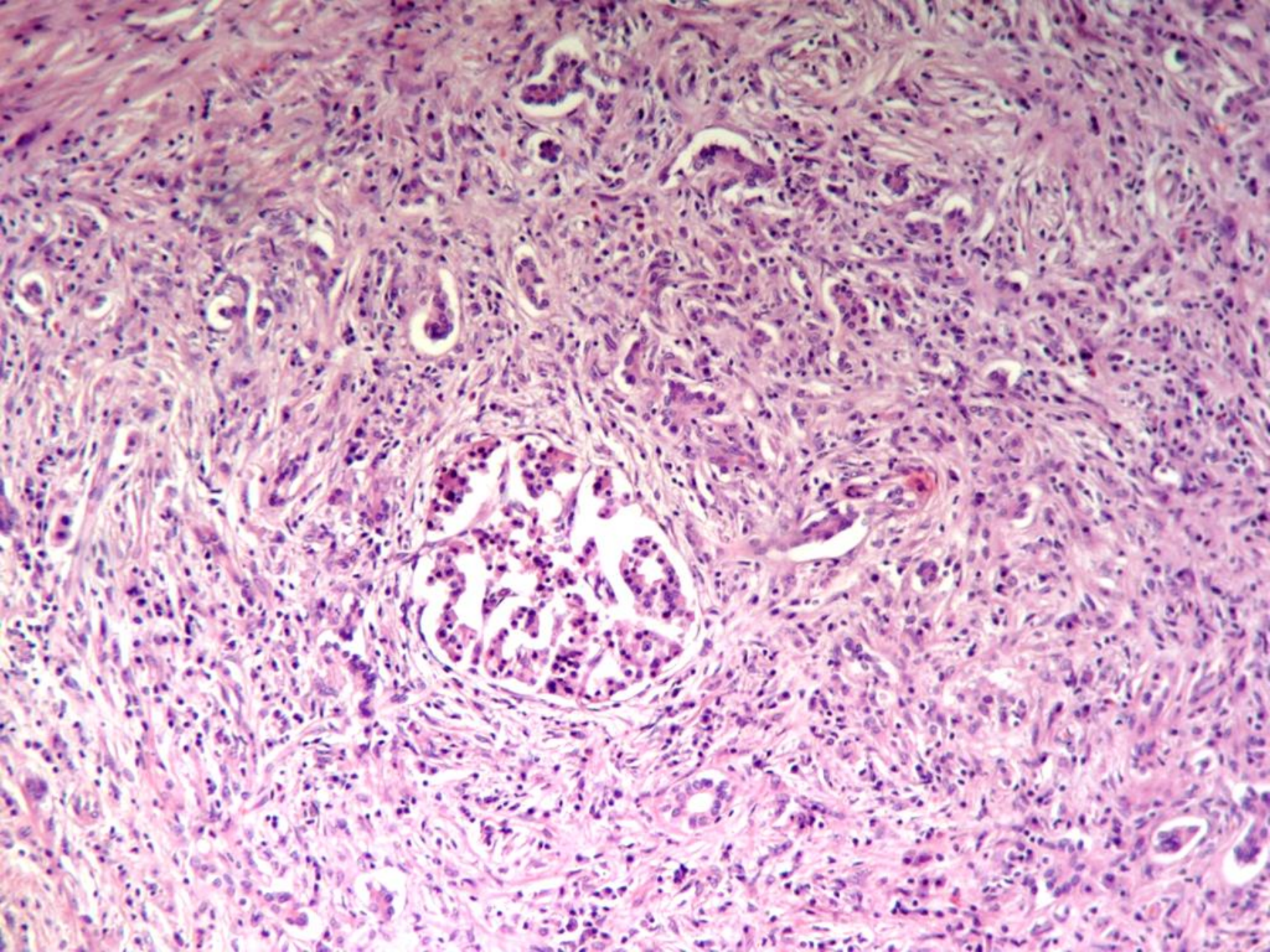


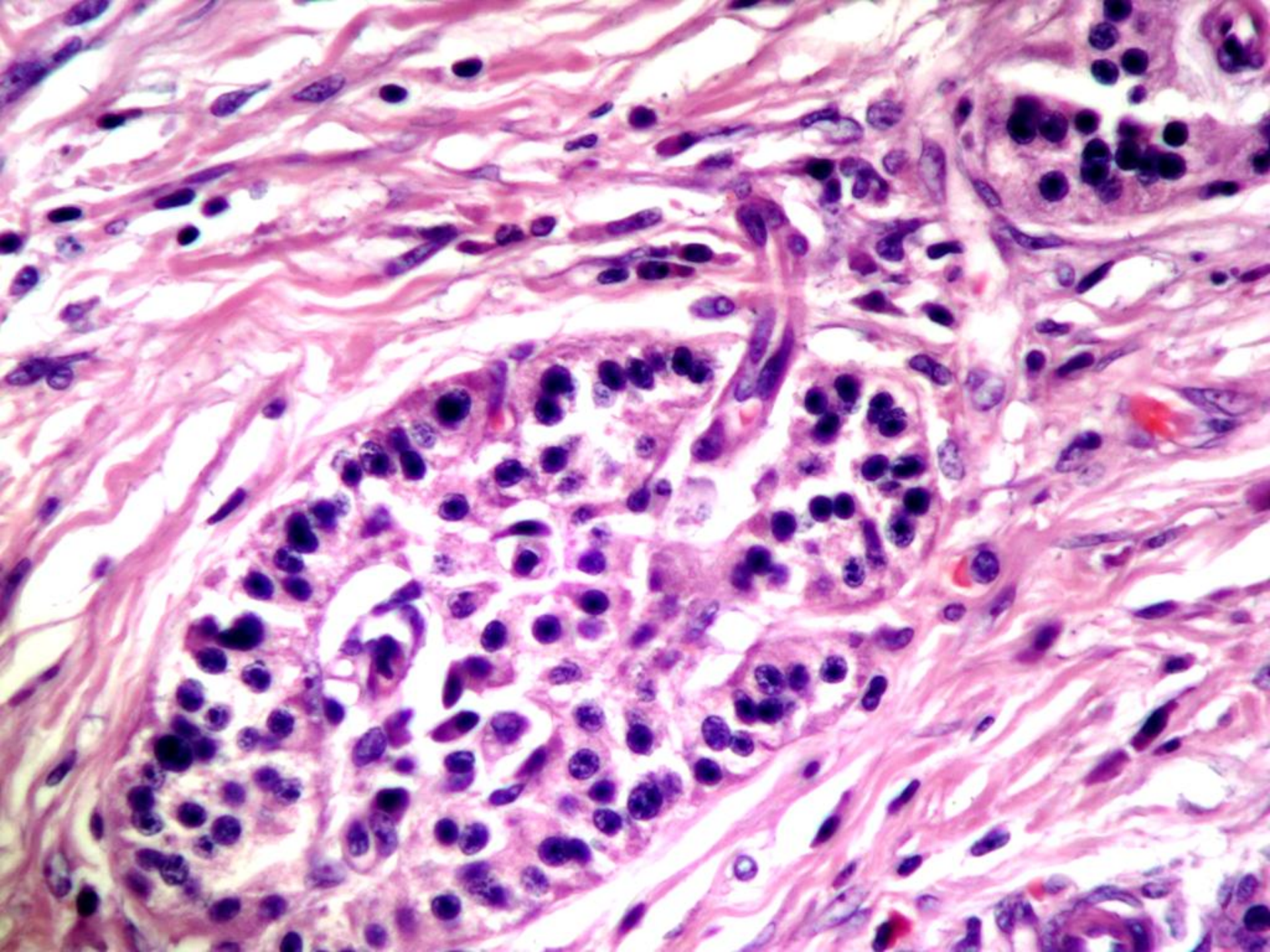


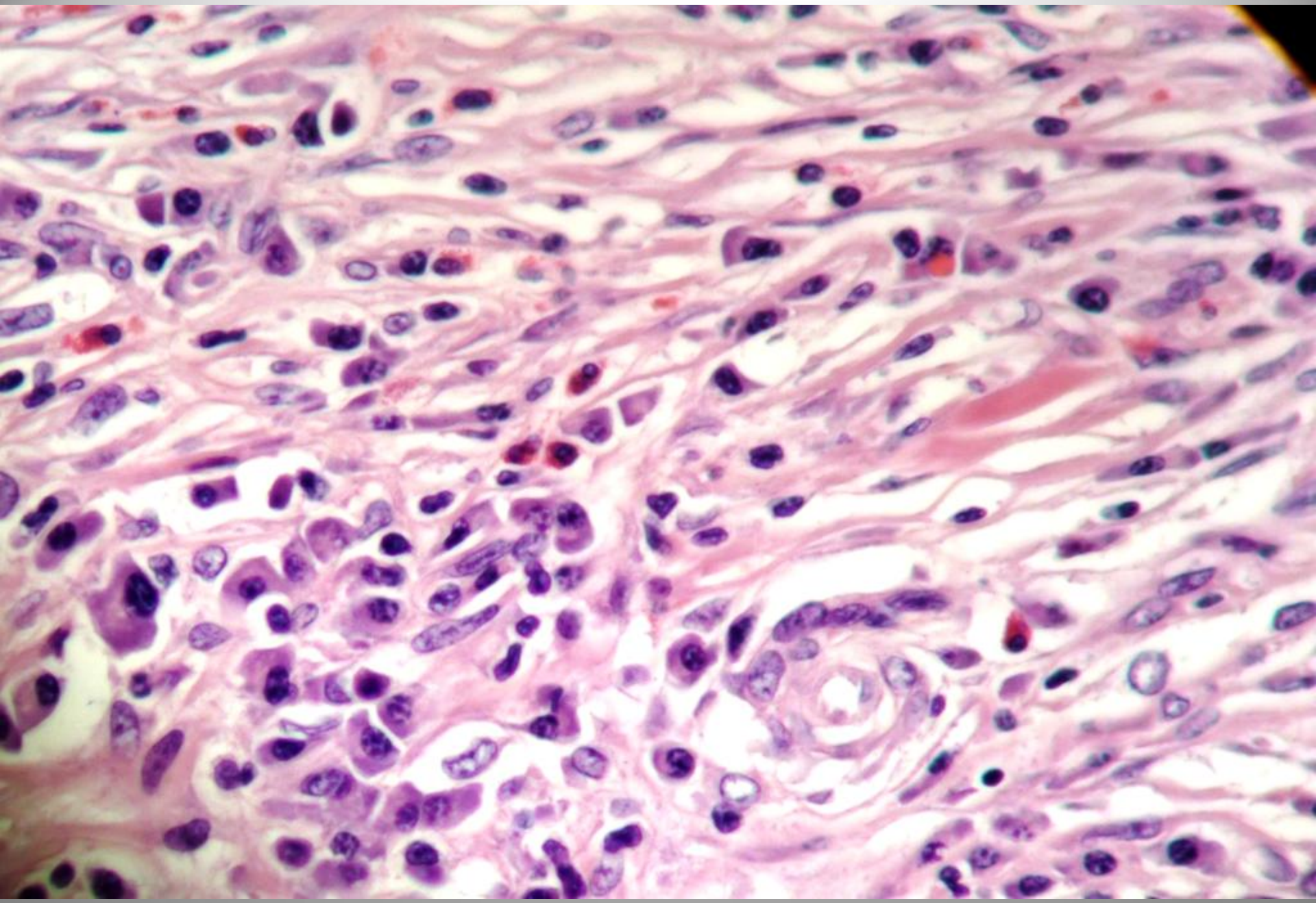


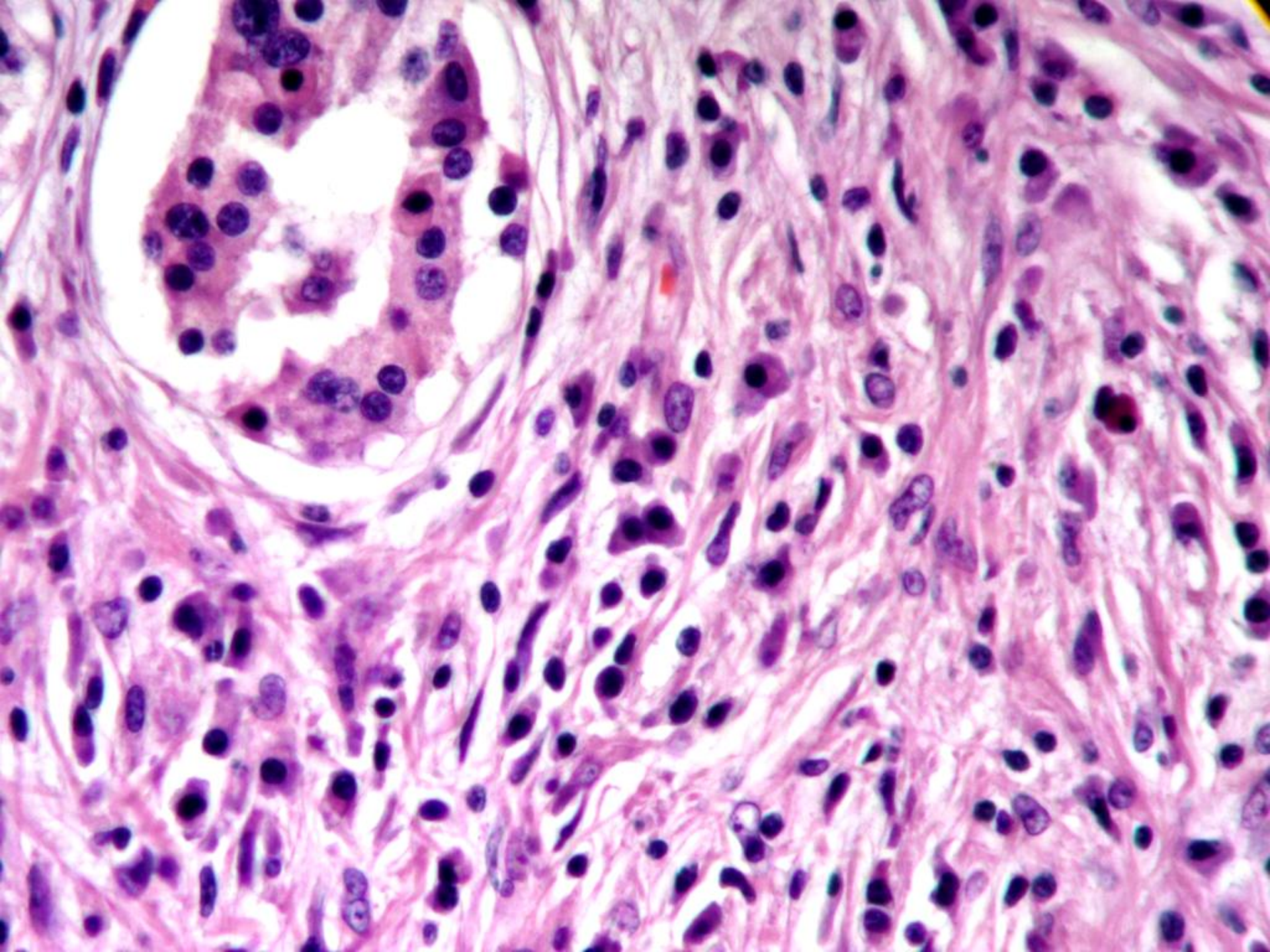


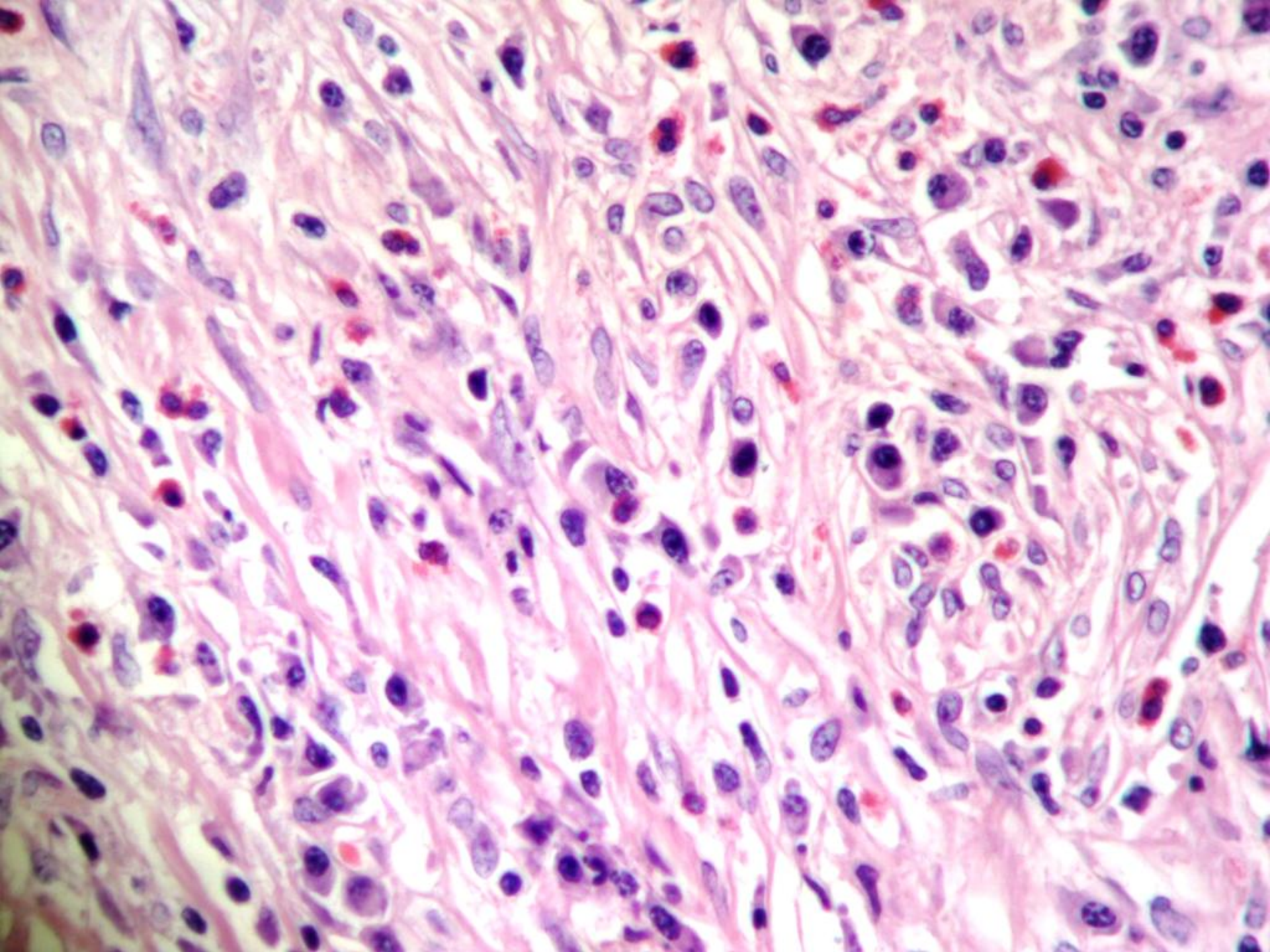


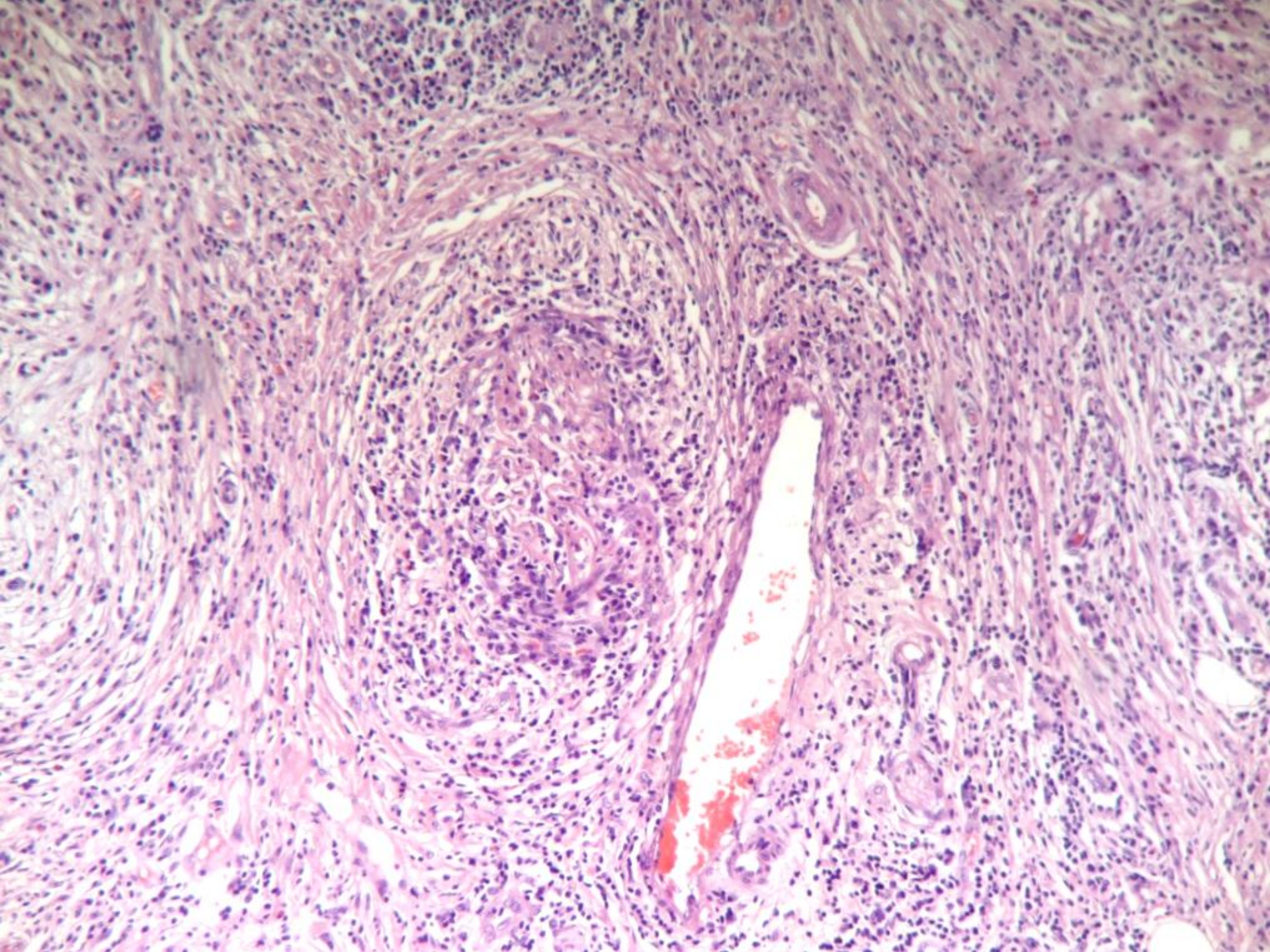


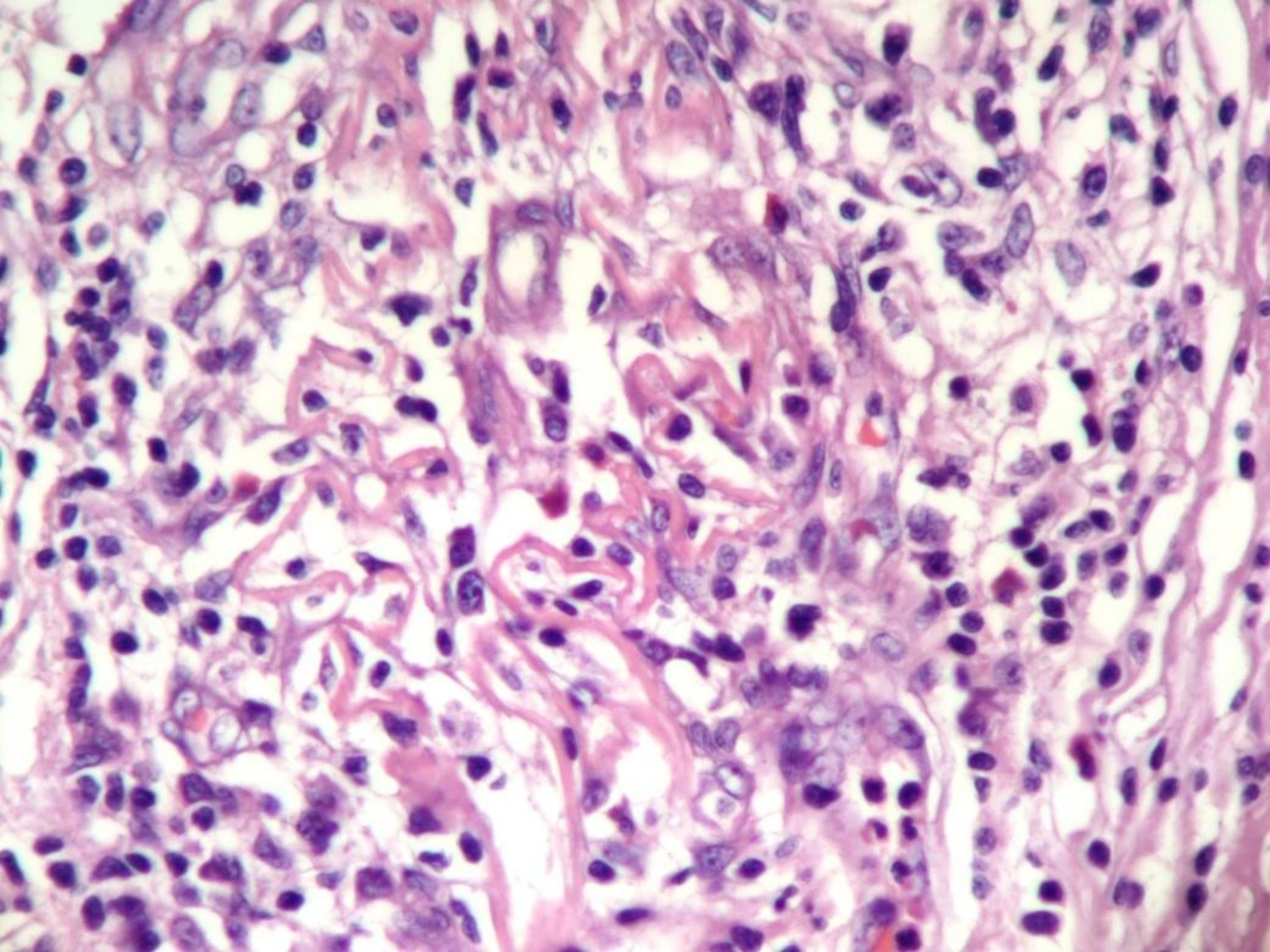




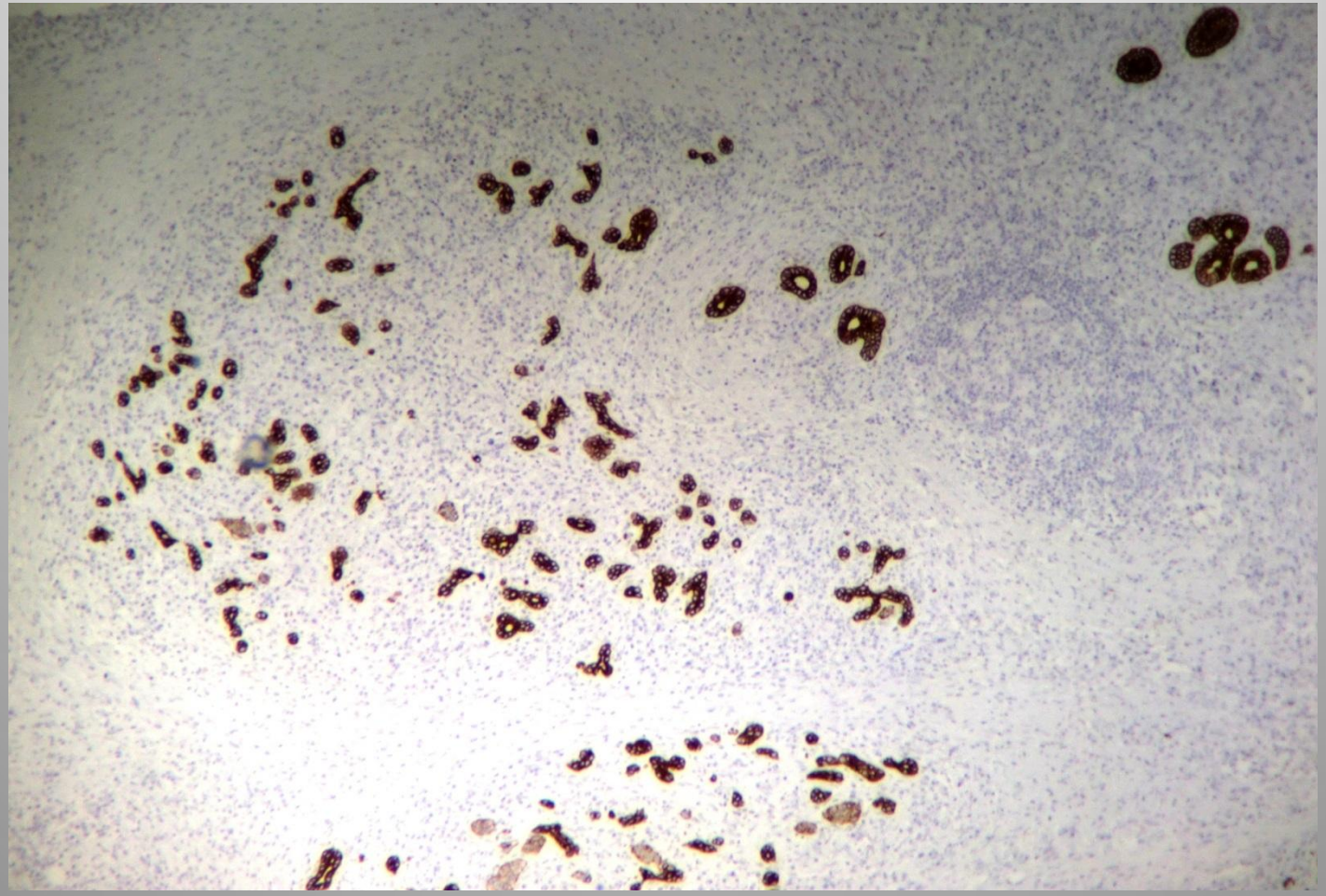








AE1-AE3



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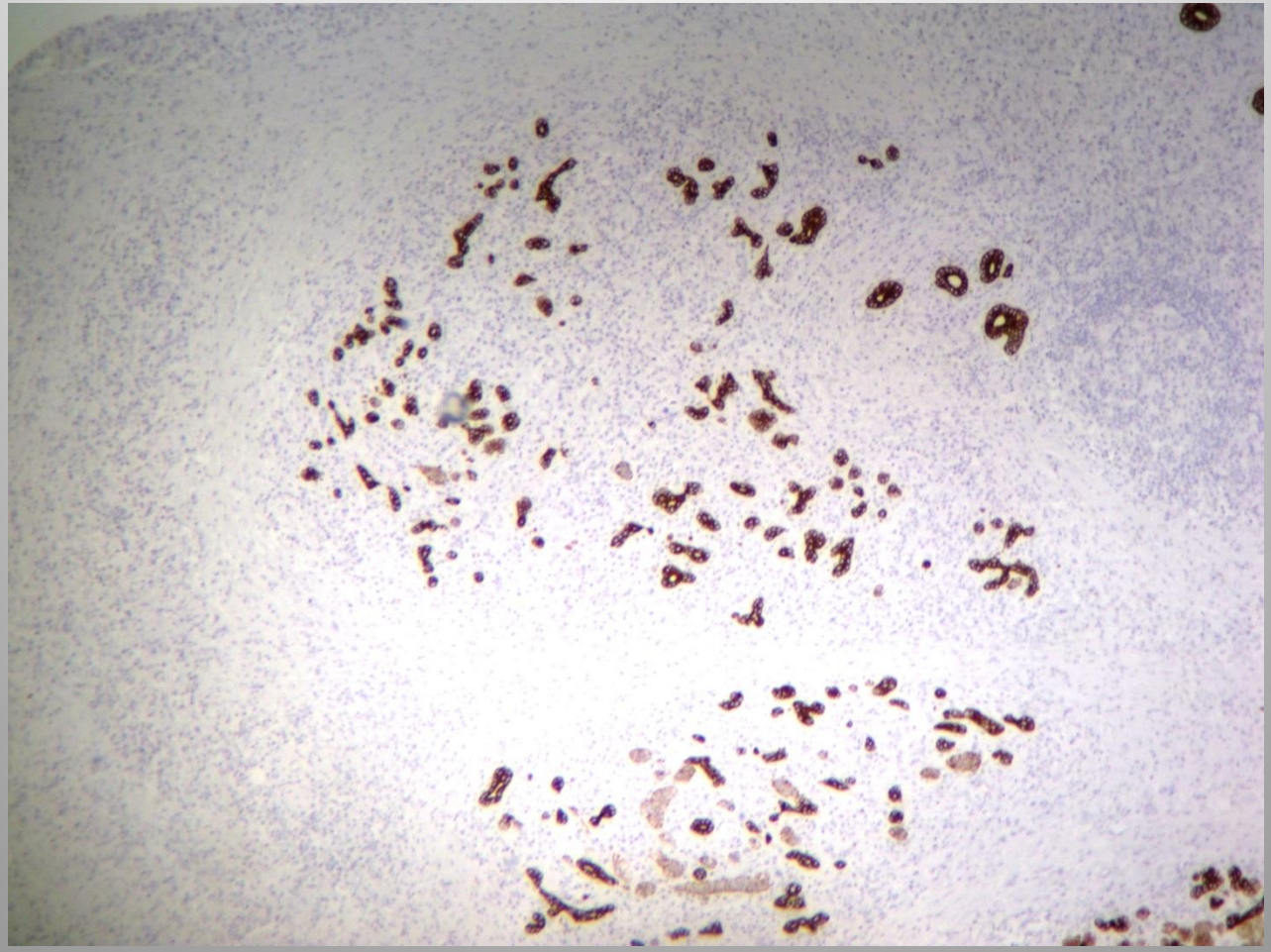

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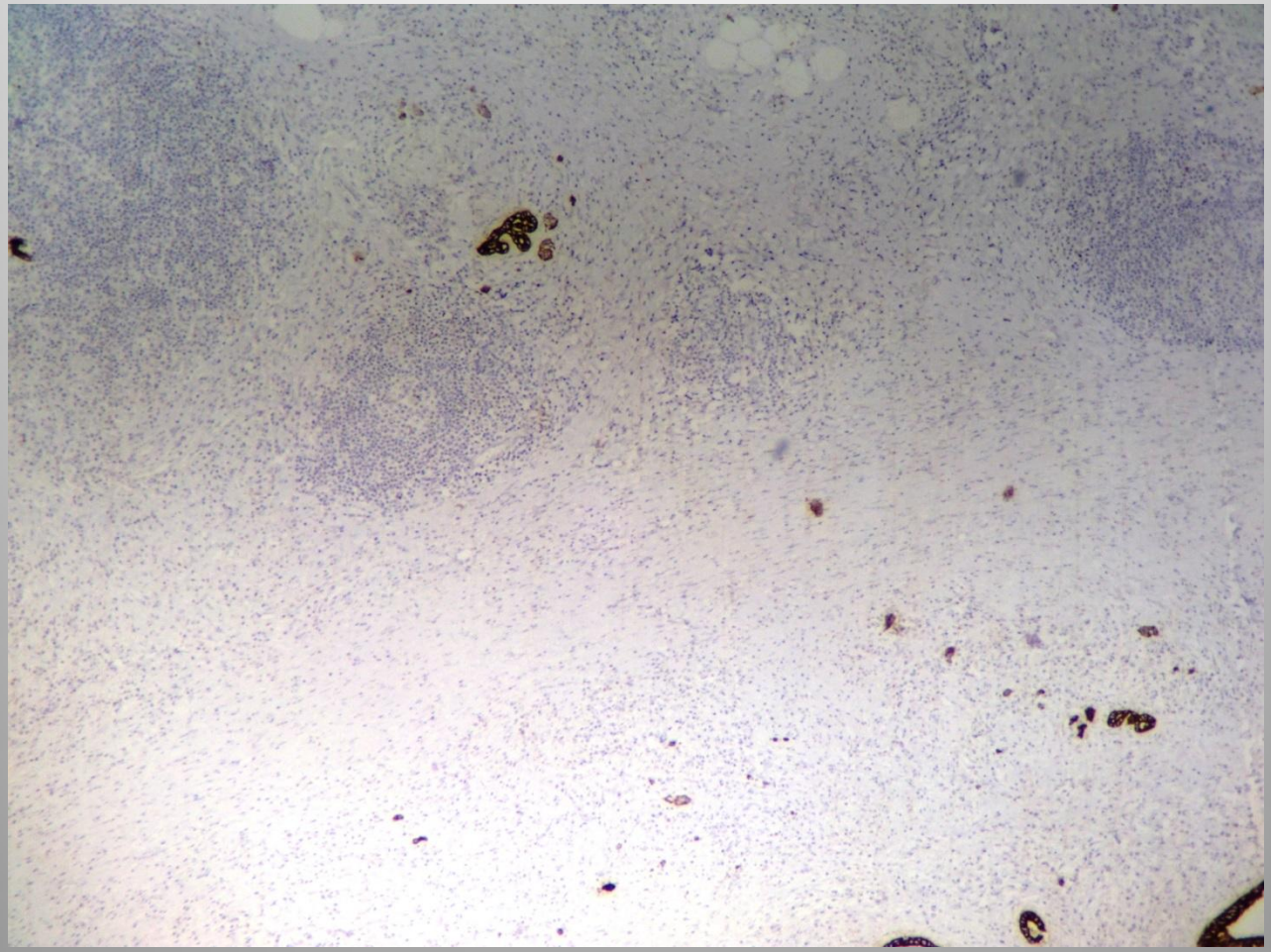

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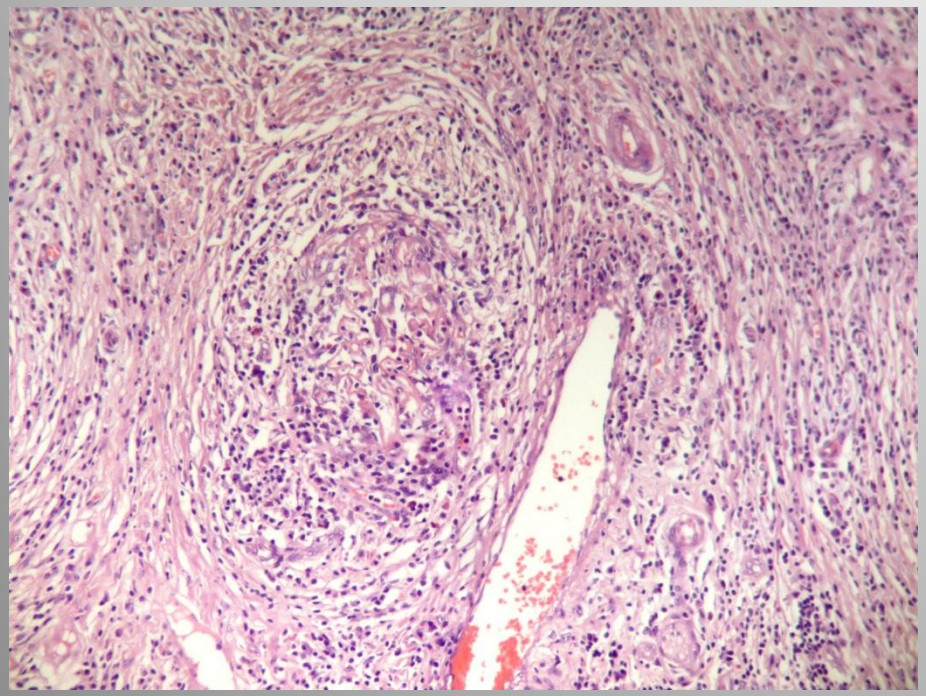

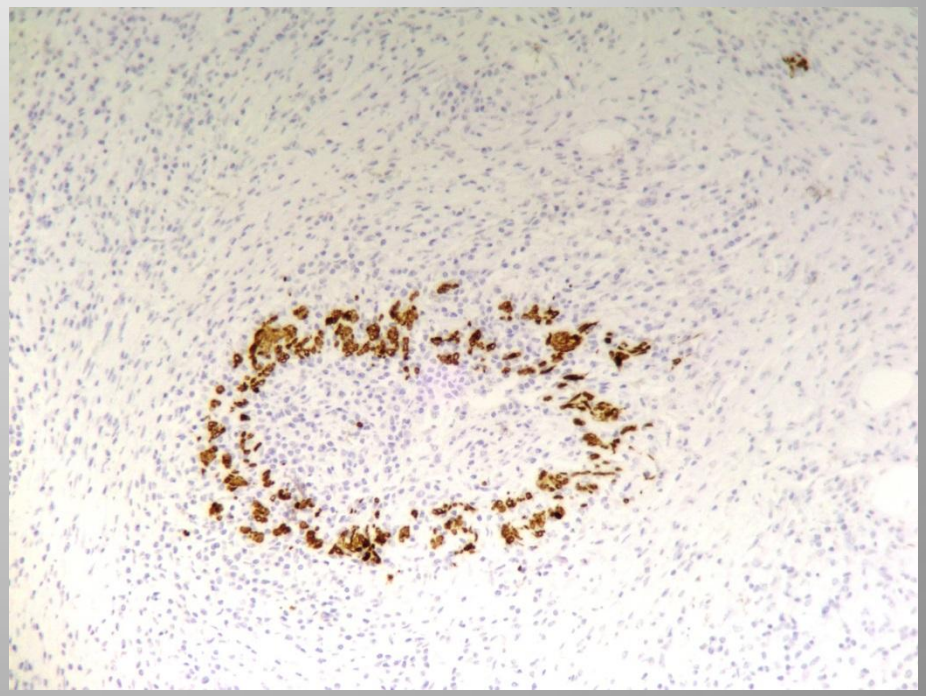

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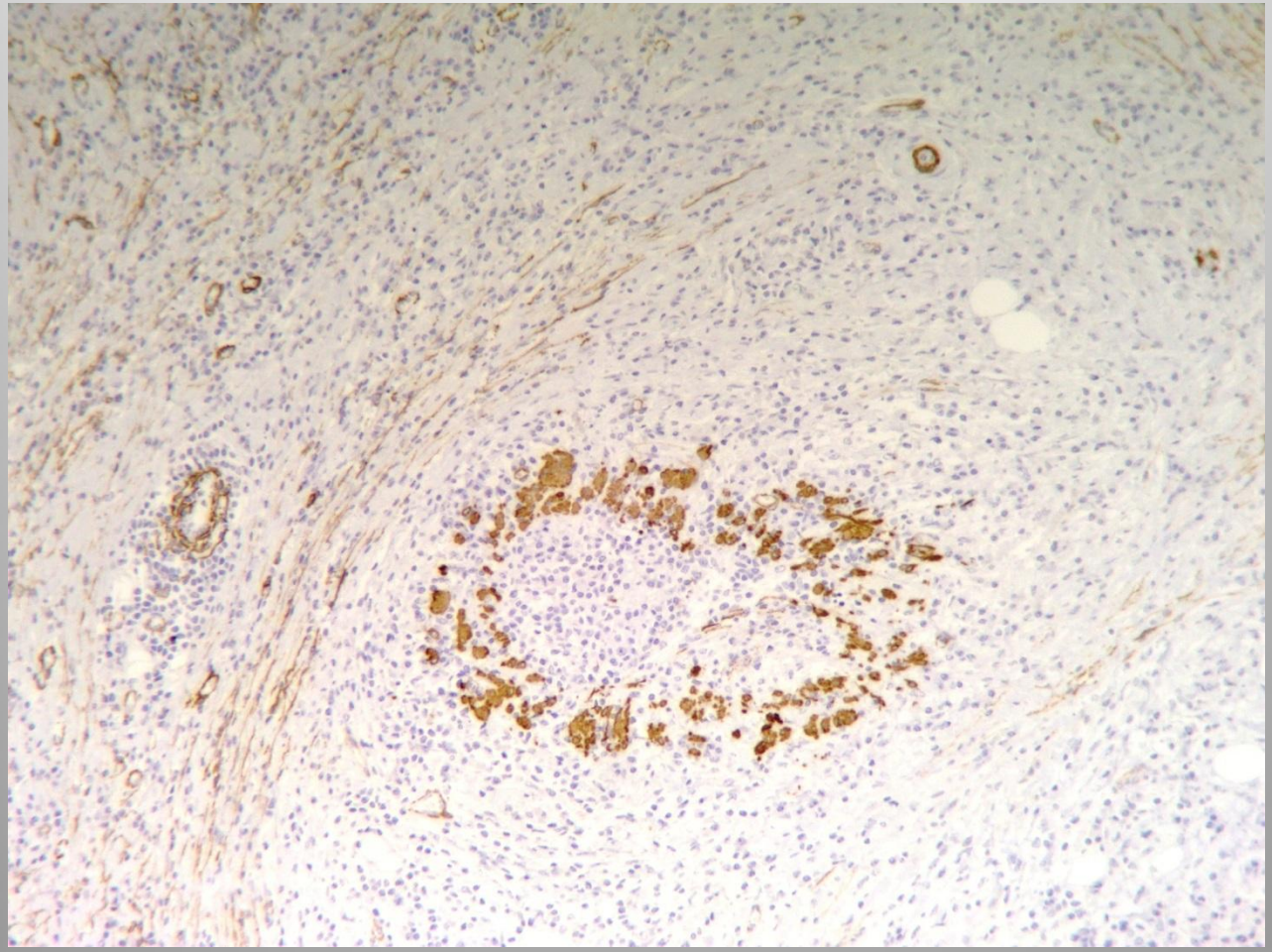
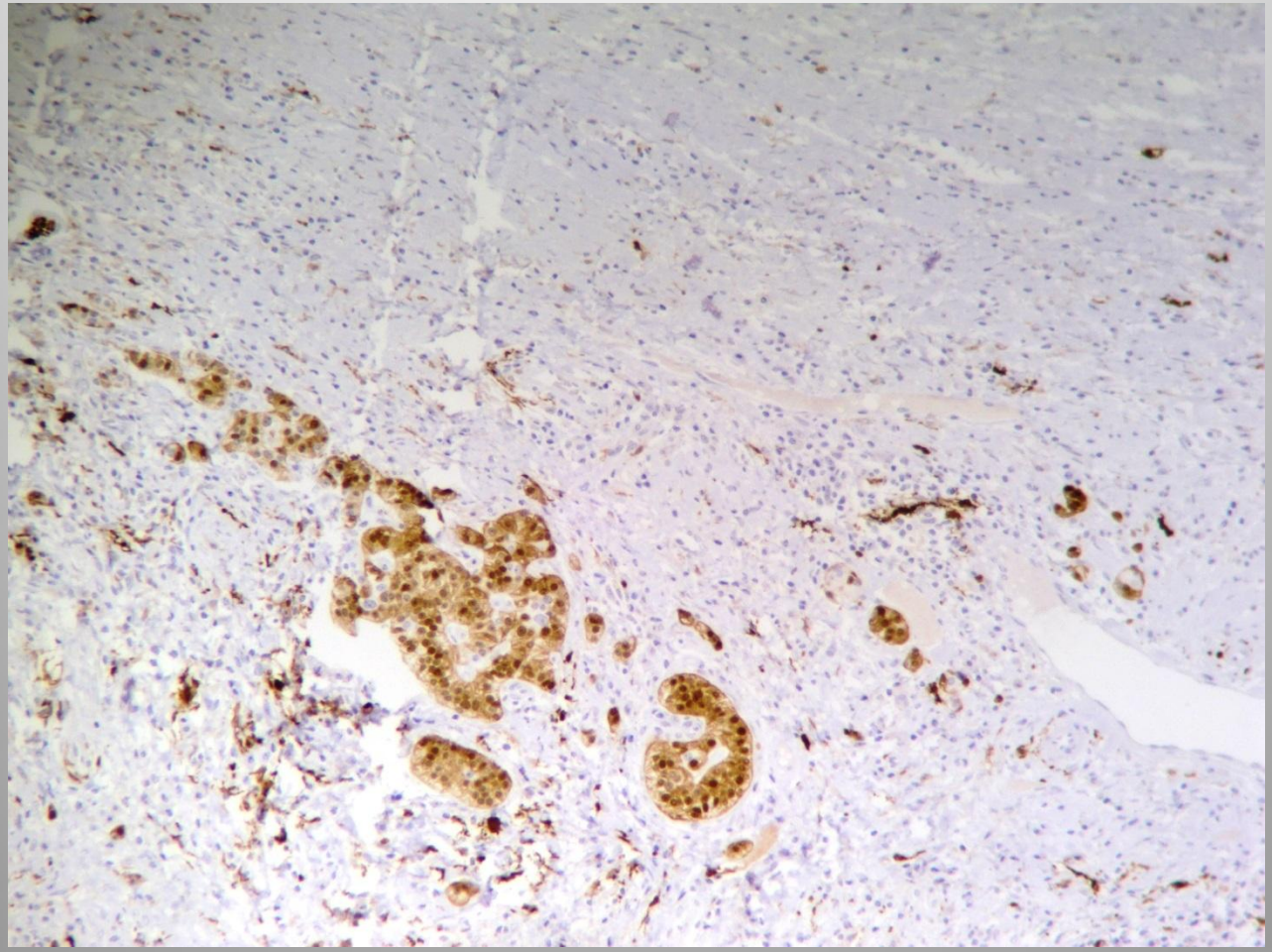
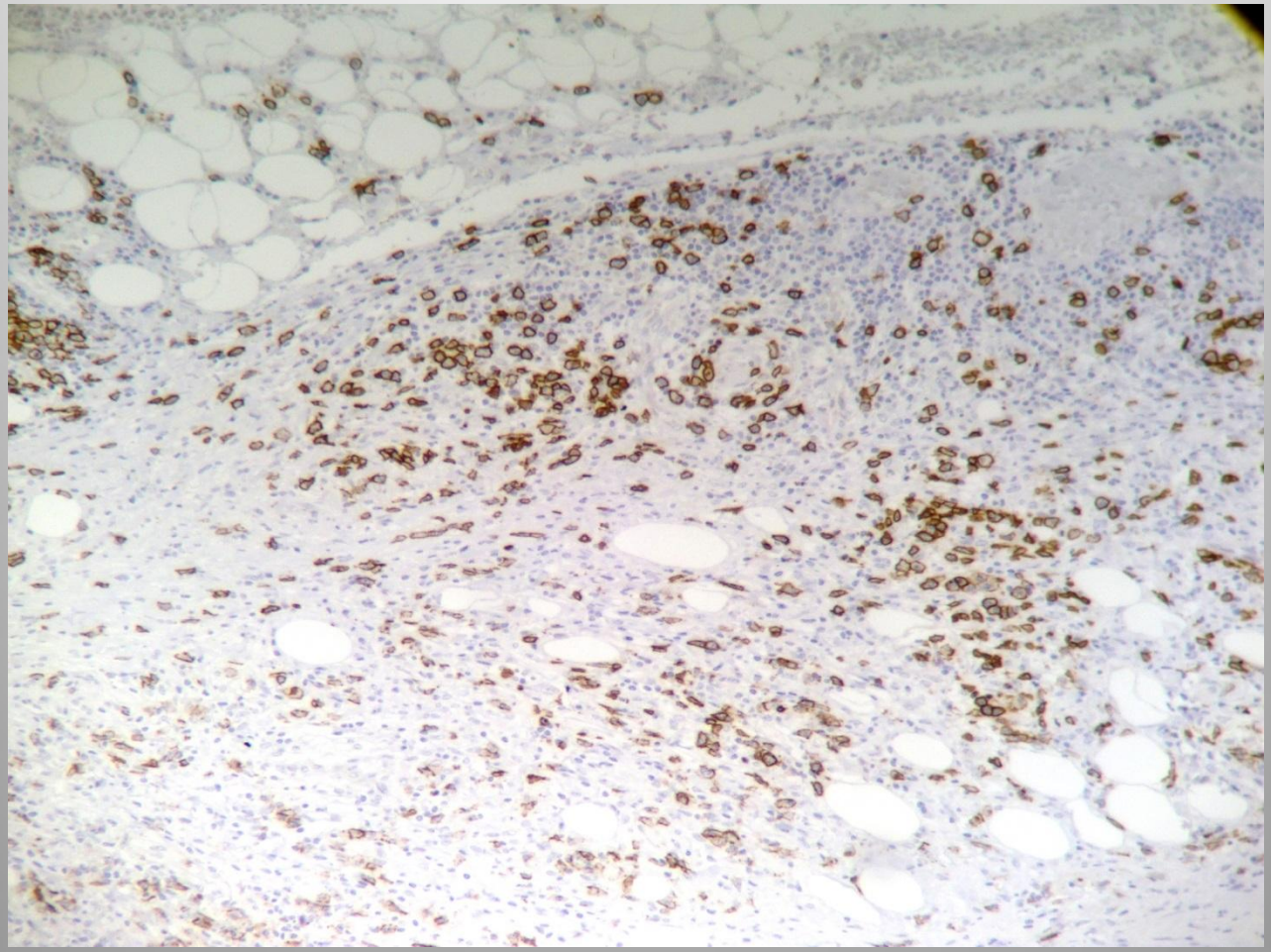


S100



CD138



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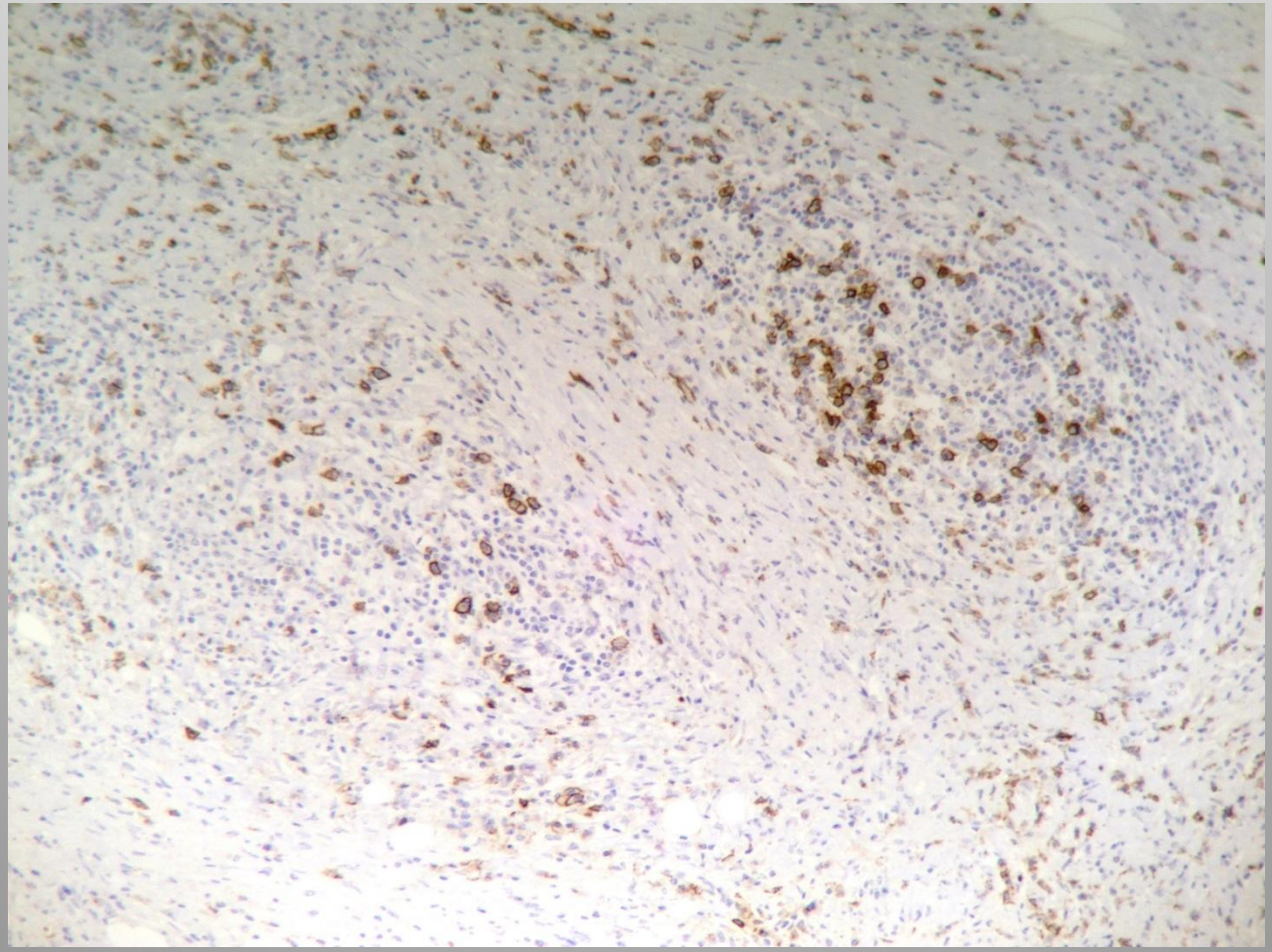

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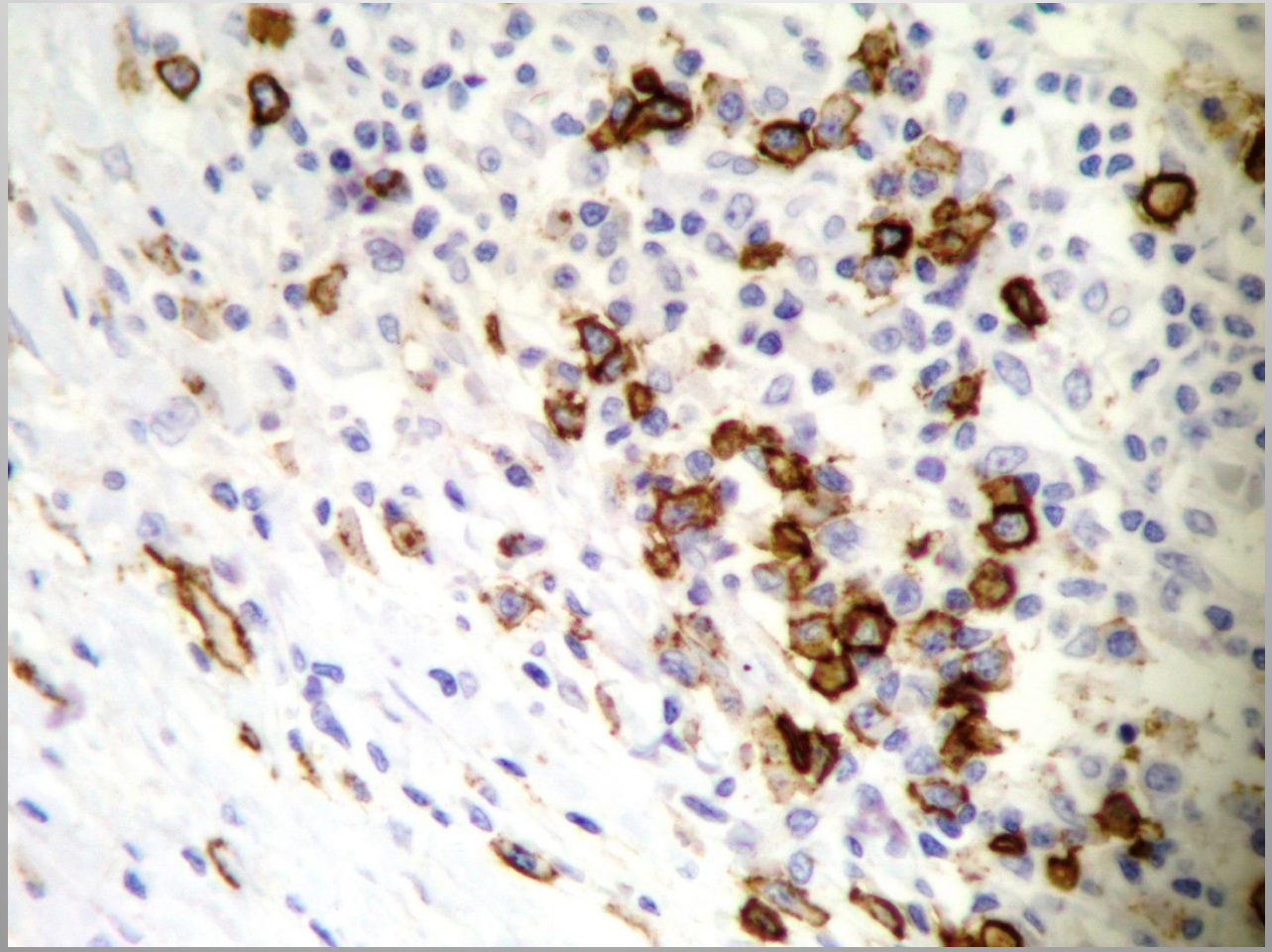
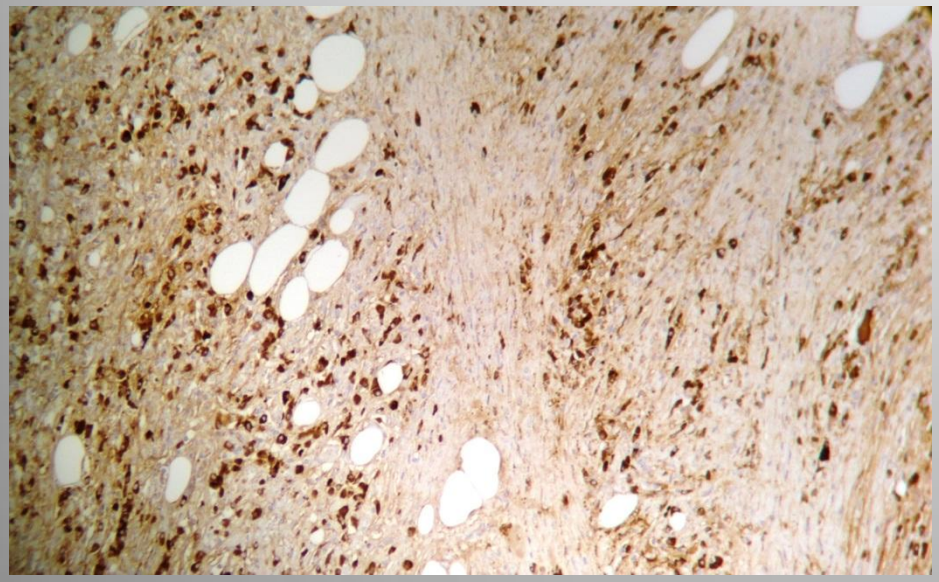
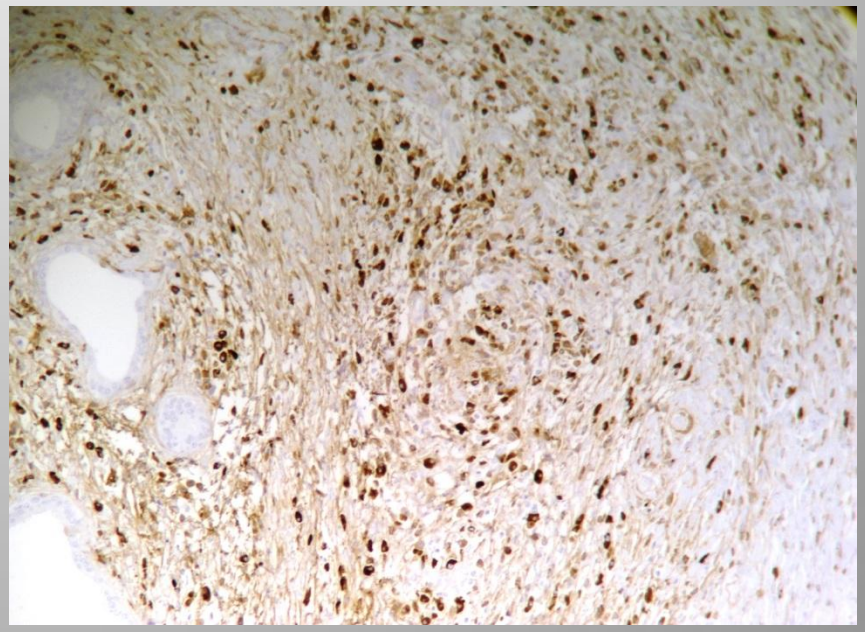


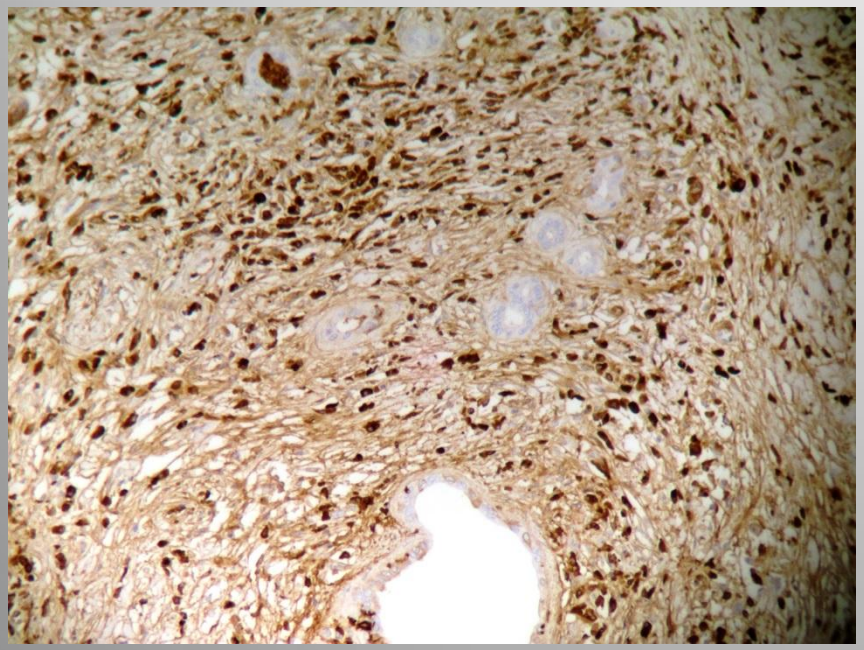
IgG



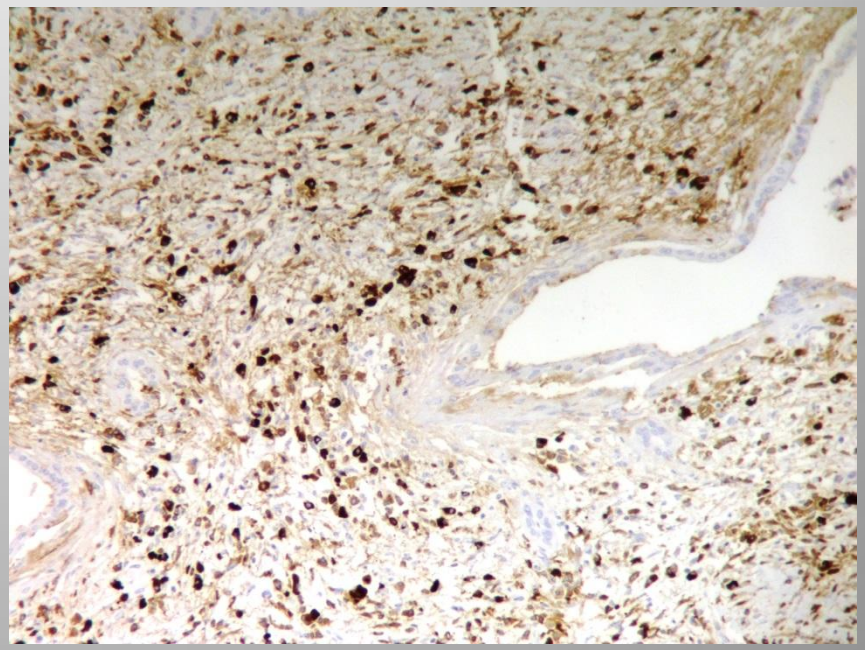
IgG4



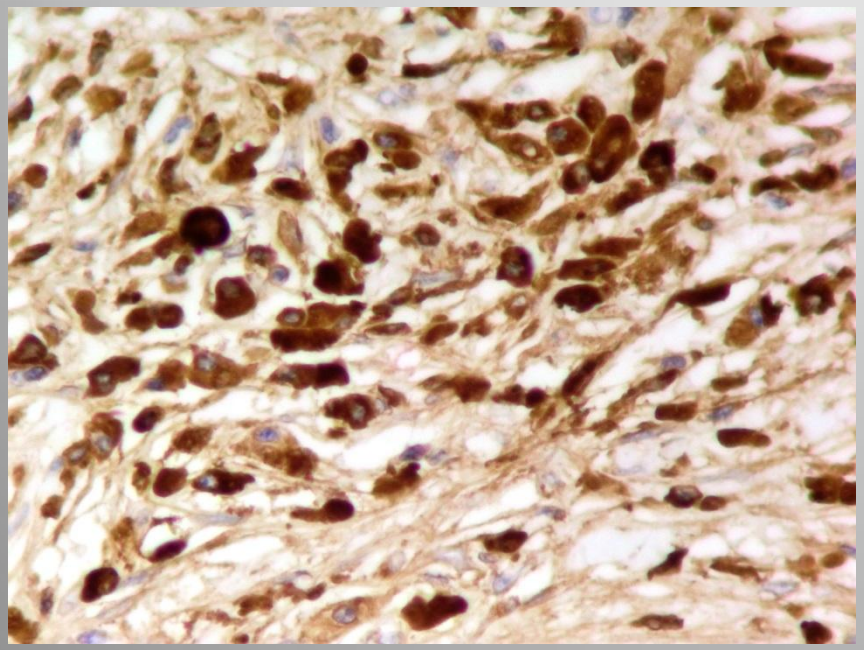
IgG



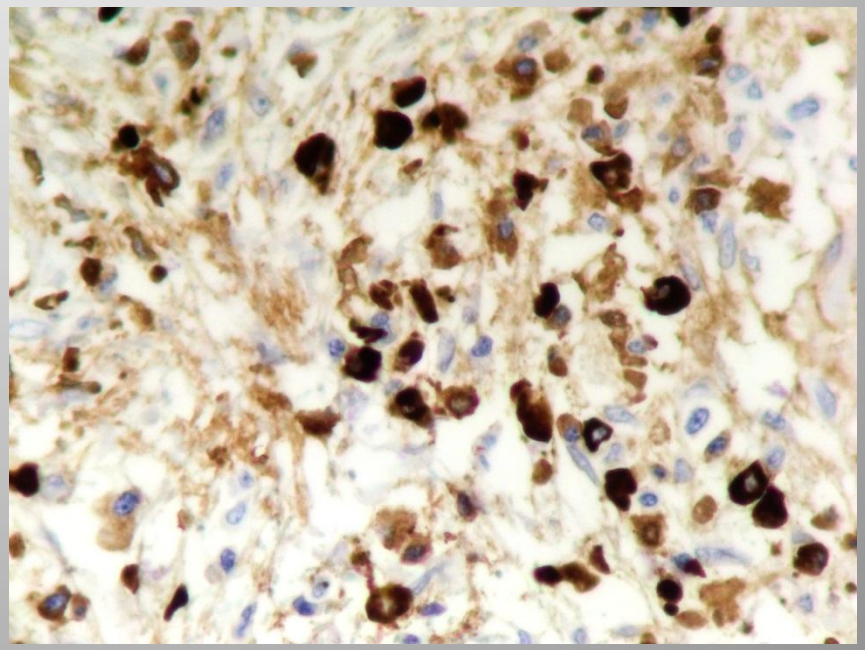
IgG4



IgG



IgG4



Anticorpos pesquisados

. S100
. ALK
. IgG
. IgG4
. Desmina
. AML
. CD138
. CD34
. AE1-AE3

Resumo

IgG4: média de 45 células / CGA

Relação IgG4/IgG: aproximadamente 45%

Esclerose do parênquima

Presença de flebite obliterativa

Diagnóstico

Pancreatite esclerosante relacionada ao IgG4

(Pancreatite auto-imune Tipo 1)

History of IgG4-related disease

- 1892 Mikulicz's disease
- 1961 Hyper-gammaglobulinemia in CP
- 1967 Familial multifocal fibrosclerosis
- 1972 Kuttner tumor
- 1991 Lymphoplasmacytic sclerosing pancreatitis
- 1995 Autoimmune pancreatitis
- 2001 High IgG4 levels in sclerosing pancreatitis (N Eng J Med)
- 2002 Japan Pancreas Society-Clinical diagnostic criteria for AIP
- 2003 Doença sistêmica relacionada ao *IgG4*
- 2006 Clinical diagnostic criteria for AIP
- 2006 Mayo criteria
- 2006 IgG4-related sclerosing disease
- 2006 IgG4-related plasmacytic disease
- 2008 IgG4-multiorgan lymphoproliferative syndrome (MOLPS)
- 2011 International Consensus
- Diagnostic Criteria (ICDC) for AIP
- 2012 Concept and comprehensive Diagnostic Criteria for IgG4-related disease
- 2012 International Pathological Consensus for IgG4-RD
- 2012 Nomenclatures of individual organ manifestation of IgG4- RD

Doença sistêmica IgG4 relacionada (IgG4-RD)

- IgG4- RD é uma entidade recentemente descrita (2003), sistêmica, sendo o orgão protótipo, o pâncreas, com origem ainda desconhecida. Lesões extrapancreáticas podem desenvolver antes, durante ou depois de um episódio de PAI, ou ocorrer sem lesão pancreática (10-20% dos casos não ocorre doença em outros orgãos)

- Histologicamente caracterizada por infiltrado linfoplasmocitário, fibrose estoriforme, flebite obliterativa e aumento de células IgG4+

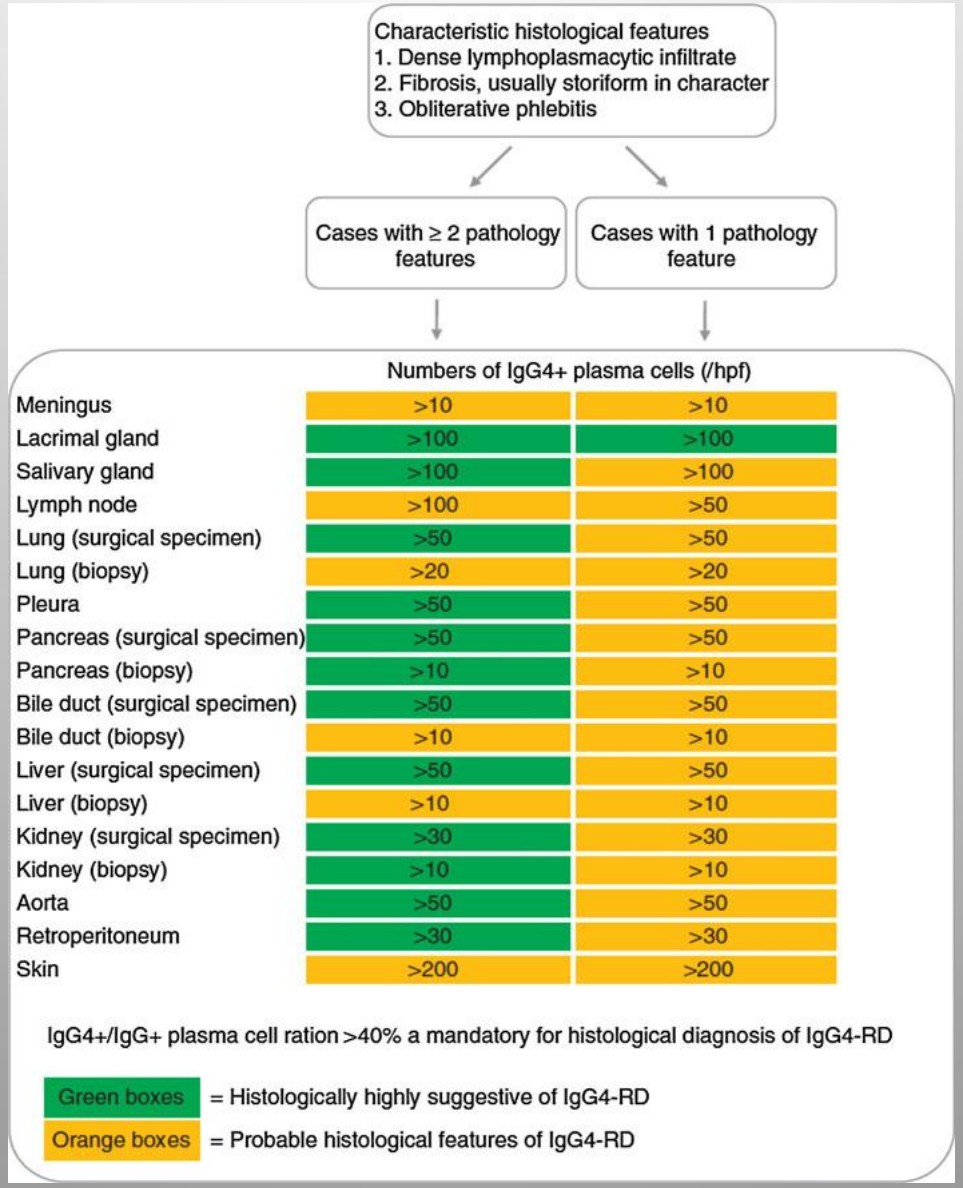
- Auto-anticorpos podem ser detectados, como: Fator reumatoide, Anidrase anticarbônica II, Antilactoferrina.

- Tumor de Kuttner (Sialadenite crônica esclerosante), descrita em 1986, é hoje considerada uma doença IgG4 relacionada e até 1/3 dos casos de todas as sialadenites crônicas inespecíficas, calculosas ou não, são IgG4 relacionadas.

Preferred nomenclature for individual organ system manifestations of IgG4-related disease

- **Pancreas** Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
- **Eye** IgG4-related ophthalmic disease isthe general term for the peri ocularmanifestations of this disease.There are several subsets, outlined below.
- **Lacrimal glands** IgG4-related dacryoadenitis
- **Orbital soft tissue** (orbital inflammatory pseudotumor) IgG4-related orbital inflammation
- **Extra-ocular muscle disease** IgG4-related orbital myositis
- **Orbit with involvement of multiple anatomic**
- **Structures** IgG4-related pan-orbital inflammation (includes lacrimal gland disease, extra-ocular muscle involvement, and other potential intra-orbital complications)
- **Salivary glands** (parotid and submandibular glands) IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
- **Pachymeninges** IgG4-related pachymeningitis
- **Hypophysis** IgG4-related hypophysitis
- Thyroid (Riedel's thyroiditis) IgG4-related thyroid disease
- **Aorta** IgG4-related aortitis/peri-aortitis
- **Arteries** IgG4-related periarteritis
- **Retroperitoneum** IgG4-related retroperitoneal fibrosis
- **Mediastinum** IgG4-related mediastinitis
- **Mesentery** IgG4-related mesenteritis
- **Skin** IgG4-related skin disease
- **Lymph node** IgG4-related lymphadenopathy
- **Bile ducts** IgG4-related sclerosing cholangitis
- **Gallbladder** IgG4-related cholecystitis
- **Liver** IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
- **Lung** IgG4-related lung disease
- **Pleura** IgG4-related pleuritis
- **Pericardium** IgG4-related pericarditis
- **Kidney** IgG4-related kidney disease. The specific renal pattern should be termed IgG4-related tubulointerstitial nephritis and membranous glomerulonephritis secondary to IgG4-RD. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis.
- **Breast** IgG4-related mastitis
- **Prostate** IgG4-related prostatitis

Histologic diagnostic schema of IgG4-related disease



Doença sistêmica IgG4 relacionada (IgG4-RD)

Malignidades associadas descritas:

- Linfoma da zona marginal ocular
- Linfoma folicular
- Linfoma de grandes células B
- Adenocarcinoma ductal do pâncreas
- Adenocarcinoma pulmonar
- Carcioma “in situ” urotelial

Pancreatite auto-imune (PAI)

- PAI é uma forma rara de pancreatite crônica, descrita pela primeira vez em 1961, como esclerose inflamatória primária do pâncreas. Em 1991, Kawagushi, fez uma descrição histopatológica de uma pancreatite esclerosante linfoplasmocítica. Porém, somente em 1995, o conceito de PAI foi proposto por Yoshida et al., num paciente com pancreatite crônica, hipergamaglobulinemia e resposta ao corticoide. Já em 2001, Hamano et al., reportou um aumento de IgG4 sérico em paciente japonês com PAI

- Pacientes com PAI geralmente possuem acometimento de outros orgãos (descrito em 2003 por Kamisawa como Doença sistêmica relacionada ao *IgG4*, porém já observado por Comings et al. em 1967, numa descrição de fibroesclerose familiar multifocal. Possuem características histopatológicas semelhantes e excelente resposta a terapia com corticoide

Pancreatite auto-imune (PAI)

- Prevalência estimada de <1/100.000 pessoas

- Estudos demonstram que representa até 1/3 dos casos benignos tratados cirurgicamente (Gastroduodenopancreatectomia)

Pancreatite auto-imune (PAI)

- Histologicamente caracterizada por infiltrado linfoplasmocitário, fibrose estoriforme, flebite obliterativa e aumento de células IgG4+
- IgG4 sérico é um critério diagnóstico porém pode estar aumentado em outras condições, como: dermatite atópica, asma, dç parasitária, pênfigo vulgar...
- IgG4 sérico aumentado foi observado em 3-10% de pacientes sem PAI, incluindo casos de colangite esclerosante primária, colangiocarcinoma e pancreatite aguda e crônica
- IgG4 sérico pode não estar elevado em até 1/3 dos casos de PAI, portanto a IH do tecido é mais sensível e específico

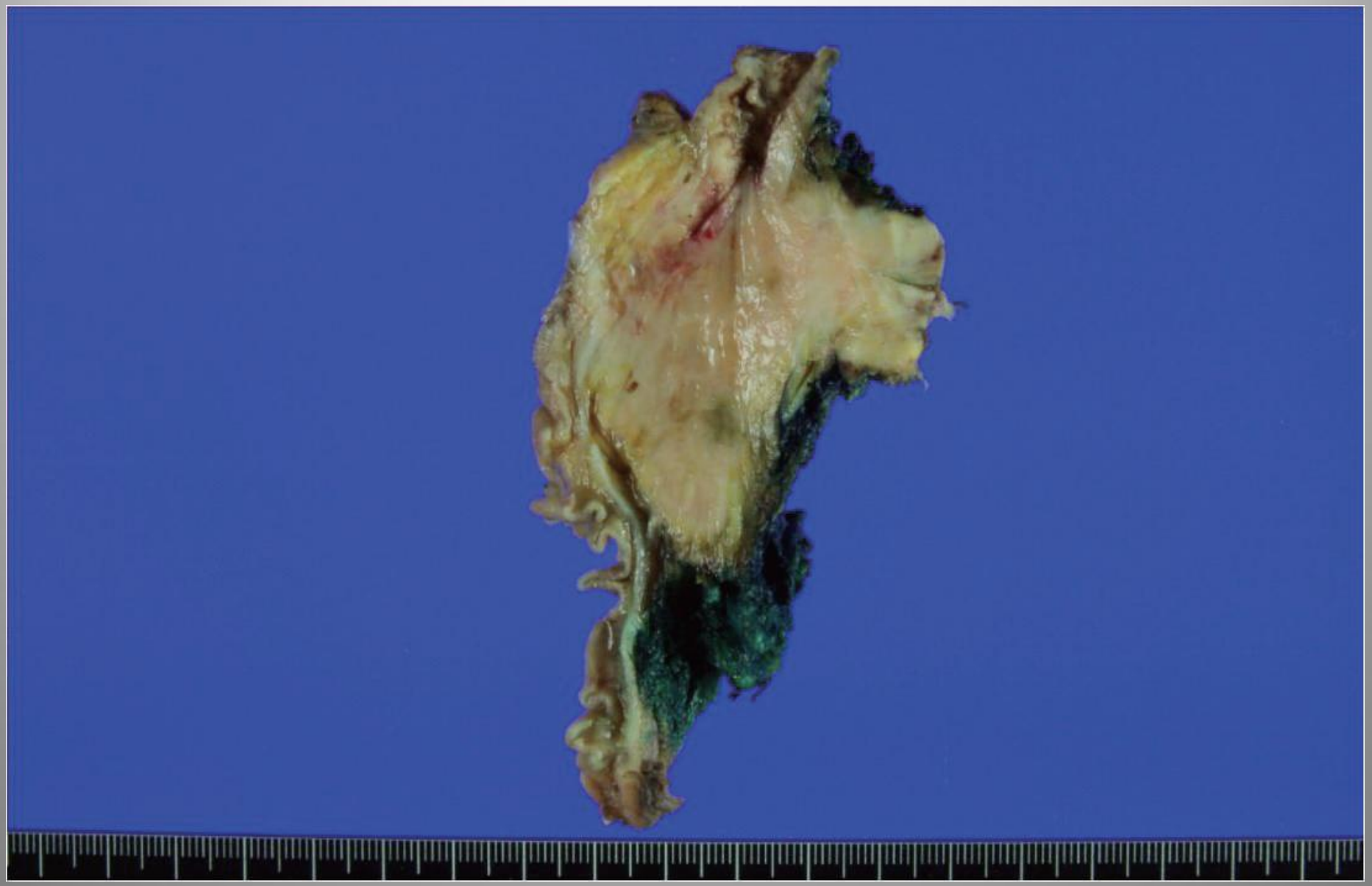
Pancreatite auto-imune (PAI)

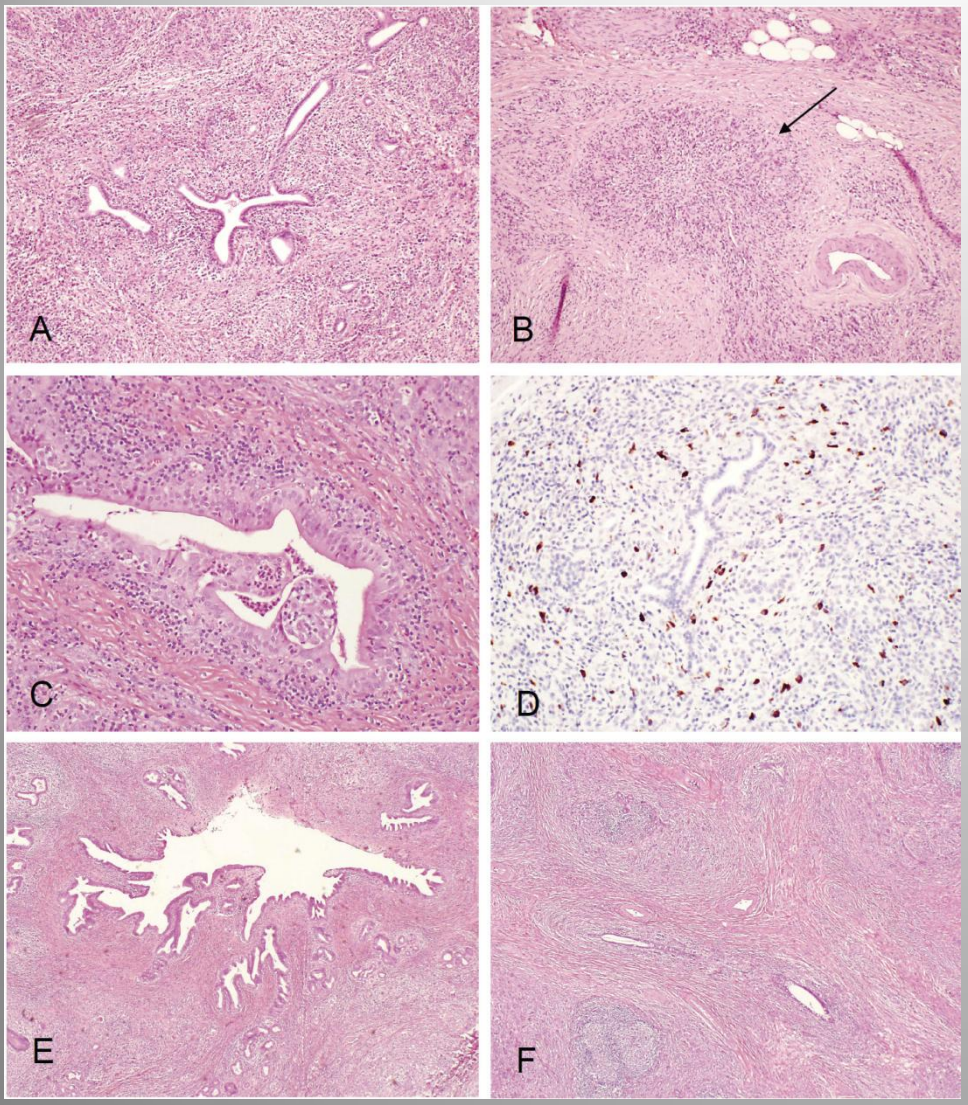
- Descrito dois tipos de PAI:

- Tipo 1: pancreatite esclerosante linfoplasmacítica

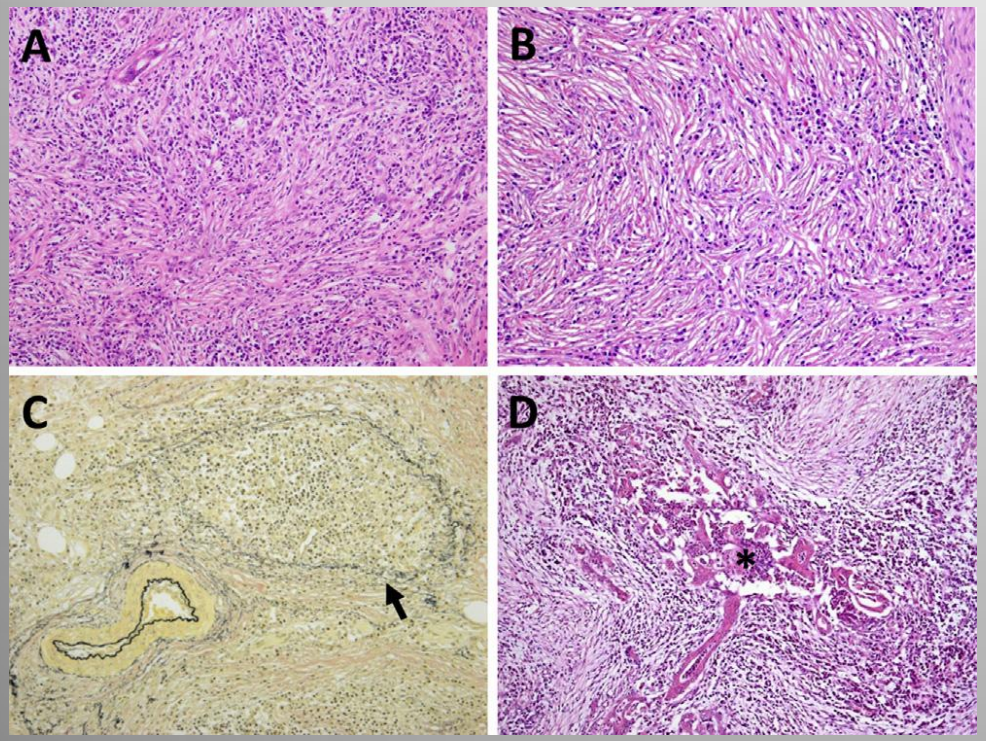
- Tipo 2: pancreatite idiopática ducto-destrutiva

OBS: nomenclatura Tipo 1 e 2 foi proposta em 2009, e muitos pesquisadores acreditam que apenas a Tipo 1 é sinônimo de doença IgG4 relacionada





- Figure 1. (A), Type 1 autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis): low power view showing
- periductal lymphoplasmacytic infiltrate and storiform fibrosis with inflammatory cellular stroma. (B), Obliterative phlebitis
- (arrow): dense peri- and intra-venular inflammatory infiltrate with fibrosis destroying the endothelium and obliterating
- the lumen. (C), Granulocyte epithelial lesion (GEL) in type 2 autoimmune pancreatitis (idiopathic duct centric
- pancreatitis): periductal lymphoplasmacytic and neutrophilic infiltrate with intra-epithelium and intra-lumen neutrophilic
- infiltrate; destruction of small ducts and ductal epithelium, lobular lymphoplasmacytic and neutrophilic infiltrate.
- (D), IgG4 immunostain: markedly increased (>30/high power filed) periductal IgG4+ plasma cell infiltrate. (E),
- IgG4 associated cholangitis: low power view showing periductal lymphoplasmacytic infiltrate and storiform fibrosis.
- (F), Chronic sclerosing sialadenitis (Küttner tumor) showing dense lymphoplasmacytic infiltrate and storiform fibrosis
- destroying glandular structures.



- Representative histopathologic features in resected pancreatic specimens from patients with (A–C) AIP and (D) IDCP, including (A) lymphoplasmacytic inflammation, (B) storiform fibrosis (in a swirled pattern), (C) obliterative phlebitis (arrow, Elastica van Gieson stain), and (D) GEL (asterisk).

Comparison of the 2 Variants of Autoimmune Pancreatitis

Characteristics	Type 1	Type 2
Age	Seventh decade	Fifth decade
Sex	Predominantly male	Equal M:F
Presentation	Jaundice (75%), acute pancreatitis (15%)	Acute pancreatitis (33%), jaundice (50%)
Extrapancreatic manifestations	Frequent	None
Serum immunoglobulin G4	↑ 80% of cases	Seldom increased
Inflammatory bowel disease	Rare	~15%–30%
Histology: Periductal inflammation with 1 or more of the following features	1. Storiform fibrosis 2. Obliterative phlebitis	1. Ductal/lobular abscesses 2. Ductal ulceration with neutrophils
Long-term outcome	Frequent relapses (20-60%)	Relapses are rare (<10%)
IgG4 tissue staining	>10cells/HPF	<10cells/HPF
Response to corticosteroids	~100%	~100%
Associated with IgG4-RD	Yes	No

Mayo Clinic Diagnostic Criteria for Autoimmune Pancreatitis (IgG4-related Sclerosing Pancreatitis): The HISORt Criteria

- **Criterion H-Histology**
- (at least one of the following)
- 1. Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis
- 2. Lymphoplasmacytic infiltrate, storiform fibrosis, abundant IgG4+ cells (≥10 HPF)

- **Criterion I-Imaging of pancreas**
- 1. Typical-diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct
- 2. Others-Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; pancreatitis

- **Criterion S-Serology**
- Elevated serum IgG4 (normal: 8-140 mg/dL)
-
- **Criterion O-Other organ involvement** (can be confirmed by biopsy or resolution/ improvement with steroid therapy)
- Hilar/intrahepatic biliary strictures; persistent distal biliary stricture; parotid/lacrimal gland involvement; mediastinal lymphadenopathy;
- retroperitoneal fibrosis

- **Criterion R-Response to steroid therapy**
- Resolution or marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy

- Diagnostic of autoimmune pancreatitis when any of the following is fulfilled
- **1. Criterion H**
- 2. Criterion I+S
- 3. Strong clinical suspicion of autoimmune pancreatitis
- (idiopathic pancreatic disease+Criterion S and/or O)+Criterion R

Clinical diagnostic criteria for autoimmune pancreatitis in 2011 by Japan Pancreas Society (JPS-2011)

A. Diagnostic criterion

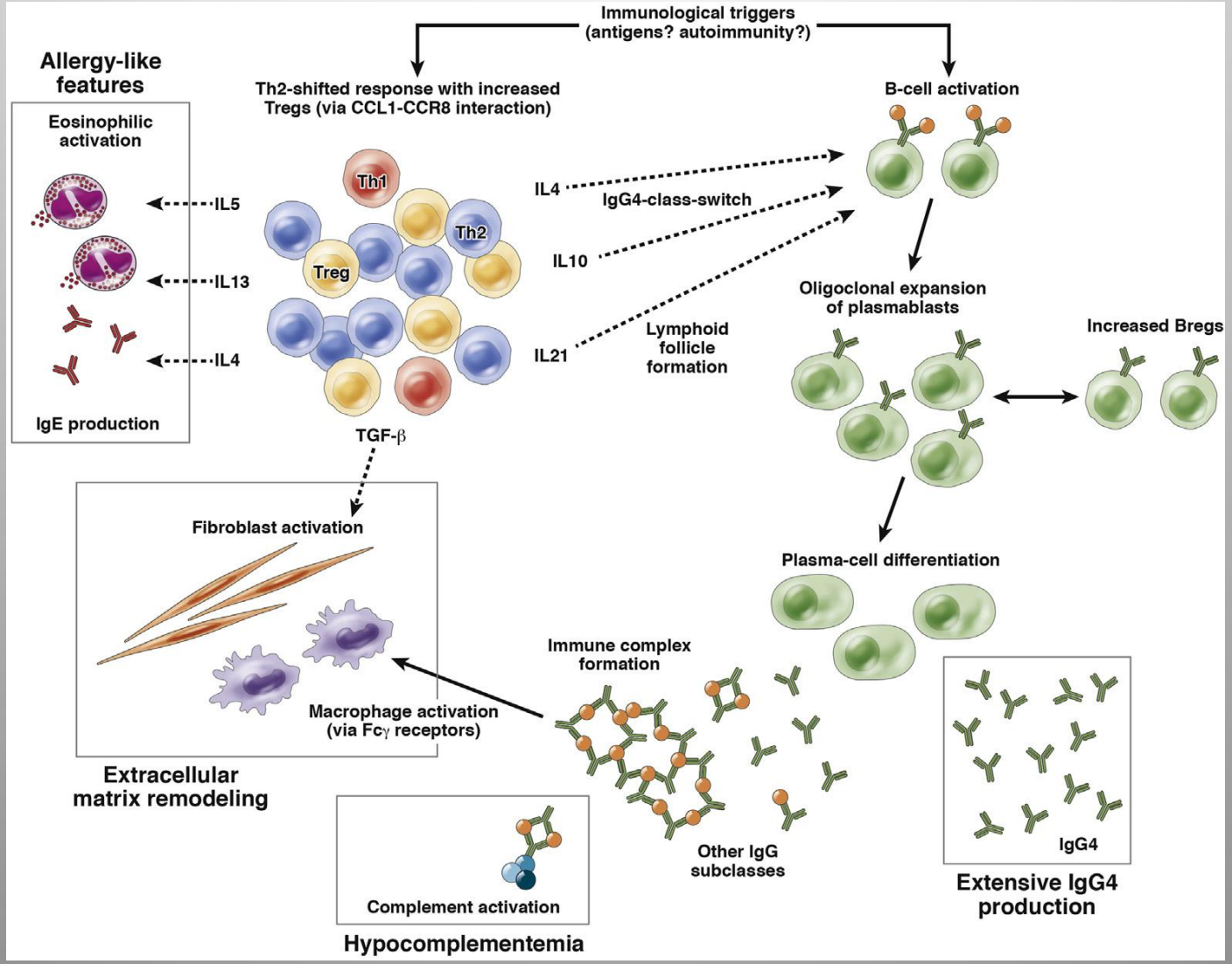
- **I.** Enlargement of the pancreas:
- a. Diffuse enlargement
- b. Segmental/focal enlargement
- **II.** ERP (endoscopic retrograde pancreatography) shows irregular narrowing of the main pancreatic duct
- **III.** Serological findings
- Elevated levels of serum IgG4 (C135 mg/dl)
- **IV**. Pathological findings: among i)–iv) listed below,
- a. Three or more are observed
- b. Two are observed
- i) Prominent infiltration and fibrosis of lymphocytes and plasmacytes
- ii) Ten or more diffuse IgG4-positive plasmacytes per high-power microscope field
- iii) Storiform fibrosis
- iv) Obliterative phlebitis
- **V.** Other organ involvement (OOI): sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, retroperitoneal fibrosis
- a. Clinical lesions
- Extra-pancreatic sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis (Mikulicz disease), or retroperitoneal fibrosis can be
- diagnosed with clinical and image findings.
- b. Pathological lesions
- Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, or retroperitoneal
- fibrosis.
- <Option> Effectiveness of steroid therapy
- A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out. When it is difficult to differentiate from malignant conditions, it is desirable to perform cytological examination using an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Facile therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled out by pathological diagnosis.

Clinical diagnostic criteria for autoimmune pancreatitis in 2011 by Japan Pancreas Society (JPS-2011)

B. Diagnosis

- **I. Definite diagnosis**
- 1 Diffuse type
- I a ?<III/IVb/V(a/b)>
- 2 Segmental/focal type
- I b + II + two or more of<III/IV b/V (a/b)>
- I b + II + <III/IV b/V (a/b)> + Option
- 3 Definite diagnosis by histopathological study
- IV a
- **II. Probable diagnosis**
- Segmental/focal type: I b ? II ?\III/IV b/V (a/b)[
- III. Possible diagnosis
- Diffuse type: I a + II + Option
- Segmental/focal type: I b + II + Option

The proposed immunologic interactions contributing to the various clinical manifestations in AIP



Etiopatogênese (PAI)

- Desconhecida
- Processo multifatorial

. Predisposição genética

. Mecanismo imunológico: auto-imunidade (anticorpos contra enzima, explicando o motivo dos ácinos pancreáticos serem mais acometidos)

. Infecção bacteriana: reação cruzada entre anidrase carbônica humana tipo II e anidrase carbônica do *H. pilory,* além de outras reações cruzadas entre proteínas do *H. pilory* e proteínas dos ácinos pancreáticos

Tratamento (PAI)

- Resposta satisfatória com corticoide
- Recidivas (20-60% dos casos): tratado com nova dose de corticoide ou terapias alternativas como Rituximab (depleção de células B); imunomoduladores (Azatioprina), porém são estudos de curto prazo e que não mostram ser melhores que o corticoide

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