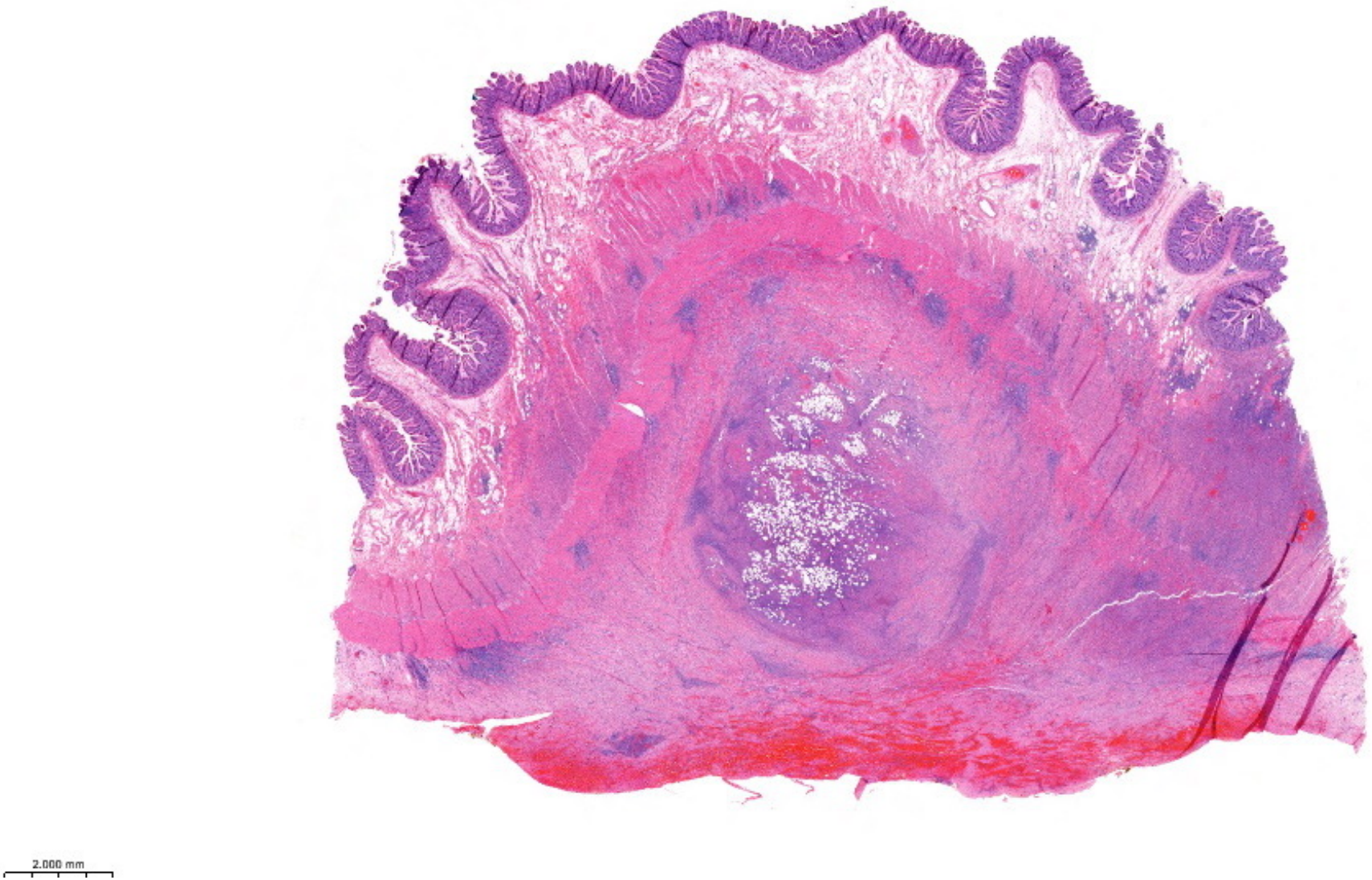
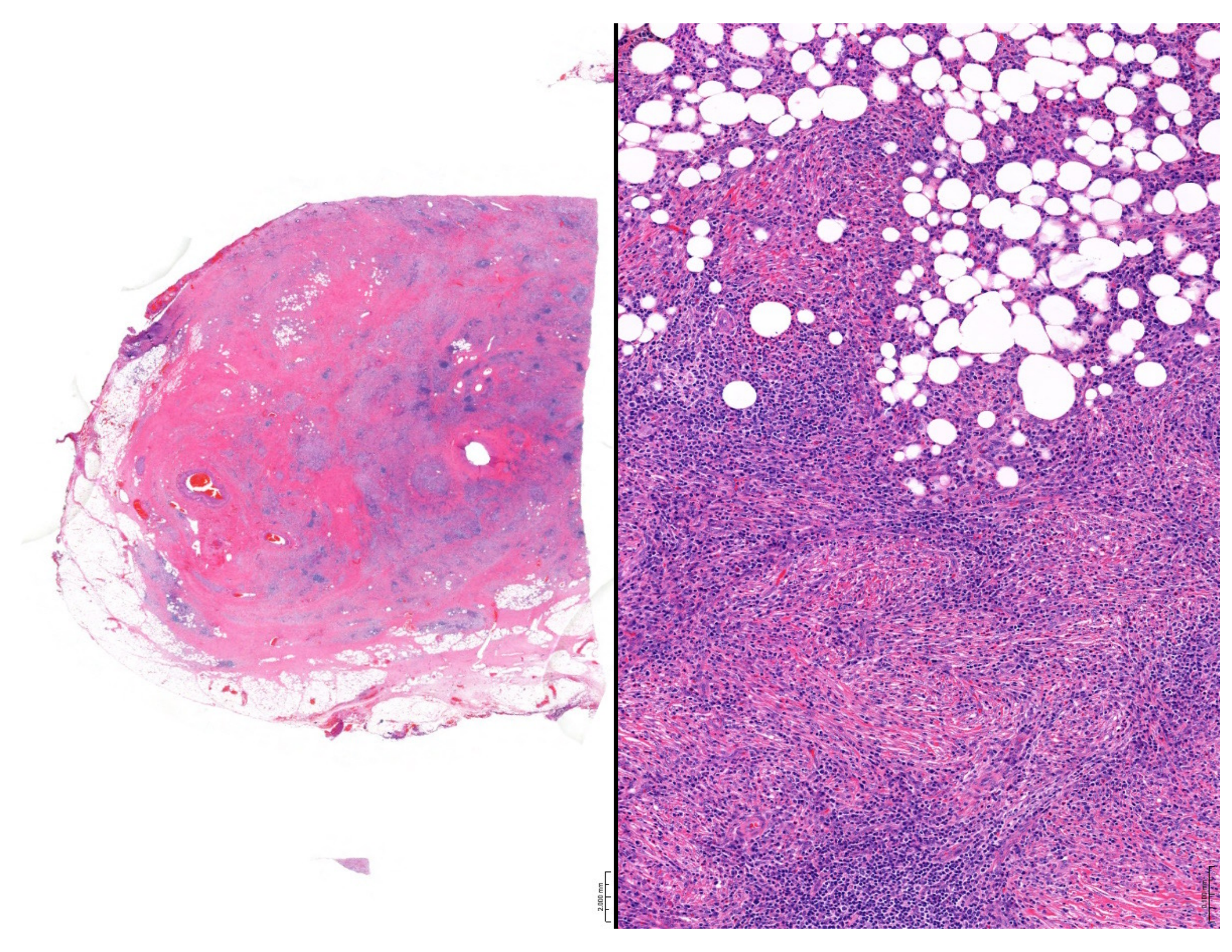
Case 1

Consult from a GI Pathology colleague last week



53-year-old man presenting with a couple episodes of SBO found to have 2.8 and 3.7 cm masses on CT; surgeon noted mass adherent to the root of mesentery at 312 cm from ligament of Treitz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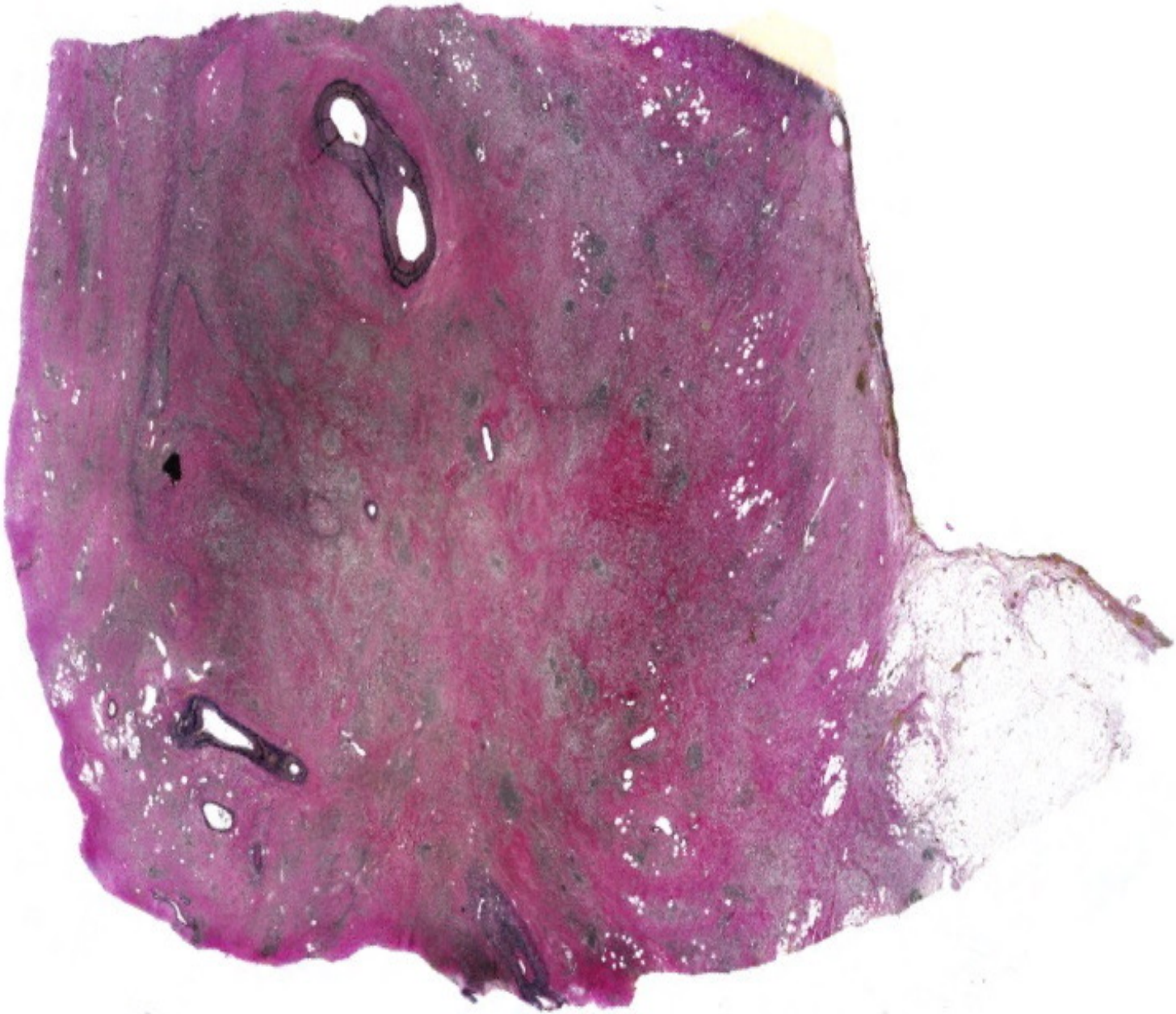
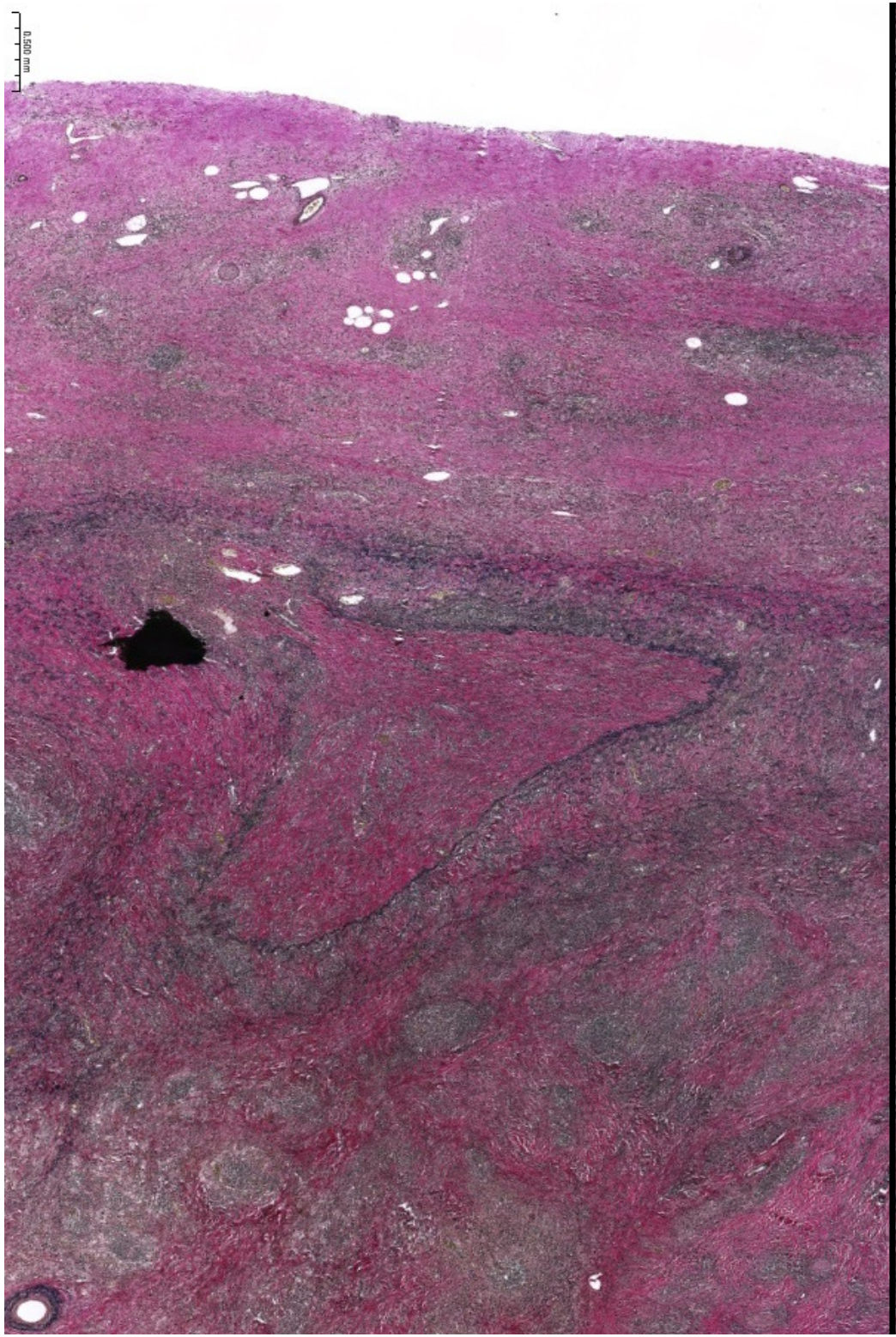


VVG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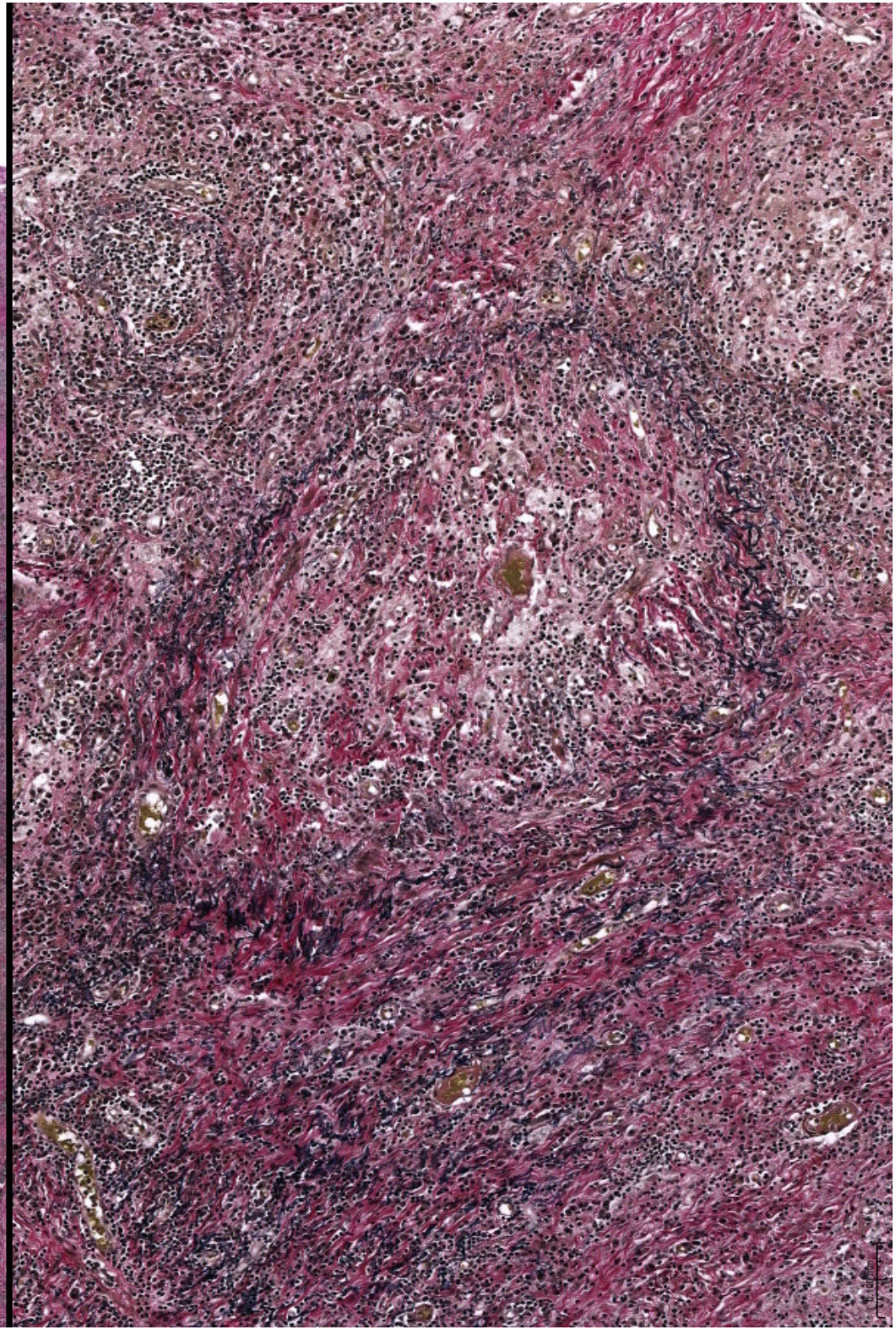
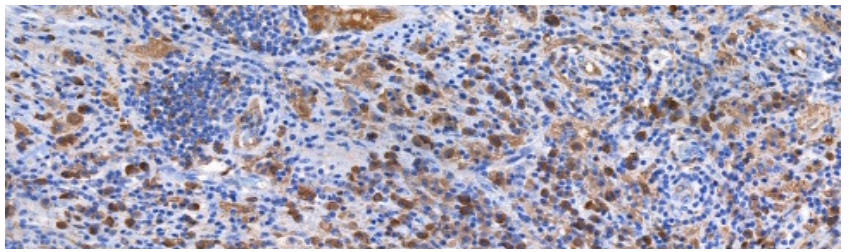
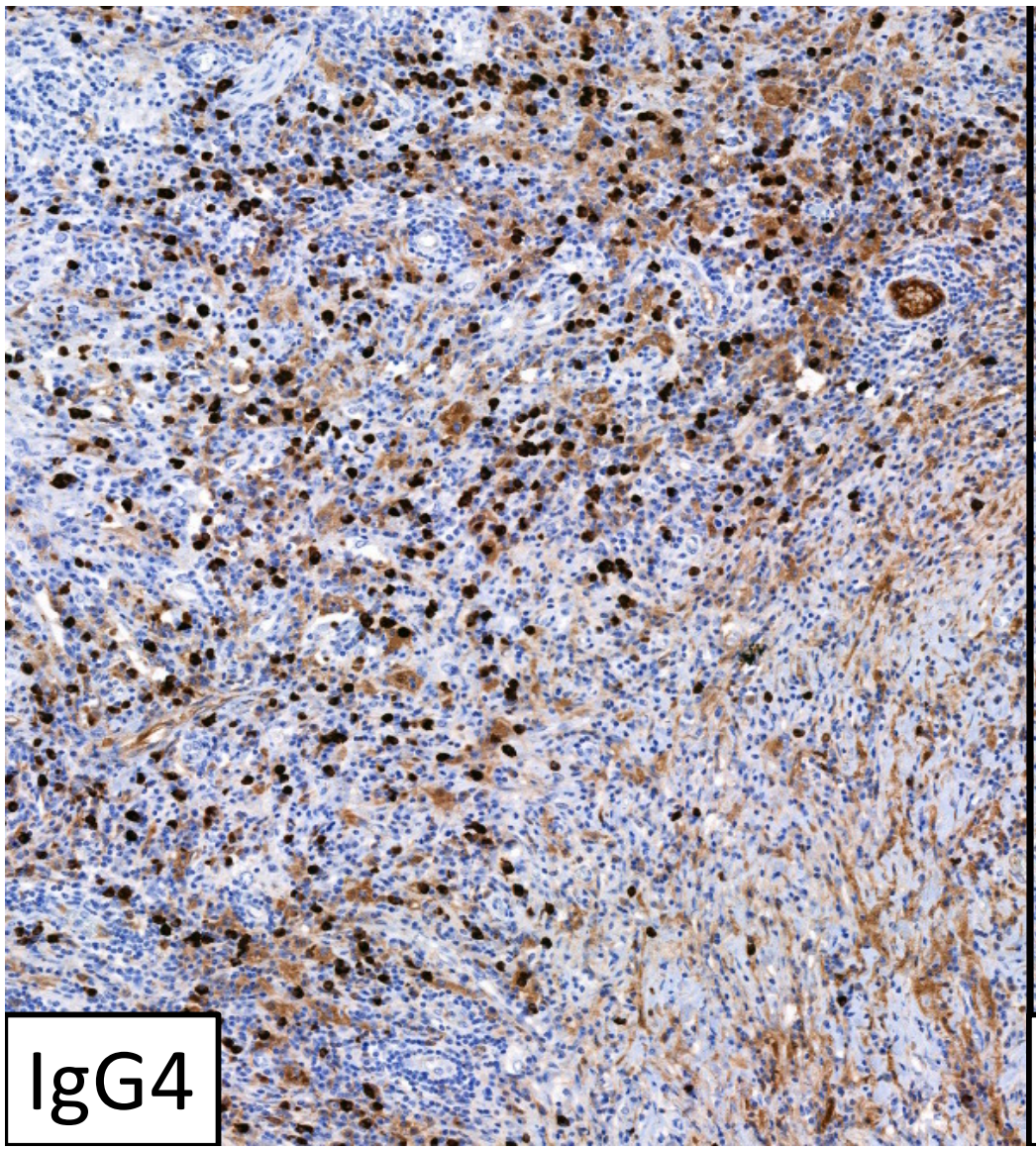


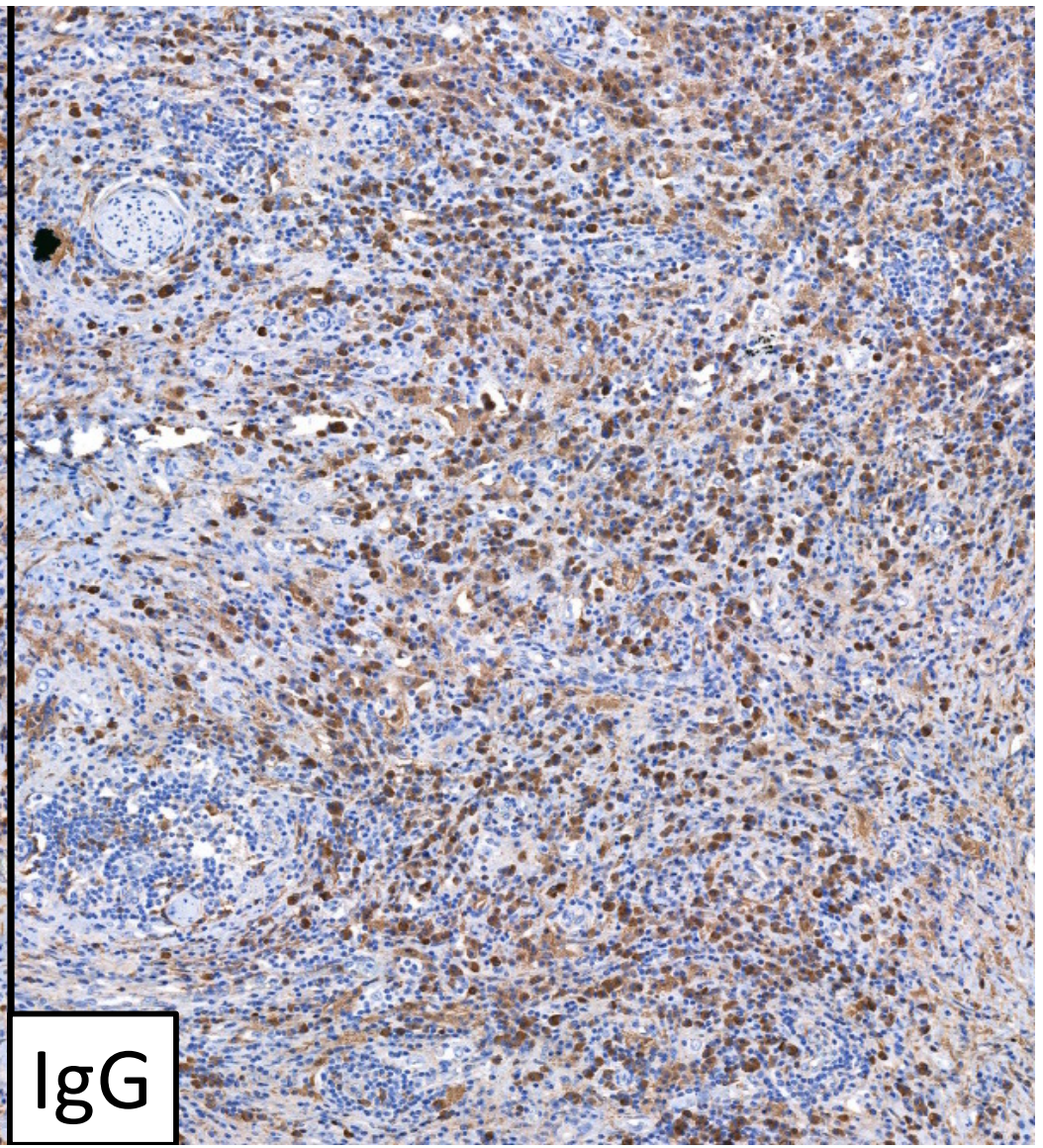
IgG4 Peak Count=198 (178, 86)

IgG4:IgG Ratio=76% (61%, 48%)

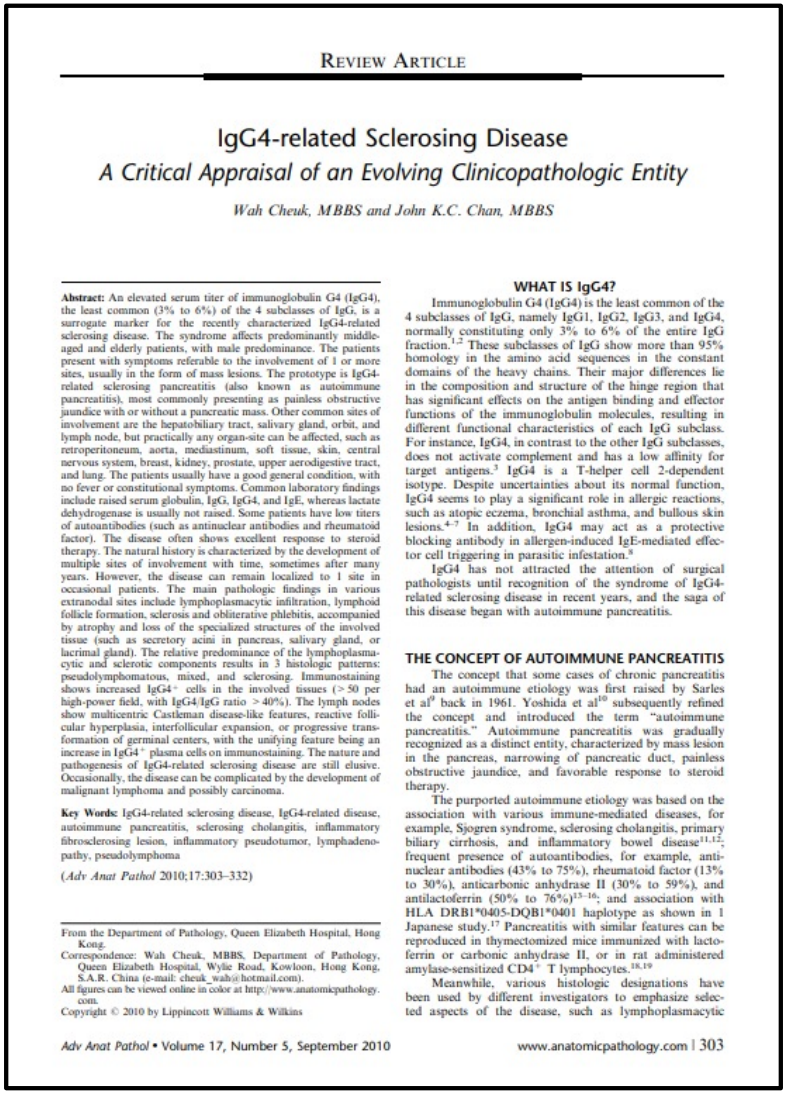


Mesenteric IgG4-Related Sclerosing Disease





Approach to IgG4-Related Sclerosing Disease



REVIEW ARTICLE

IgG4-related Sclerosing Disease

A Critical Appraisal of an Evolving Clinicopathologic Entity

Wah Cheuk, MBBS and John K.C. Chan, MBBS

Abstract: An elevated serum titer of immunoglobulin G4 (IgG4), the least common (3% to 6%) of the 4 subclasses of IgG, is a surrogate marker for the recently characterized IgG4-related sclerosing disease. The syndrome affects predominantly middle-aged and elderly patients, with male predominance. The patients present with symptoms referable to the involvement of 1 or more sites, usually in the form of mass lesions. The prototype is IgG4-related sclerosing pancreatitis (also known as autoimmune pancreatitis), most commonly presenting as painless obstructive jaundice with or without a pancreatic mass. Other common sites of involvement are the hepatobiliary tract, salivary gland, orbit, and lymph node, but practically any organ-site can be affected, such as retroperitoneum, aorta, mediastinum, soft tissue, skin, central nervous system, breast, kidney, prostate, upper aerodigestive tract, and lung. The patients usually have a good general condition, with no fever or constitutional symptoms. Common laboratory findings include raised serum globulin, IgG, IgG4, and IgE, whereas lactate dehydrogenase is usually not raised. Some patients have low titers of autoantibodies (such as antinuclear antibodies and rheumatoid factor). The disease often shows excellent response to steroid therapy. The natural history is characterized by the development of multiple sites of involvement with time, sometimes after many years. However, the disease can remain localized to 1 site in occasional patients. The main pathologic findings in various extranodal sites include lymphoplasmacytic infiltration, lymphoid follicle formation, sclerosis and obliterative phlebitis, accompanied by atrophy and loss of the specialized structures of the involved tissue (such as secretory acini in pancreas, salivary gland, or lacrimal gland). The relative predominance of the lymphoplasmacytic and sclerotic components results in 3 histologic patterns: pseudolymphomatous, mixed, and sclerosing. Immunostaining shows increased IgG4$^+$ cells in the involved tissues (> 50 per high-power field, with IgG4/IgG ratio > 40%). The lymph nodes show multicentric Castleman disease-like features, reactive follicular hyperplasia, interfollicular expansion, or progressive transformation of germinal centers, with the unifying feature being an increase in IgG4$^+$ plasma cells on immunostaining. The nature and pathogenesis of IgG4-related sclerosing disease are still elusive. Occasionally, the disease can be complicated by the development of malignant lymphoma and possibly carcinoma.

Key Words: IgG4-related sclerosing disease, IgG4-related disease, autoimmune pancreatitis, sclerosing cholangitis, inflammatory fibrosclerosing lesion, inflammatory pseudotumor, lymphadenopathy, pseudolymphoma

(*Adv Anat Pathol* 2010;17:303–332)

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WHAT IS IgG4?

Immunoglobulin G4 (IgG4) is the least common of the 4 subclasses of IgG, namely IgG1, IgG2, IgG3, and IgG4, normally constituting only 3% to 6% of the entire IgG fraction.[1,2] These subclasses of IgG show more than 95% homology in the amino acid sequences in the constant domains of the heavy chains. Their major differences lie in the composition and structure of the hinge region that has significant effects on the antigen binding and effector functions of the immunoglobulin molecules, resulting in different functional characteristics of each IgG subclass. For instance, IgG4, in contrast to the other IgG subclasses, does not activate complement and has a low affinity for target antigens.[3] IgG4 is a T-helper cell 2-dependent isotype. Despite uncertainties about its normal function, IgG4 seems to play a significant role in allergic reactions, such as atopic eczema, bronchial asthma, and bullous skin lesions.[4–7] In addition, IgG4 may act as a protective blocking antibody in allergen-induced IgE-mediated effector cell triggering in parasitic infestation.[8]

IgG4 has not attracted the attention of surgical pathologists until recognition of the syndrome of IgG4-related sclerosing disease in recent years, and the saga of this disease began with autoimmune pancreatitis.

THE CONCEPT OF AUTOIMMUNE PANCREATITIS

The concept that some cases of chronic pancreatitis had an autoimmune etiology was first raised by Sarles et al[9] back in 1961. Yoshida et al[10] subsequently refined the concept and introduced the term "autoimmune pancreatitis." Autoimmune pancreatitis was gradually recognized as a distinct entity, characterized by mass lesion in the pancreas, narrowing of pancreatic duct, painless obstructive jaundice, and favorable response to steroid therapy.

The purported autoimmune etiology was based on the association with various immune-mediated diseases, for example, Sjogren syndrome, sclerosing cholangitis, primary biliary cirrhosis, and inflammatory bowel disease[11,12]; frequent presence of autoantibodies, for example, antinuclear antibodies (43% to 75%), rheumatoid factor (13% to 30%), anticarbonic anhydrase II (30% to 59%), and antilactoferrin (50% to 76%)[13–16]; and association with HLA DRB1*0405-DQB1*0401 haplotype as shown in 1 Japanese study.[17] Pancreatitis with similar features can be reproduced in thymectomized mice immunized with lactoferrin or carbonic anhydrase II, or in rat administered amylase-sensitized CD4$^+$ T lymphocytes.[18,19]

Meanwhile, various histologic designations have been used by different investigators to emphasize selected aspects of the disease, such as lymphoplasmacytic

- Diagnostic Criteria
  - IgG4 peak count >50 in HPF
  - IgG4:IgG ratio >40%
  - Characteristic histology
    - Lymphoplasmacytic inflammation
    - Follicular lymphoid hyperplasia
    - Sclerosis (storiform fibrosis)
    - Obliterative phlebitis
- Patterns
  - Pseudolymphomatous
  - Mixed
  - Sclerosing

What is the relationship between “Sclerosing Mesenteritis” and Mesenteric IgG4-Related Sclerosing Disease?

› Am J Surg Pathol. 1997 Apr;21(4):392-8. doi: 10.1097/00000478-199704000-00004.

Sclerosing mesenteritis, mesenteric panniculitis and mesenteric lipodystrophy: a single entity?

T S Emory [1], J M Monihan, N J Carr, L H Sobin

Affiliations + expand

PMID: 9130985 DOI: 10.1097/00000478-199704000-00004

Abstract

We reviewed 84 cases coded as mesenteric lipodystrophy (ML), mesenteric panniculitis (MP), or retractile mesenteritis and sclerosing mesenteritis (SM), grading fibrosis, inflammation, and fat necrosis, and evaluating clinical subgroups. There was no gender or racial predominance. Patient age range was 23-87 years (average 60). Patients most often presented with abdominal pain or a palpable mass. A history of trauma or surgery was present in four of 84 patients. The most common site of involvement was the small bowel mesentery as a single mass (58 of 84) with an average size of 10 cm, multiple masses (15 of 84), or diffuse mesenteric thickening (11 of 84). All patients had some degree of fibrosis, chronic inflammation, and fat necrosis. Although a few patients showed a sufficient prominence of fibrosis, inflammation, or fat necrosis to permit a separation into SM, MP, or ML, respectively, in most patients these three components were too mixed for a clear separation. The clinical, demographic, and gross features did not help in defining these three entities. Contributors diagnosed 12 as sarcoma. Of 39 patients followed beyond the postoperative period, none died of these lesions. We conclude that SM, MP, and ML appear to represent histologic variants of one clinical entity, and in most cases "sclerosing mesenteritis" is the most appropriate diagnostic term.

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:589–596

Sclerosing Mesenteritis: Clinical Features, Treatment, and Outcome in Ninety-Two Patients

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*Division of Gastroenterology and Hepatology and ‡Division of Anatomic Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota

See CME exam on page 524.

Background & Aims: **Sclerosing mesenteritis is a rare non-neoplastic disease that affects the small bowel mesentery with chronic fibrosing inflammation. There are few data on the natural history and therapeutic options for this condition.** ***Methods:*** **We performed a retrospective and prospective study to describe the clinical characteristics, therapy, and outcome of all cases of sclerosing mesenteritis diagnosed at the Mayo Clinic, Rochester, from 1982–2005.** ***Results:*** **Ninety-two cases were identified; 70% were male, with a median age of 65 years (interquartile range, 55–72). Common presenting symptoms included abdominal pain in 70%, diarrhea in 25%, and weight loss in 23%. Treatment included medical therapy alone in 26%, surgery alone in 13%, surgery followed by medical therapy in 9%, and 52% received no treatment. Ten percent responded to surgery alone, 20% responded to additional medical treatment after surgery, and 38% responded to medical therapy alone. Tamoxifen in combination with prednisone was used in 20 patients, and 60% improved. Non-tamoxifen–based regimens were used in 12 patients, and 8% improved. Eighteen deaths were noted during the study period, and 17% were attributed to complications of sclerosing mesenteritis or its treatment.** ***Conclusions:*** **Although a relatively benign condition, sclerosing mesenteritis can have a prolonged debilitating course with a fatal outcome. Our results suggest that symptomatic patients might benefit from medical therapy, particularly tamoxifen and prednisone combination treatment. Long-term follow-up is needed to substantiate these results.**

Sclerosing mesenteritis (SM) is a rare fibroinflammatory disorder of unknown etiology that primarily affects the small bowel mesentery.[1] The first known series, comprising 34 cases of “retractile mesenteritis and mesenteric sclerosis,” was published in 1924.[2] Subsequently, on the basis of the predominant histology, numerous terms have been used to describe this entity, including mesenteric lipodystrophy (predominantly fatty degeneration and necrosis),[3] mesenteric panniculitis (marked chronic inflammation),[4,5] and retractile mesenteritis or mesenteric fibrosis (predominant fibrosis).[6] In 1997 after a review of 84 cases, Emory et al[1] concluded that these histologic variants are part of the spectrum of one disease process, and SM would be an appropriate umbrella term. The rarity of this condition has limited the ability to study demographic and clinical features, natural history, and response to therapy. Thus, treatment decisions are guided by anecdotal experience and small case series. Different therapeutic modalities, including corticosteroids, colchicine, immunosuppressive drugs, and hormonal therapies have been used with varying success.[7–10] Recently, successful use of thalidomide has been reported in an open-label pilot study of 5 patients with symptomatic SM.[11] In the present study, we sought to describe the clinical features, treatment, and outcomes of patients with SM seen at our institution during the past 23 years.

Methods

After approval by the Mayo Clinic’s Institutional Review Board, 65 patients with a diagnosis of SM and its variants were retrospectively identified from January 1982–November 2002 through the Mayo Clinic diagnostic index and Department of Pathology database. An additional 28 cases were prospectively identified as referrals to our gastroenterology outpatient clinic between December 2002–November 2005. One patient denied research authorization and was excluded from the study. All pathology slides were reviewed by a single pathologist (T.C.S.) for confirmation of diagnosis and identification of histologic subtype. Demographic, clinical, and treatment data were abstracted from the medical records, and outcome data were supplemented by follow-up telephone interviews for prospectively enrolled subjects and previously diagnosed patients who were alive at initiation of the study. Response to treatment was assessed by clinical and radiographic parameters and categorized as responsive (improved/resolution), persistent (nonprogressive/stable), and progressive (deterioration/worsening).

Statistical Analysis

Descriptive statistics were used to summarize the results. Medians and interquartile ranges (IQRs) were calculated as summaries of continuous variables. For categorical variables, percentages of patients in each category were computed, and group comparison was done with Fisher exact test. A 2-tailed P value $<.05$ was considered statistically significant.

Results

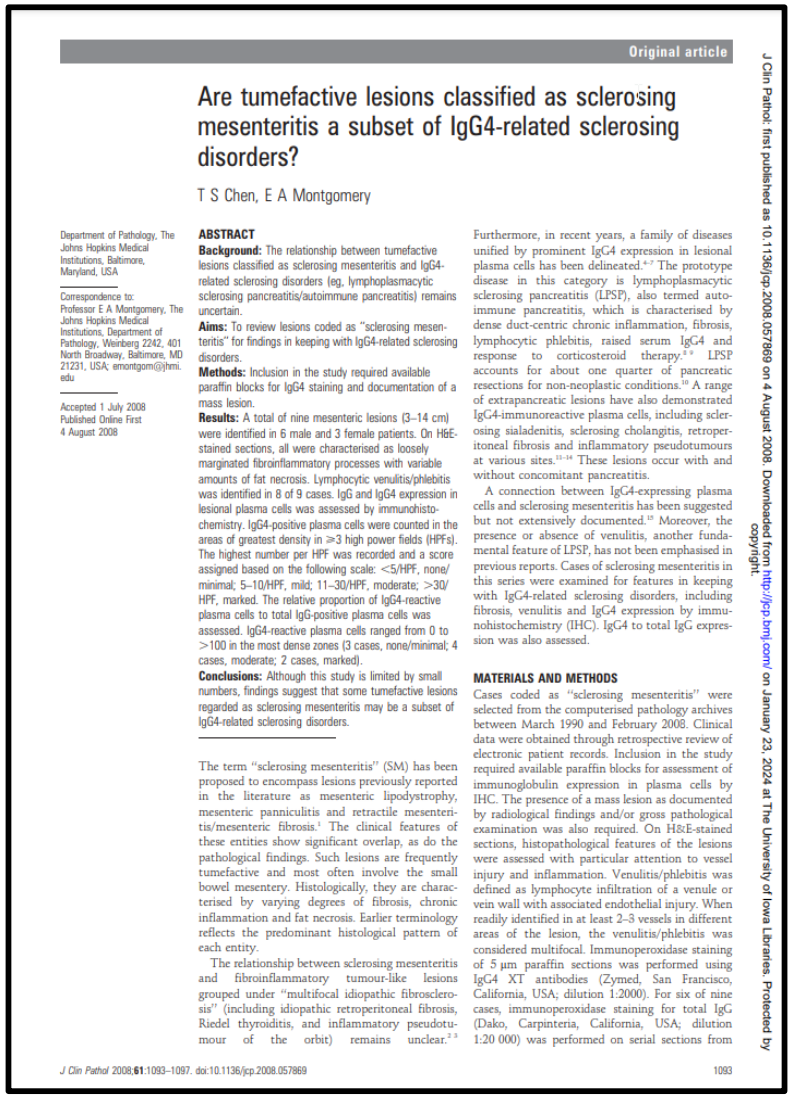
Clinical Presentation and Diagnosis

Ninety-two cases of SM were identified during the study period. Patient characteristics at presentation are shown in Table 1. The most frequent presenting symptoms were abdominal pain in 70%, bloating and distention in 26%, diarrhea in 25%, and weight loss in 23% (Table 2). SM was an incidental finding in 10% of cases when an abdominal surgery (3%), computed tomography (CT) scan (5%), or autopsy (1%) was performed for another indication, and there were no symptoms attributable to mesenteric disease.

Abbreviations used in this paper: CT, computed tomography; IQR, interquartile range; MGUS, monoclonal gammopathy of unknown significance; NHL, non-Hodgkin’s lymphoma; RPF, retroperitoneal fibrosis; SM, sclerosing mesenteritis; SP, sclerosing pancreatitis; TGF-β, transforming growth factor–beta.

1542-3565/07/$32.00
doi:10.1016/j.cgh.2007.02.032

What is the relationship between "Sclerosing Mesenteritis" and Mesenteric IgG4-Related Sclerosing Disease?



Original article

Are tumefactive lesions classified as sclerosing mesenteritis a subset of IgG4-related sclerosing disorders?

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Published Online First 4 August 2008

ABSTRACT

Background: The relationship between tumefactive lesions classified as sclerosing mesenteritis and IgG4-related sclerosing disorders (eg, lymphoplasmacytic sclerosing pancreatitis/autoimmune pancreatitis) remains uncertain.

Aims: To review lesions coded as "sclerosing mesenteritis" for findings in keeping with IgG4-related sclerosing disorders.

Methods: Inclusion in the study required available paraffin blocks for IgG4 staining and documentation of a mass lesion.

Results: A total of nine mesenteric lesions (3–14 cm) were identified in 6 male and 3 female patients. On H&E-stained sections, all were characterised as loosely marginated fibroinflammatory processes with variable amounts of fat necrosis. Lymphocytic venulitis/phlebitis was identified in 8 of 9 cases. IgG and IgG4 expression in lesional plasma cells was assessed by immunohistochemistry. IgG4-positive plasma cells were counted in the areas of greatest density in ≥3 high power fields (HPFs). The highest number per HPF was recorded and a score assigned based on the following scale: <5/HPF, none/minimal; 5–10/HPF, mild; 11–30/HPF, moderate; >30/HPF, marked. The relative proportion of IgG4-reactive plasma cells to total IgG-positive plasma cells was assessed. IgG4-reactive plasma cells ranged from 0 to >100 in the most dense zones (3 cases, none/minimal; 4 cases, moderate; 2 cases, marked).

Conclusions: Although this study is limited by small numbers, findings suggest that some tumefactive lesions regarded as sclerosing mesenteritis may be a subset of IgG4-related sclerosing disorders.

The term "sclerosing mesenteritis" (SM) has been proposed to encompass lesions previously reported in the literature as mesenteric lipodystrophy, mesenteric panniculitis and retractile mesenteritis/mesenteric fibrosis.[1] The clinical features of these entities show significant overlap, as do the pathological findings. Such lesions are frequently tumefactive and most often involve the small bowel mesentery. Histologically, they are characterised by varying degrees of fibrosis, chronic inflammation and fat necrosis. Earlier terminology reflects the predominant histological pattern of each entity.

The relationship between sclerosing mesenteritis and fibroinflammatory tumour-like lesions grouped under "multifocal idiopathic fibrosclerosis" (including idiopathic retroperitoneal fibrosis, Riedel thyroiditis, and inflammatory pseudotumour of the orbit) remains unclear.[2 3] Furthermore, in recent years, a family of diseases unified by prominent IgG4 expression in lesional plasma cells has been delineated.[4–7] The prototype disease in this category is lymphoplasmacytic sclerosing pancreatitis (LPSP), also termed autoimmune pancreatitis, which is characterised by dense duct-centric chronic inflammation, fibrosis, lymphocytic phlebitis, raised serum IgG4 and response to corticosteroid therapy.[8 9] LPSP accounts for about one quarter of pancreatic resections for non-neoplastic conditions.[10] A range of extrapancreatic lesions have also demonstrated IgG4-immunoreactive plasma cells, including sclerosing sialadenitis, sclerosing cholangitis, retroperitoneal fibrosis and inflammatory pseudotumours at various sites.[11–14] These lesions occur with and without concomitant pancreatitis.

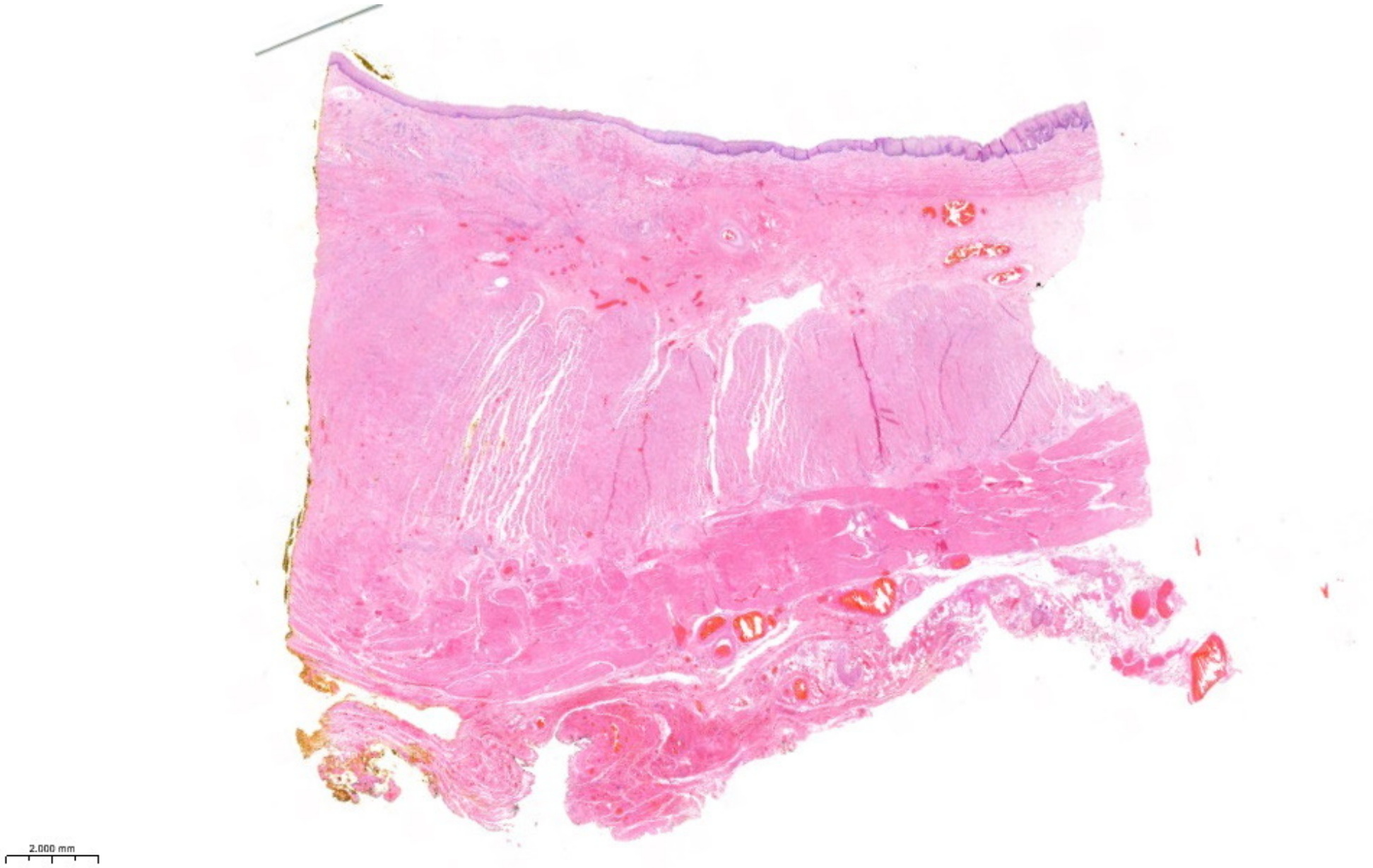
A connection between IgG4-expressing plasma cells and sclerosing mesenteritis has been suggested but not extensively documented.[15] Moreover, the presence or absence of venulitis, another fundamental feature of LPSP, has not been emphasised in previous reports. Cases of sclerosing mesenteritis in this series were examined for features in keeping with IgG4-related sclerosing disorders, including fibrosis, venulitis and IgG4 expression by immunohistochemistry (IHC). IgG4 to total IgG expression was also assessed.

MATERIALS AND METHODS

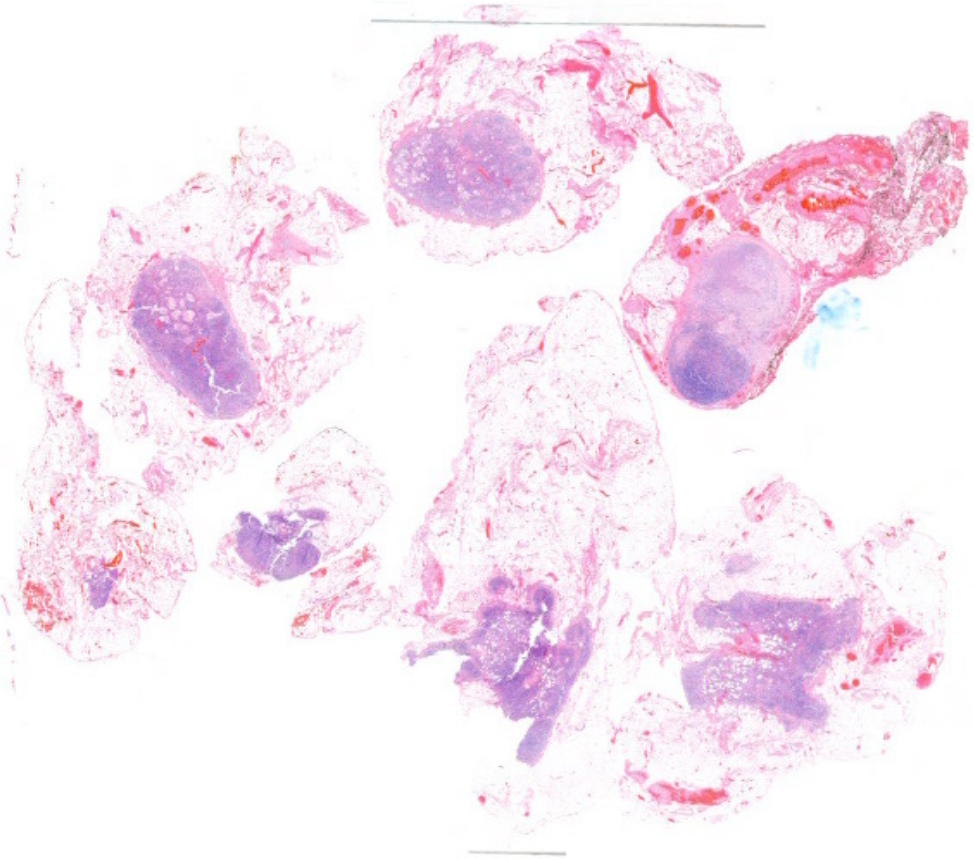
Cases coded as "sclerosing mesenteritis" were selected from the computerised pathology archives between March 1990 and February 2008. Clinical data were obtained through retrospective review of electronic patient records. Inclusion in the study required available paraffin blocks for assessment of immunoglobulin expression in plasma cells by IHC. The presence of a mass lesion as documented by radiological findings and/or gross pathological examination was also required. On H&E-stained sections, histopathological features of the lesions were assessed with particular attention to vessel injury and inflammation. Venulitis/phlebitis was defined as lymphocyte infiltration of a venule or vein wall with associated endothelial injury. When readily identified in at least 2–3 vessels in different areas of the lesion, the venulitis/phlebitis was considered multifocal. Immunoperoxidase staining of 5 μm paraffin sections was performed using IgG4 XT antibodies (Zymed, San Francisco, California, USA; dilution 1:2000). For six of nine cases, immunoperoxidase staining for total IgG (Dako, Carpinteria, California, USA; dilution 1:20 000) was performed on serial sections from

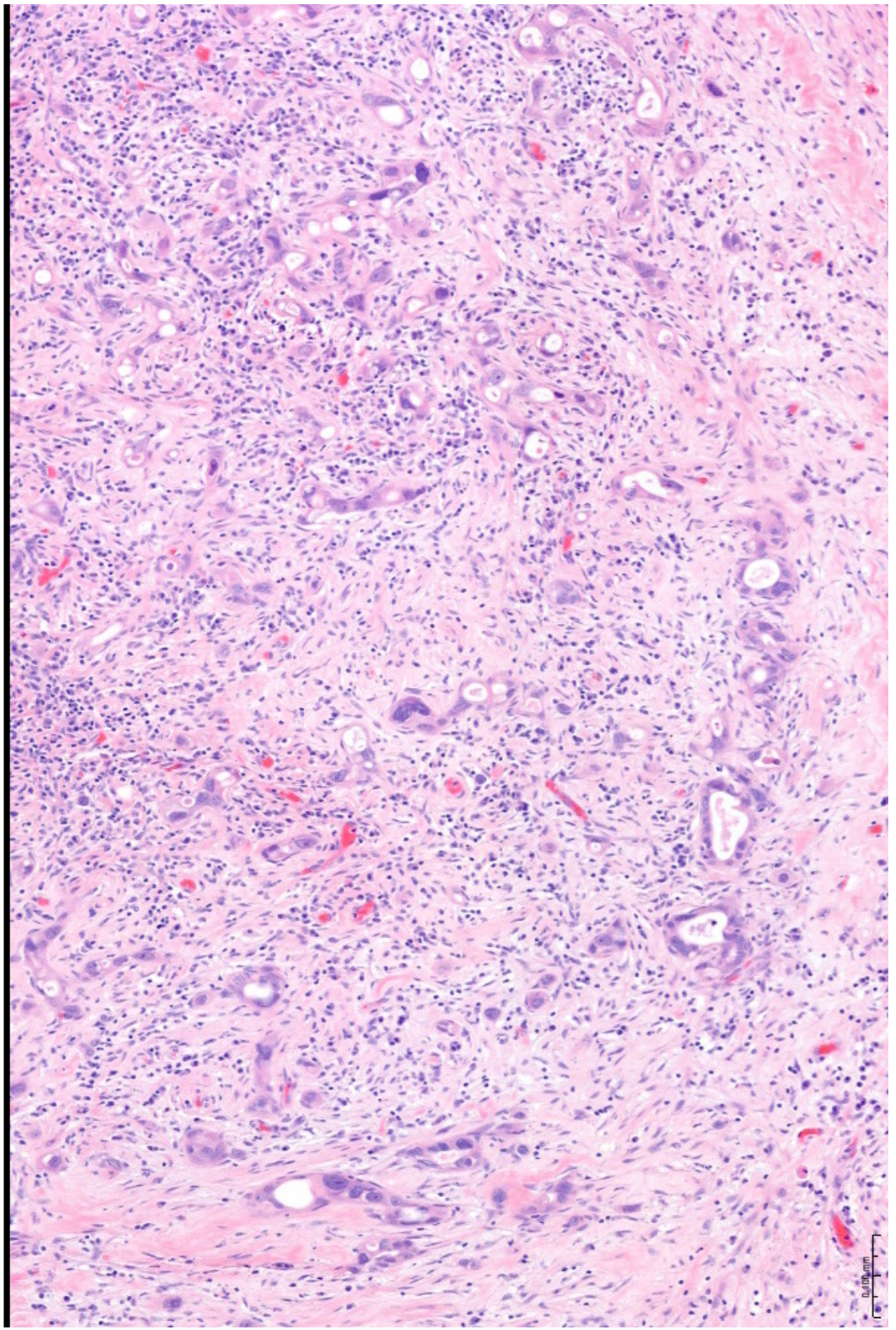
- N=9
- Lymphocytic phlebitis 8/9
- IgG4 Peak Count
  - <5/HPF=3
  - 5-10/HPF=0
  - **11-30/HPF=4**
  - **>30/HPF=2**
- Conclusion: at least some cases of sclerosing mesenteritis represent IgG4-related sclerosing disease

Case 2



Esophagectomy after neoadjuvant tx for esophageal AdCA

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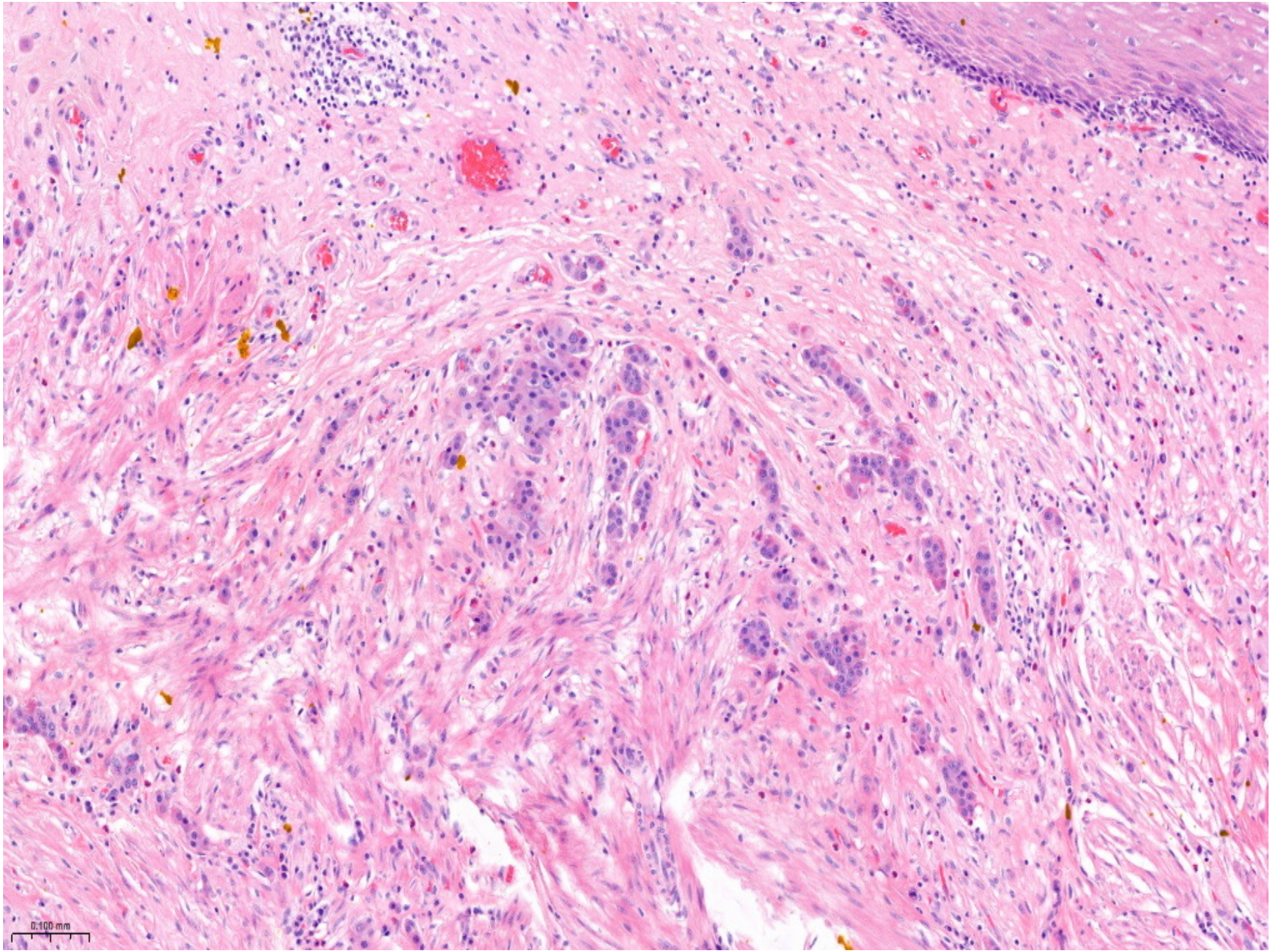
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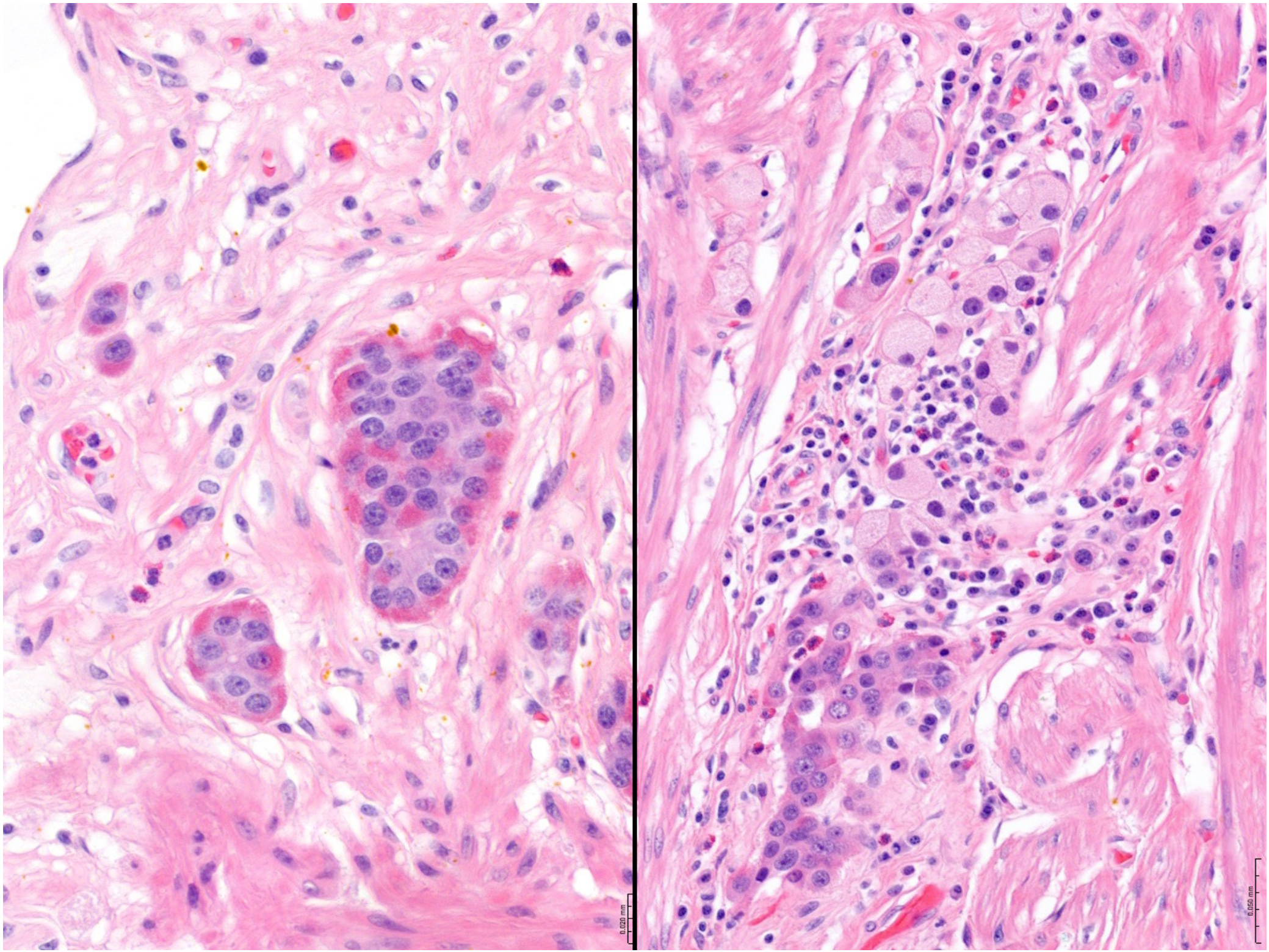
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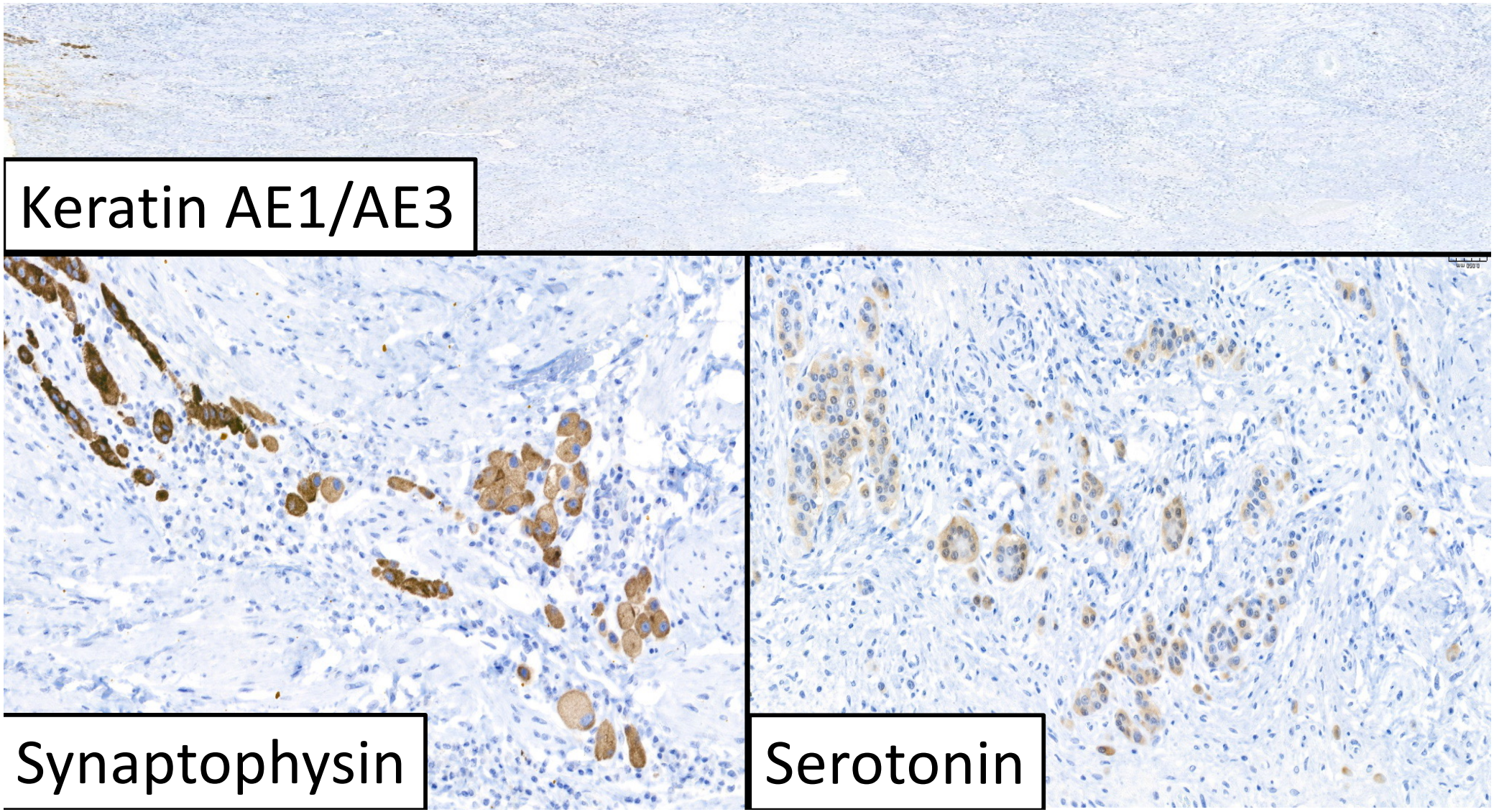
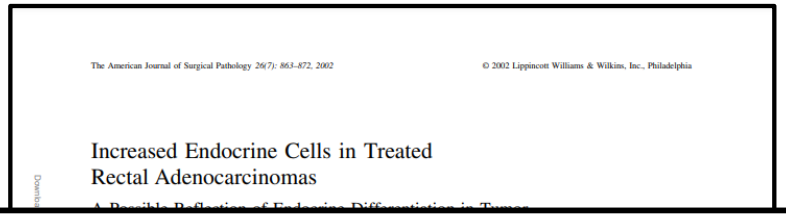
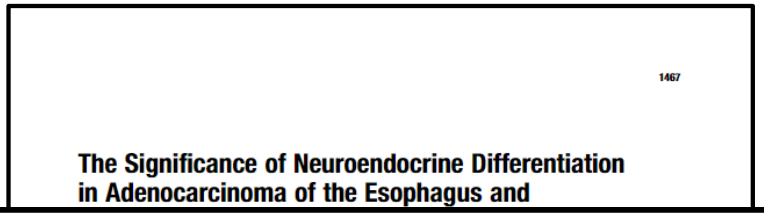
Induction of Neuroendocrine Differentiation (Preferential Survival of NE Cells?) in the Setting of Neoadjuvant Therapy



Induction of NE Diff s/p Neoadjuvant CRT



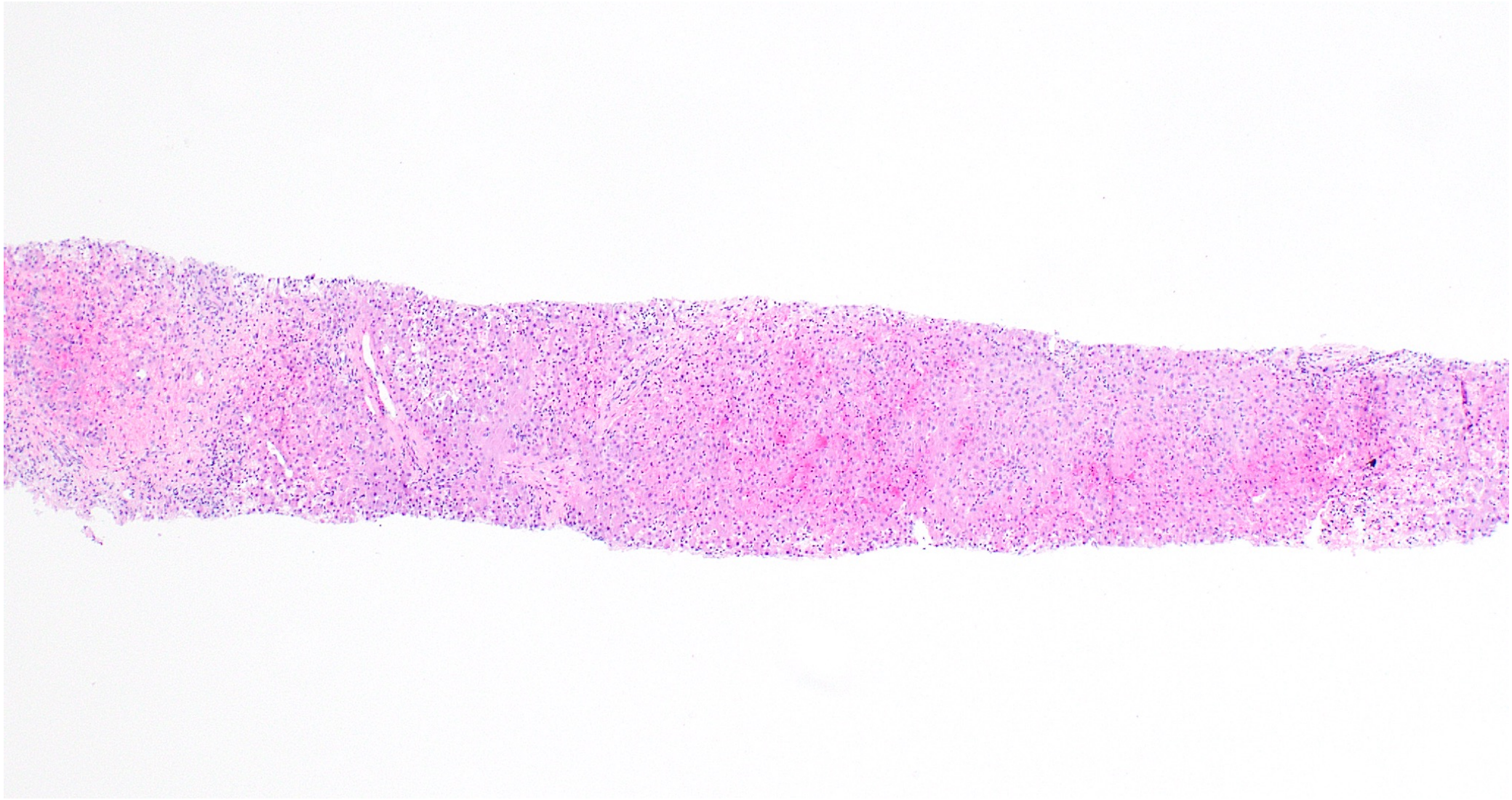
- Any CgA+ in 68% of resections (compared to 30% of pre-tx bxs)
- CgA+ >20% in 38%
- Correlated with tx response
- Low Ki-67 (<5%)
- <u>Aberrant p53 IHC</u>



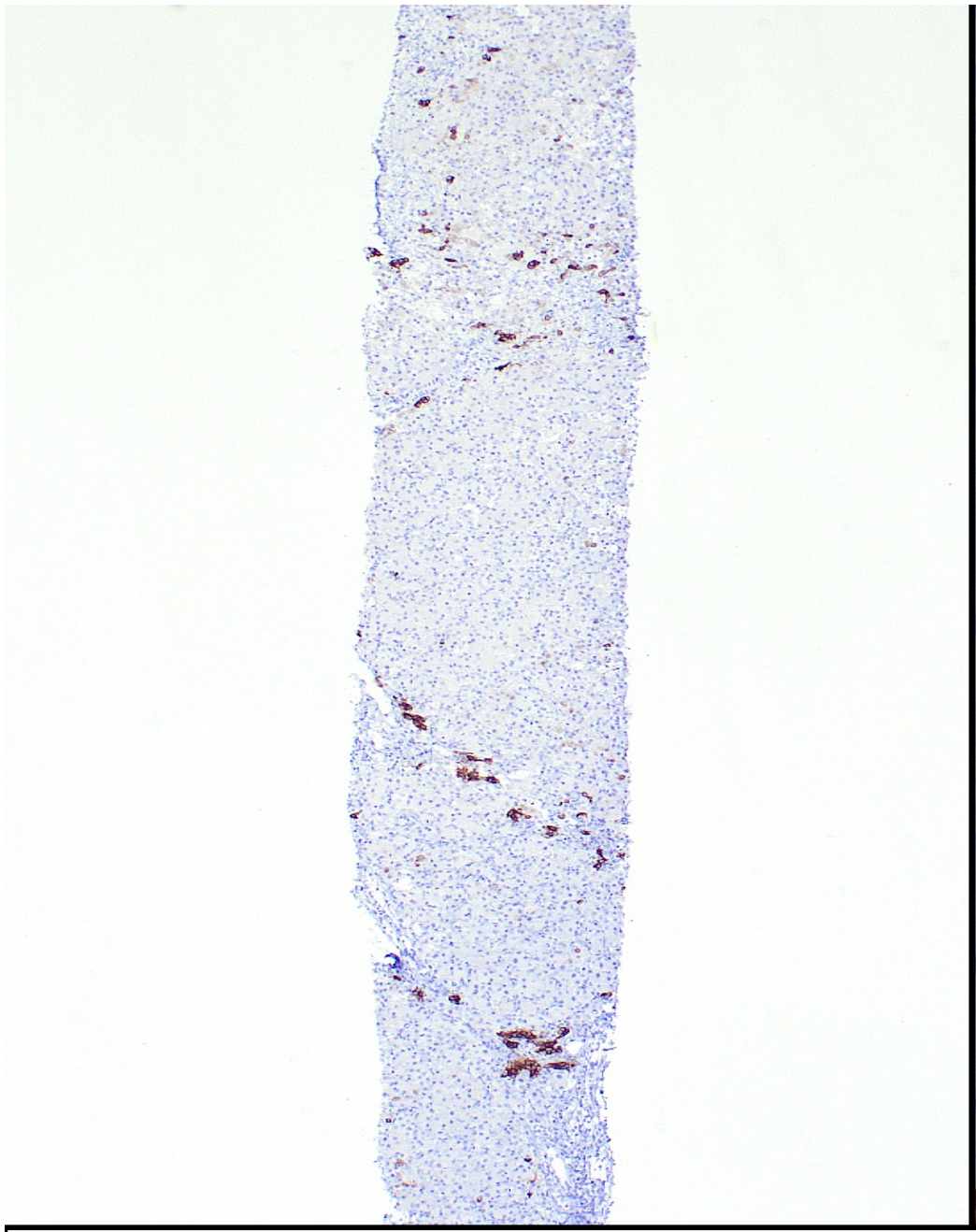
- Any CgA+ in 52% of 73 pts w/ residual tumor
- % of CgA+ cells increased from 6% to 47% in matched pre/post-tx bxs
- CgA+ residual disease associated w/ <u>adverse DFS and OS</u>

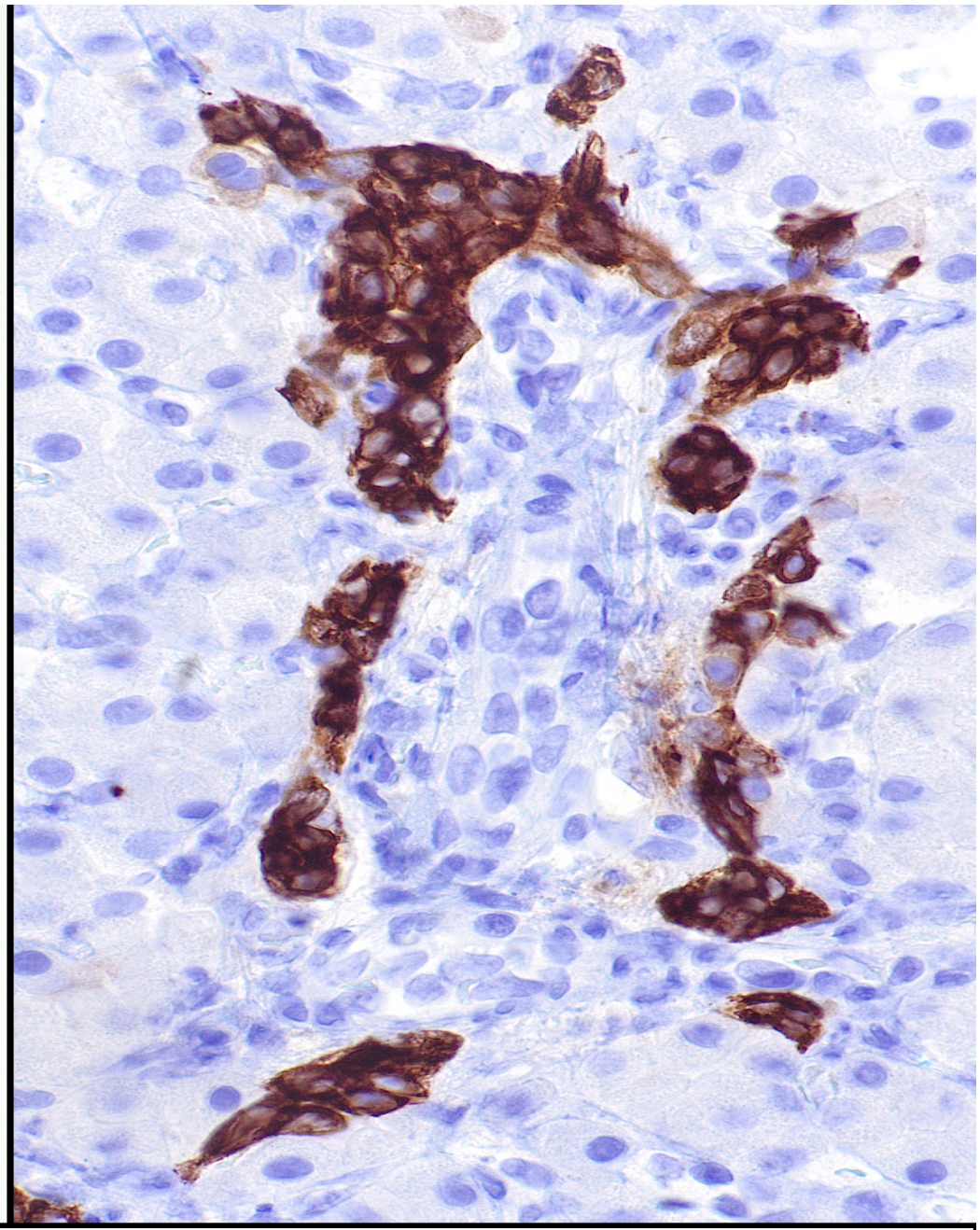
Case 3

Consult from a GI Pathology colleague last week: How do I distinguish telangiectatic hepatic adenoma from congestive hepatopathy?



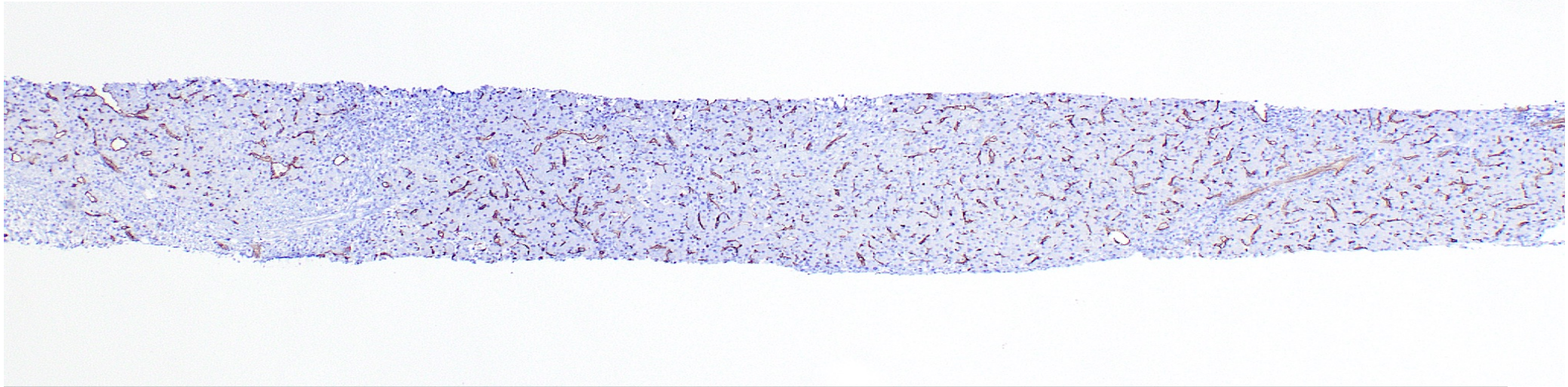
29-year-old woman with liver lesion





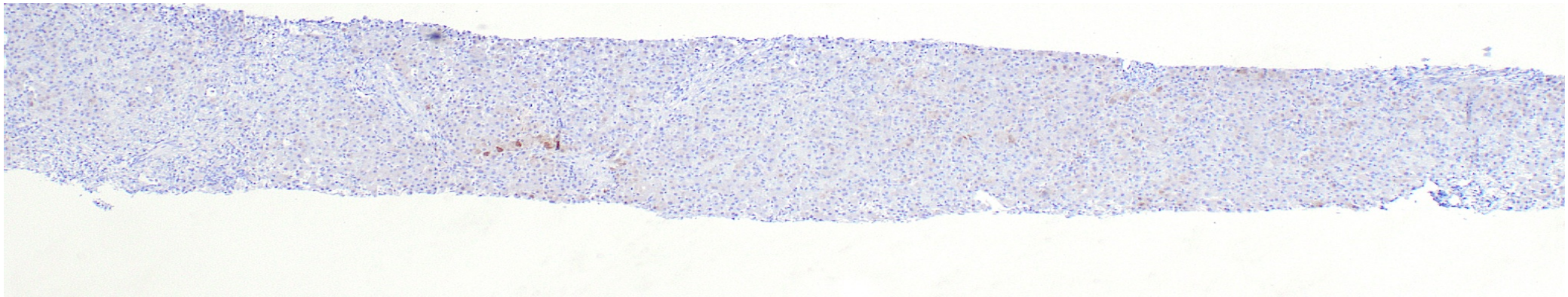
CK7: This led to some diagnostic confusion by the referring pathologist and my colleague

“Diffuse sinusoidal labeling”=hepatocellular lesion

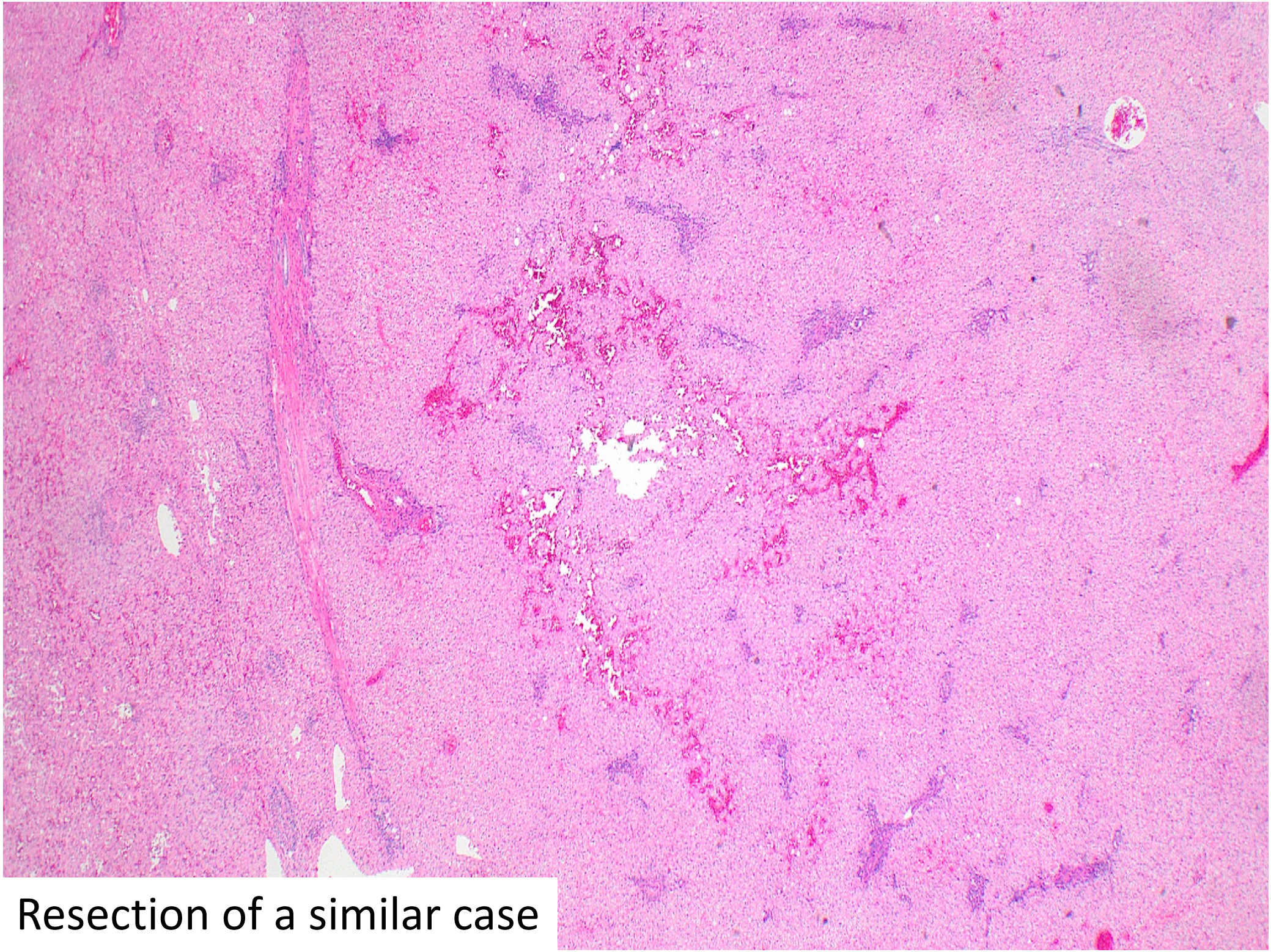


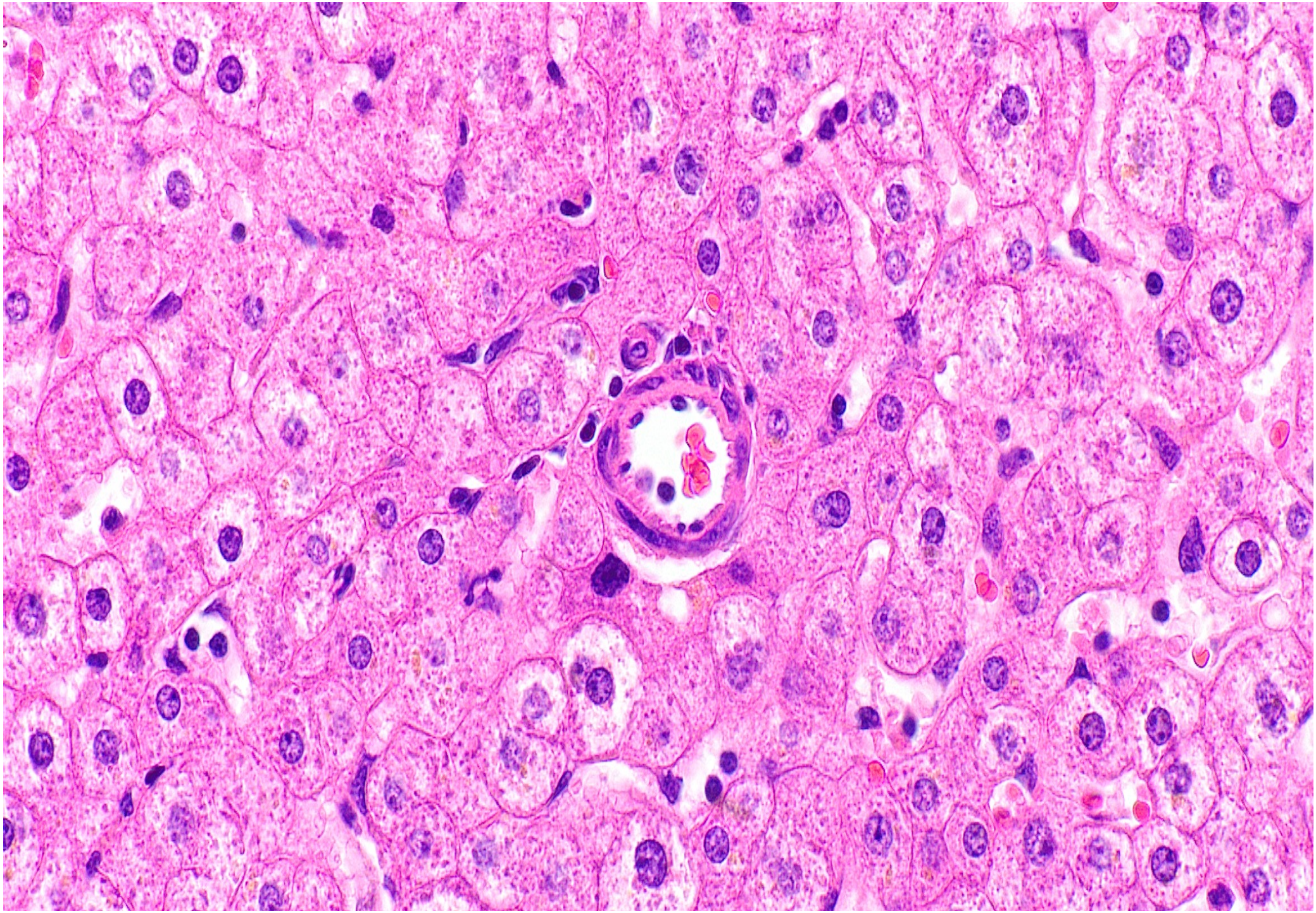
CD34: Describe the pattern; what is its significance?

Nearly “null pattern”=hepatocellular lesion (but almost certainly not FNH or HCC)

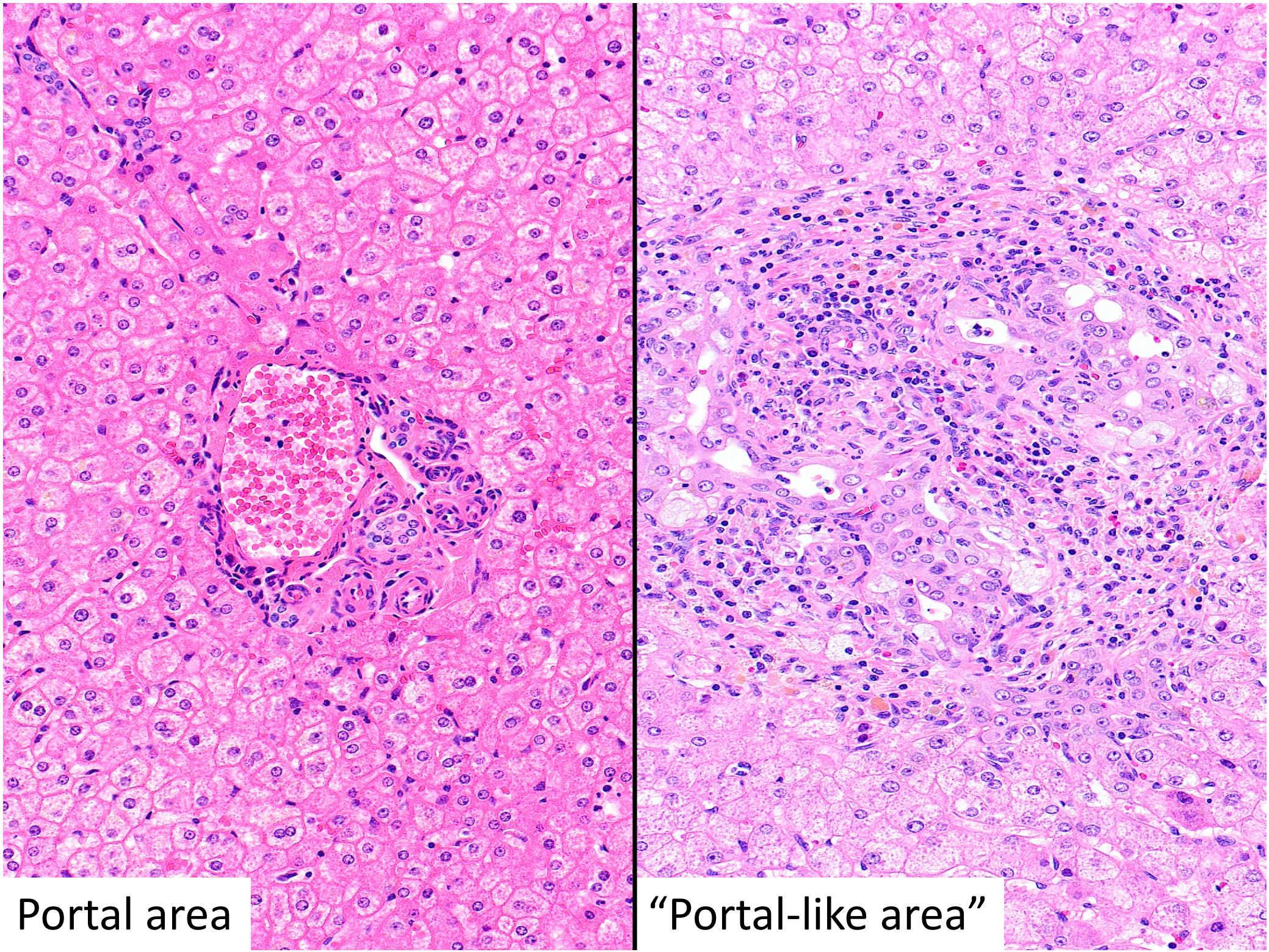


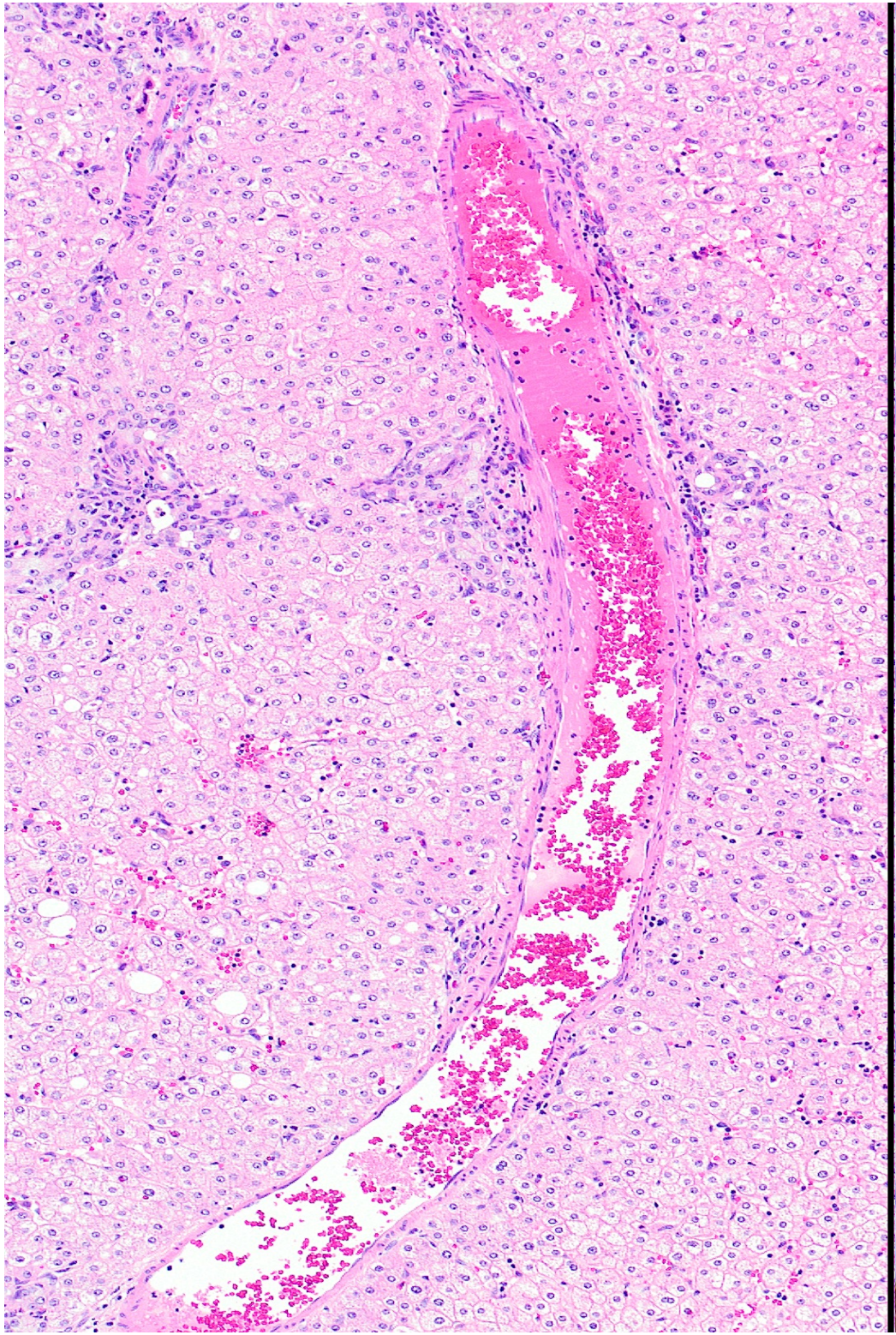
Glutamine synthetase: Describe pattern; significance?

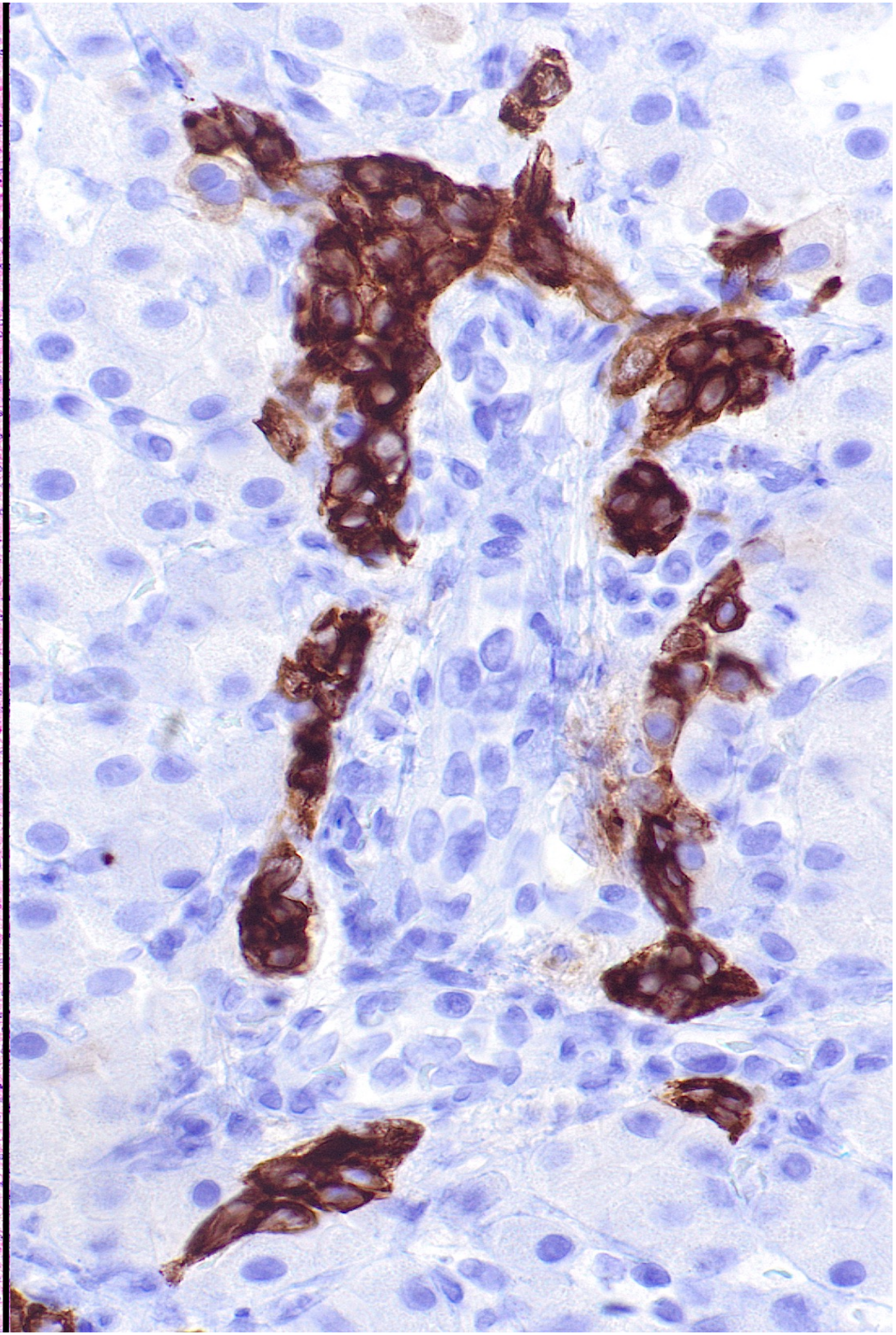

Resection of a similar case

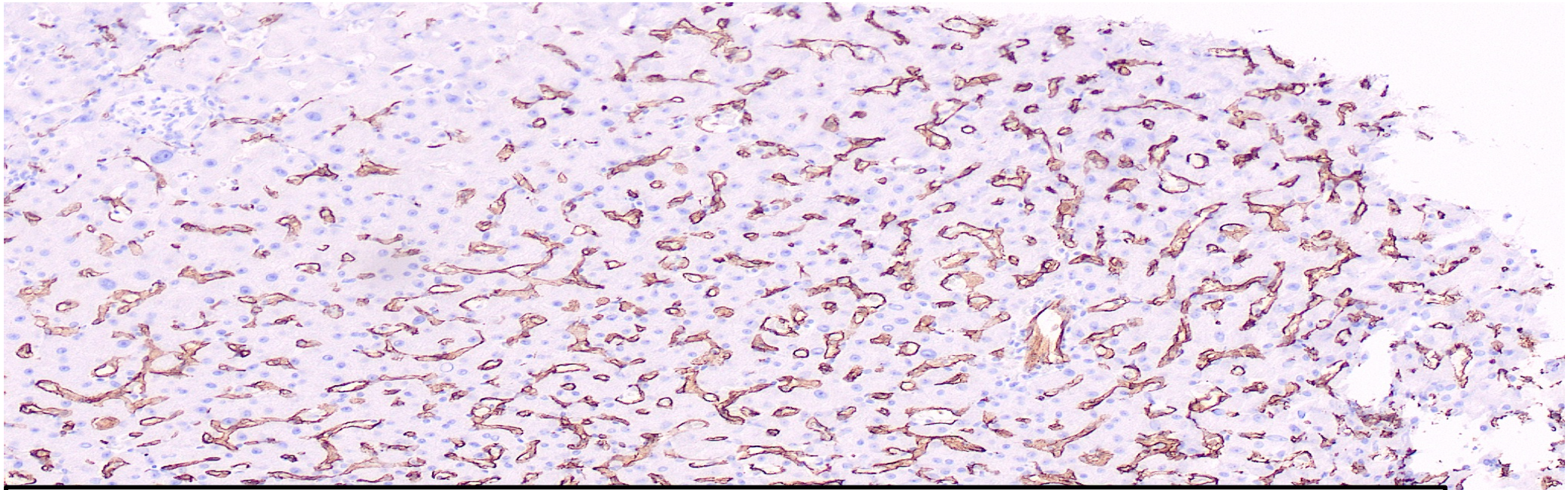


Isolated arteriole: “platonic ideal” histologic fx of hepatic adenoma

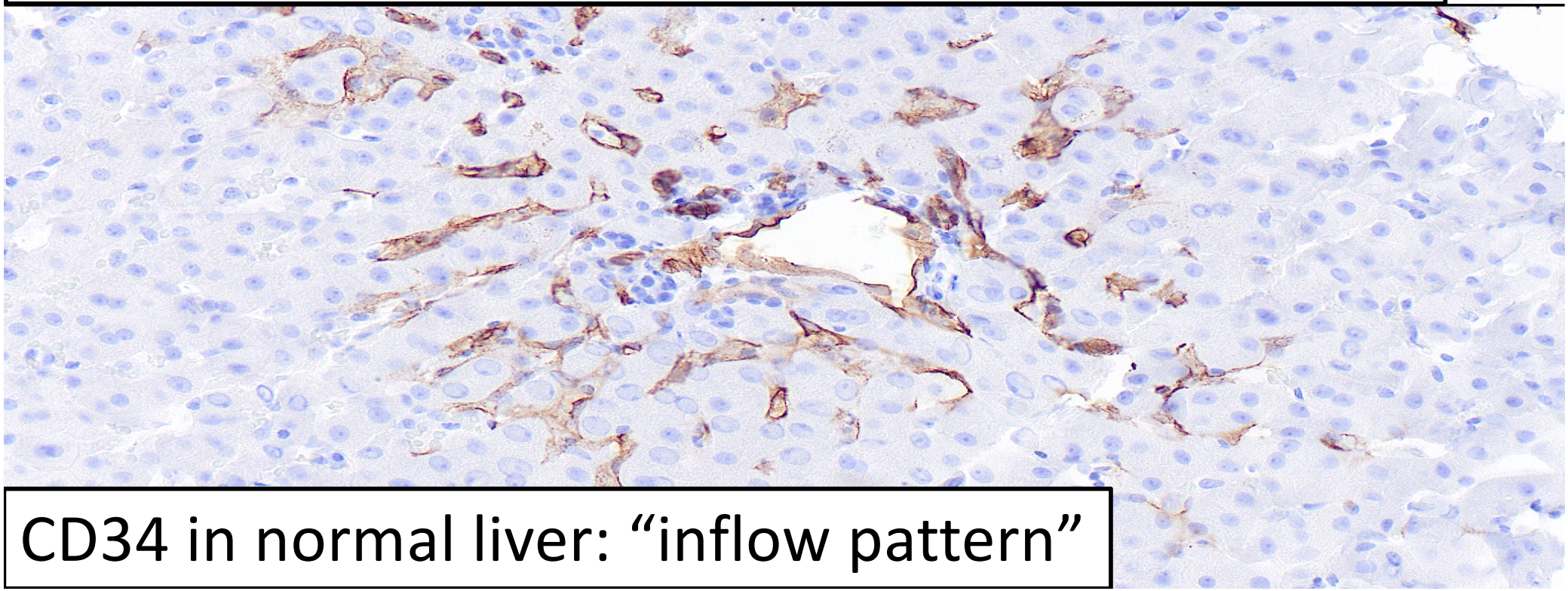

Portal area
“Portal-like area”



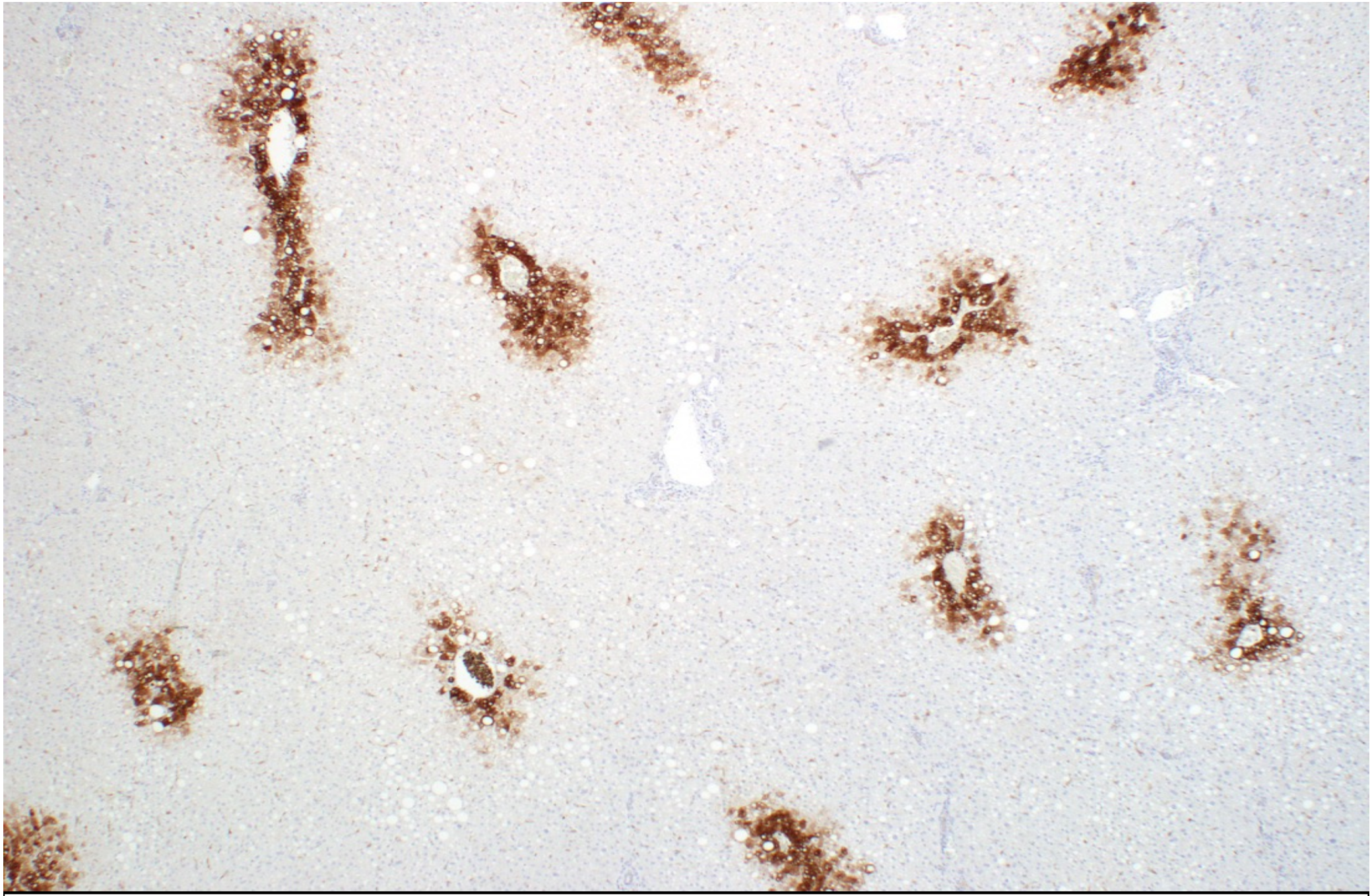




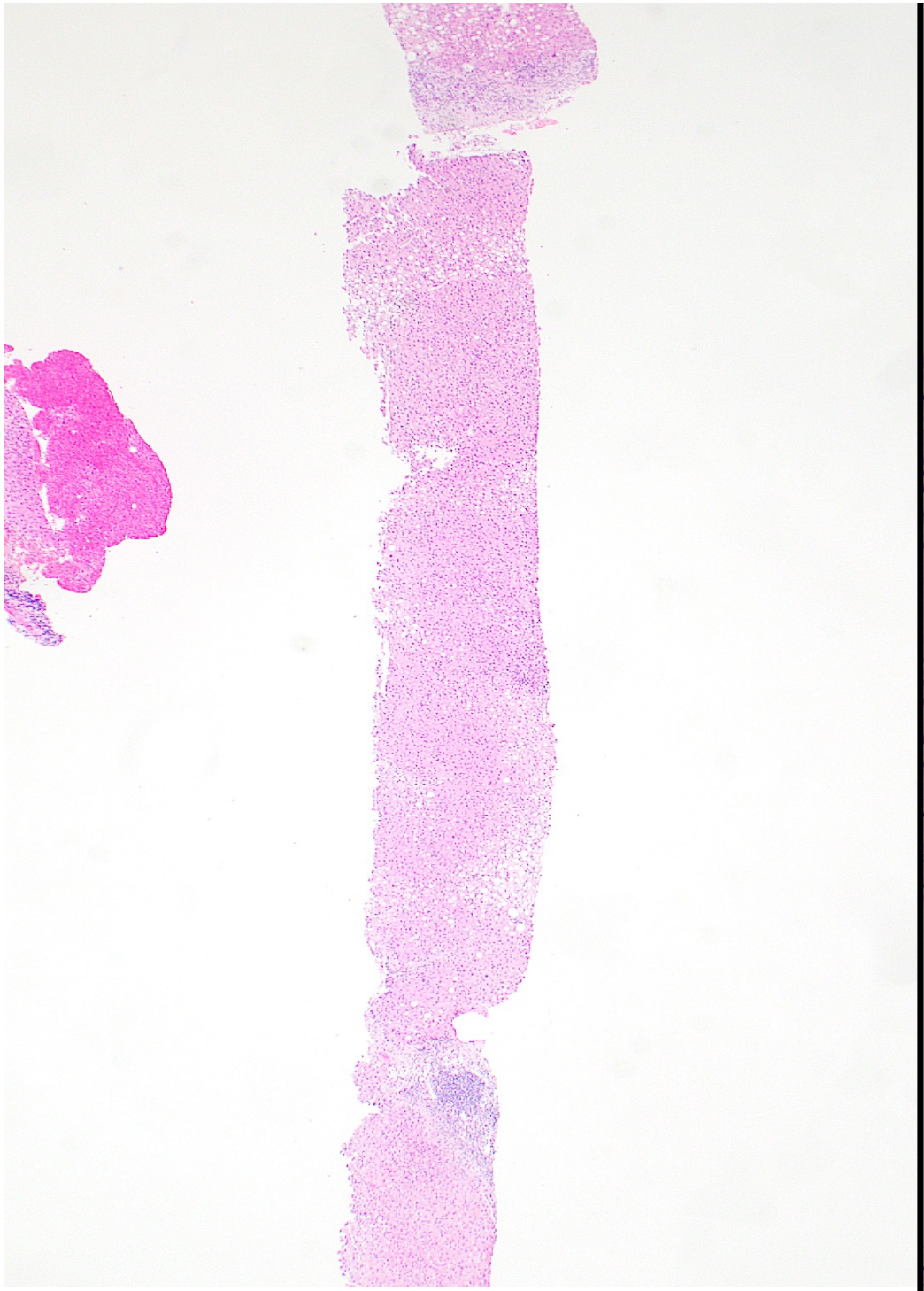
CD34 in HA/HCC>FNH: diffuse sinusoidal labeling



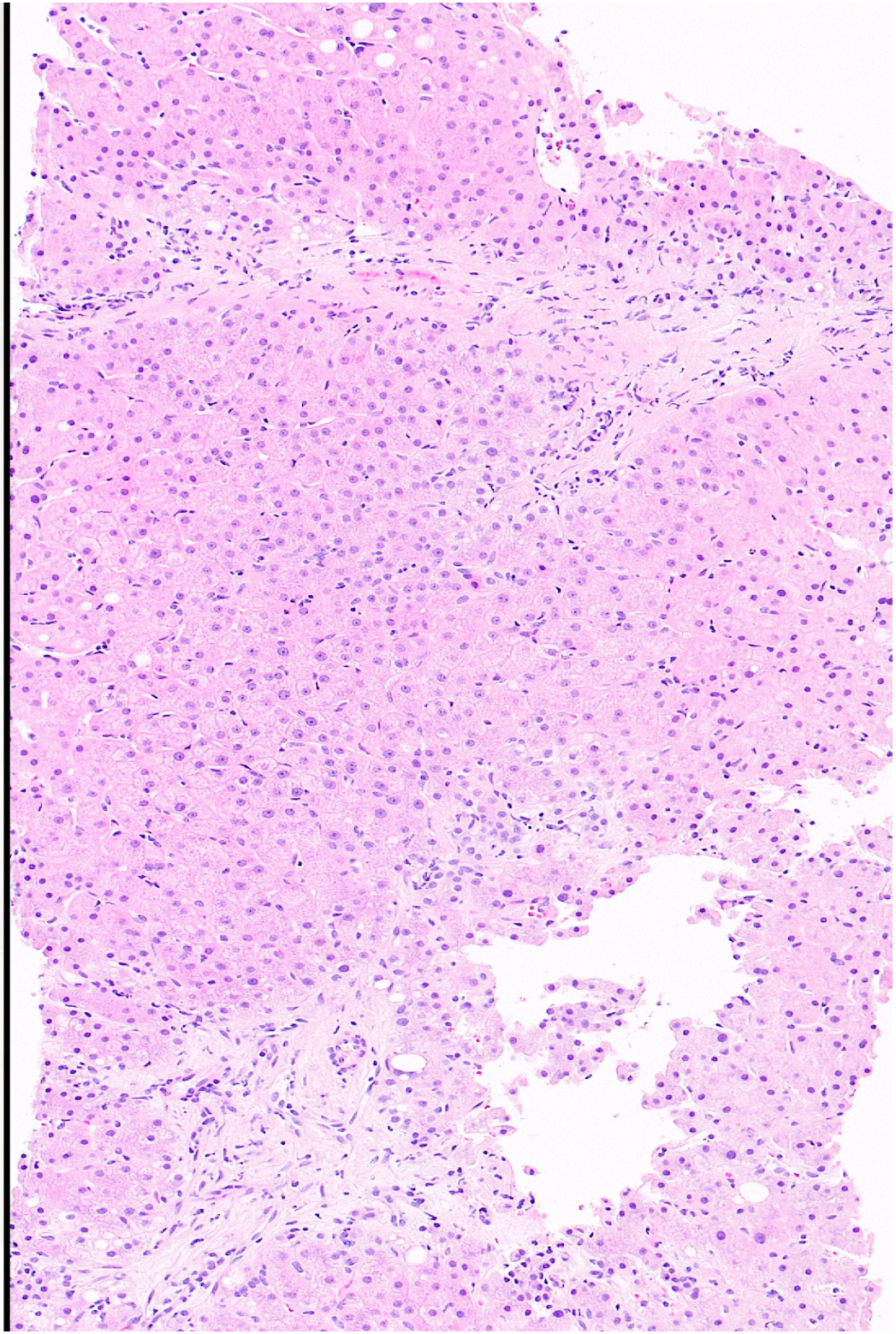
CD34 in normal liver: “inflow pattern”



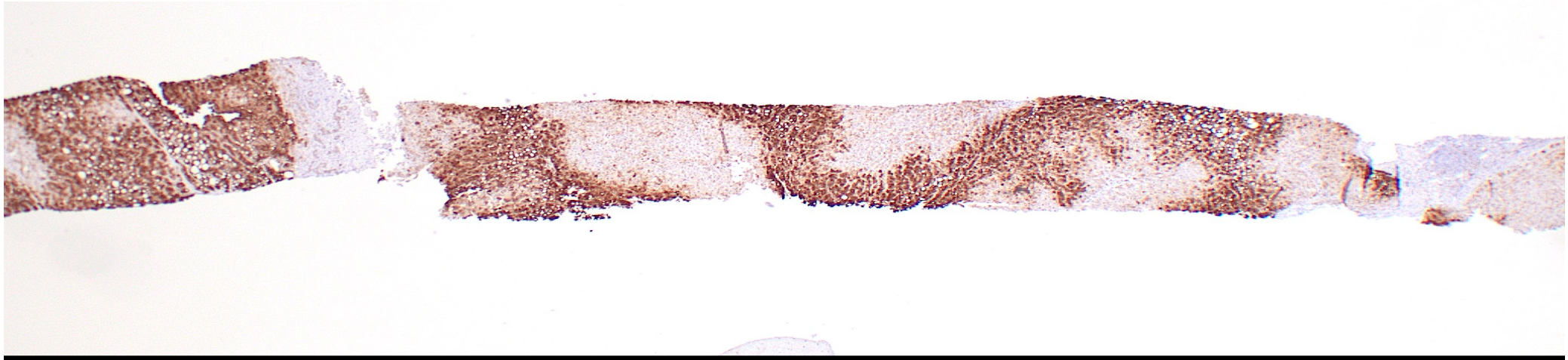
Glutamine synthetase expression in normal liver –
expression is restricted to centrilobular (zone 3) hepatocytes



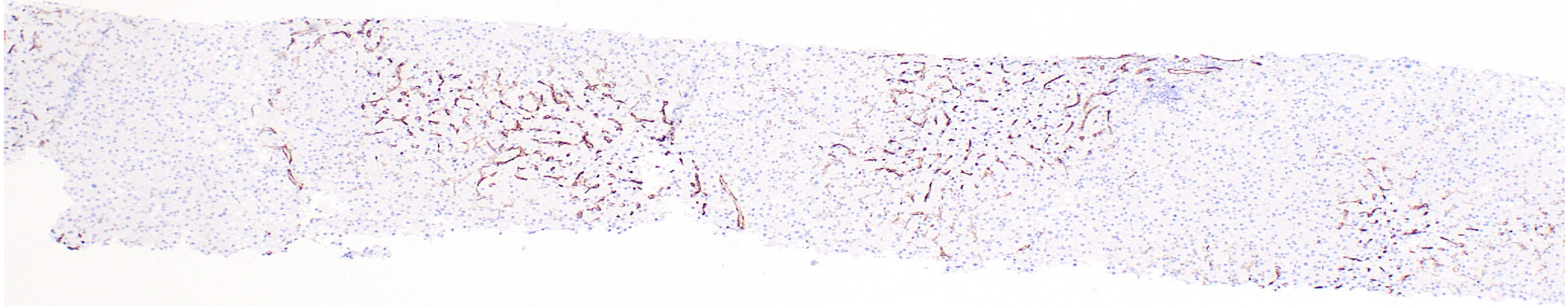
39-year-old woman with liver lesion



Focal Nodular Hyperplasia

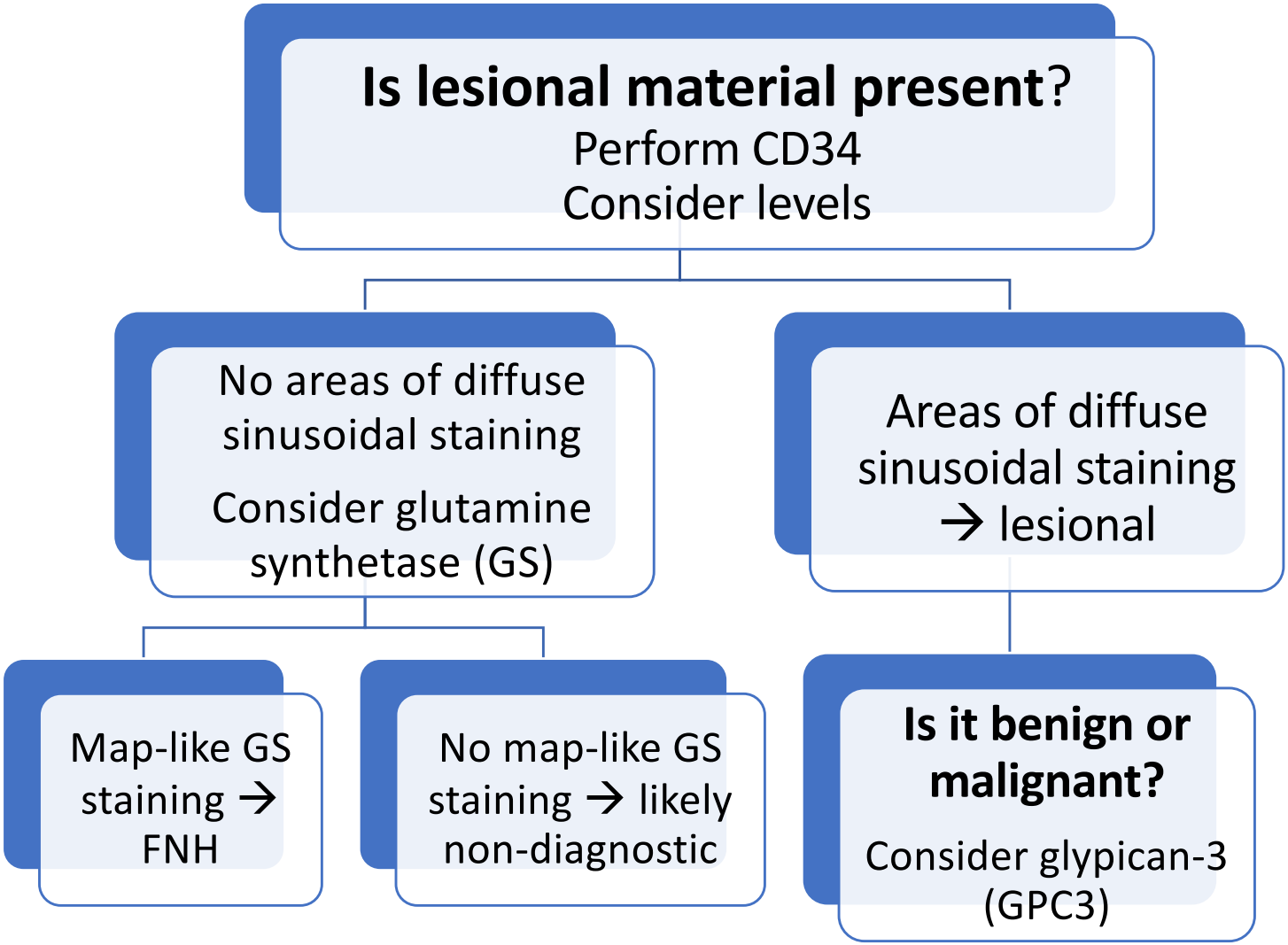


Glutamine synthetase: map-like/anastomosing pattern



CD34: ?more than inflow; less than diffuse

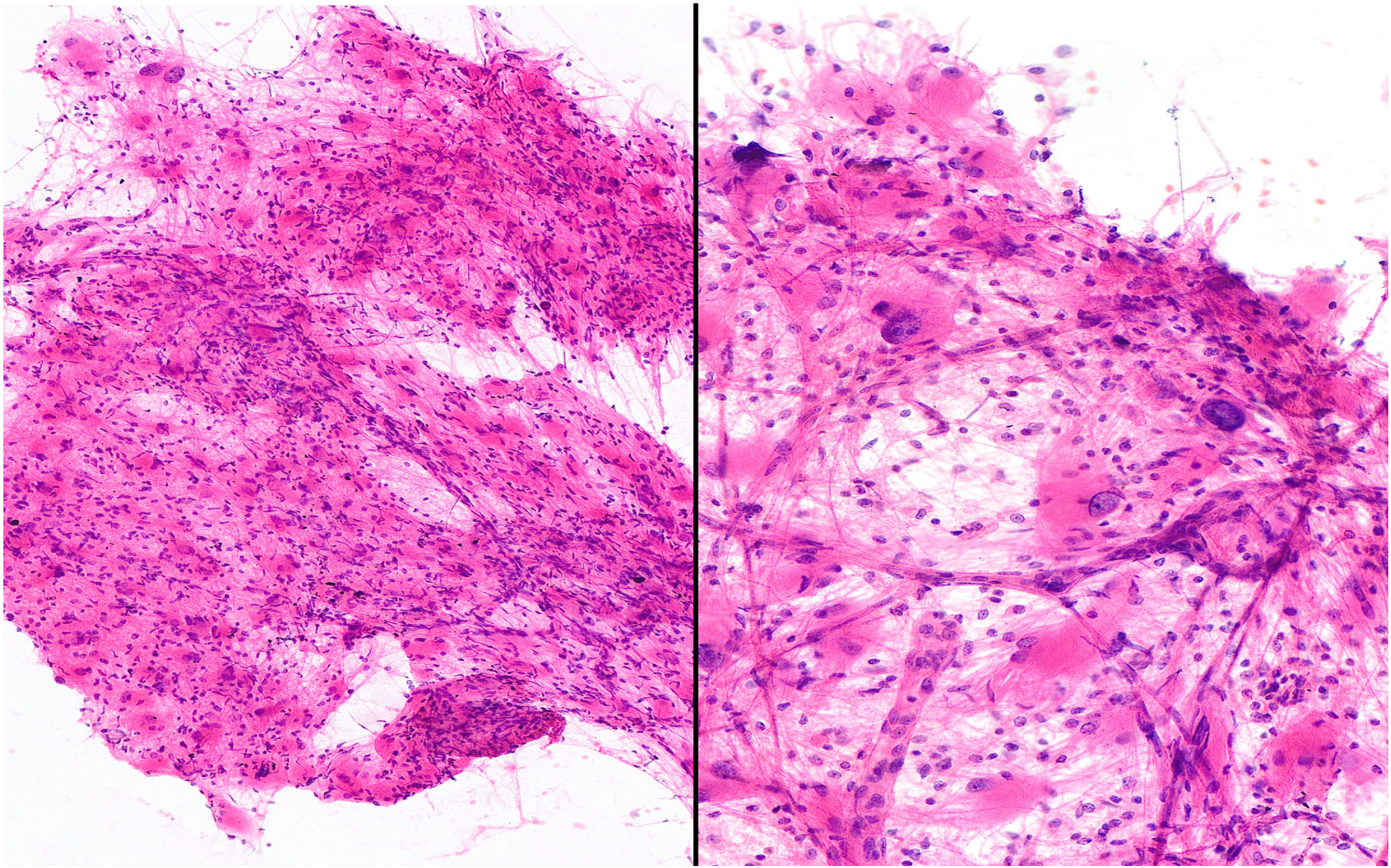
Doing as Well with Less
Dx Algorithm: Core Biopsy of a Mass



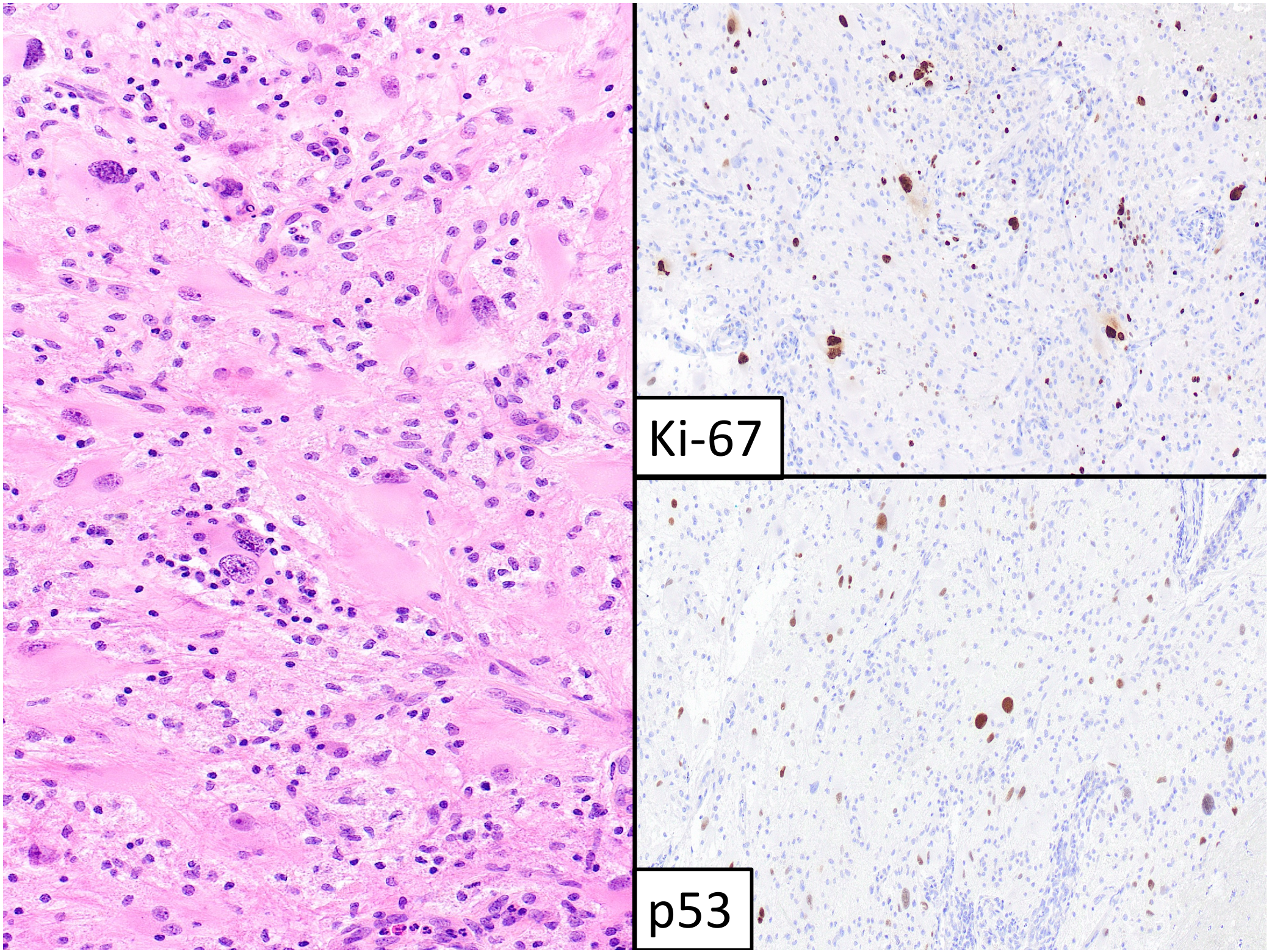
IHC menu for this application:
- CD34
- GPC3
- GS

Possibly:
- SAA
- L-FABP
- HSP-70

Case 4



68-year-old woman with h/o follicular lymphoma p/w right-sided weakness and left frontal lobe white matter hypodensity with mass effect
Frozen section dx: lesional tissue, favor glioma


Ki-67
p53

Progressive Multifocal Leukoencephalopathy

> Am J Surg Pathol. 1996 Sep;20(9):1086-90. doi: 10.1097/00000478-199609000-00006.

Role of p53 immunohistochemistry in differentiating reactive gliosis from malignant astrocytic lesions

H Yaziji [1], R Massarani-Wafai, M Gujrati, J G Kuhns, A W Martin, J C Parker Jr

Affiliations + expand

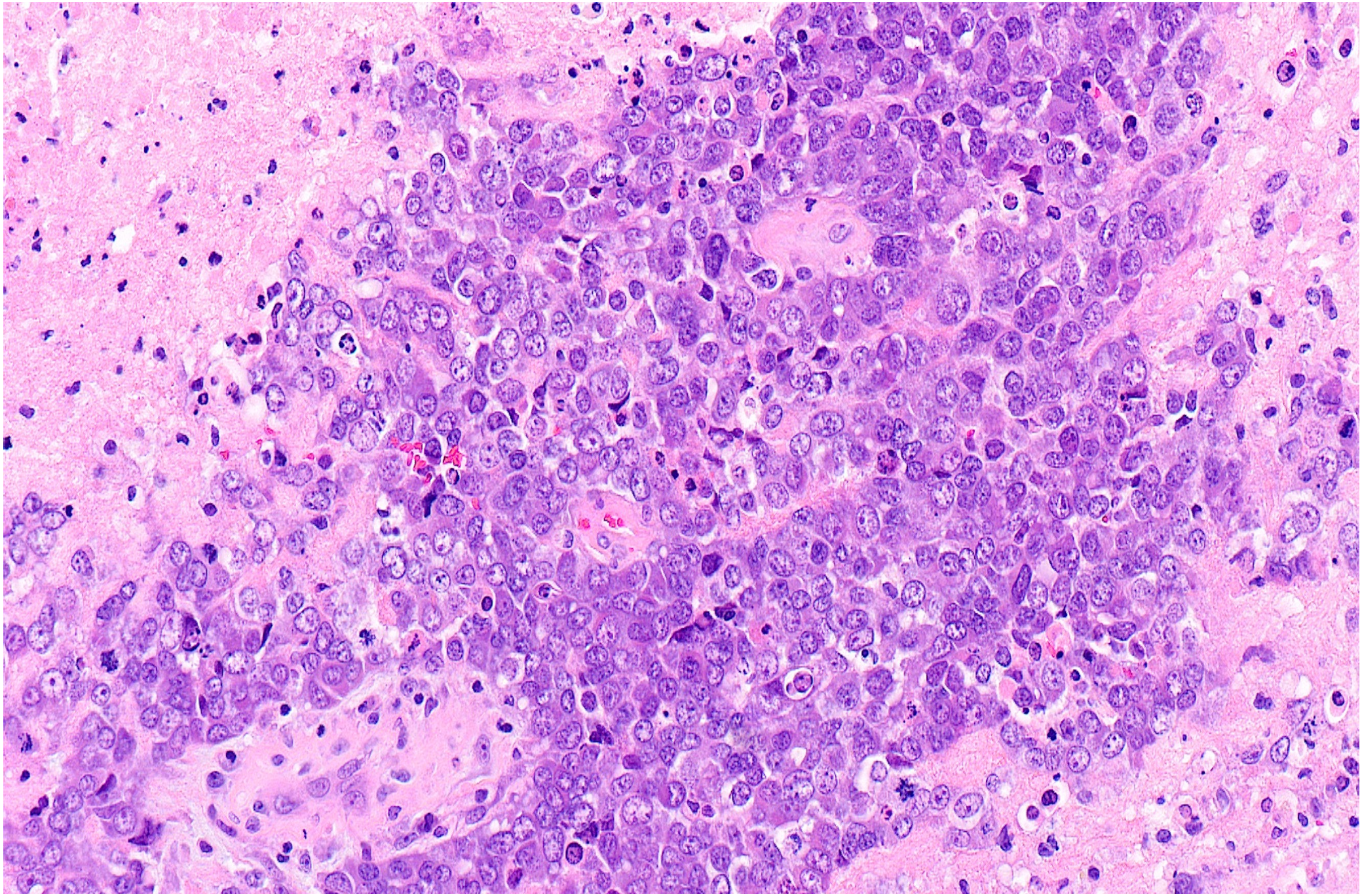
PMID: 8764745 DOI: 10.1097/00000478-199609000-00006

Abstract

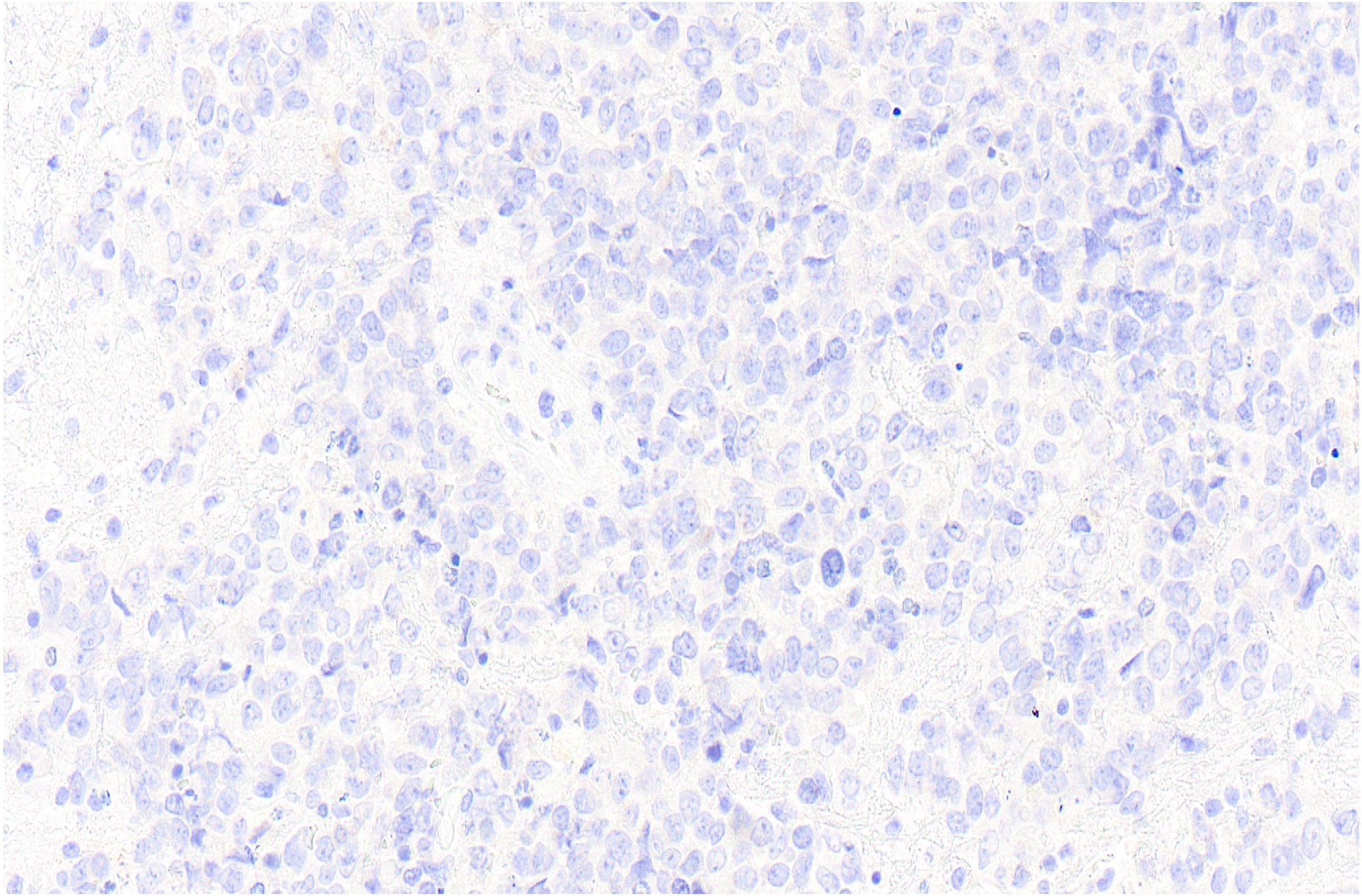
P53 immunohistochemistry has been used to distinguish between malignant tumors and morphologically similar benign processes. In the central nervous system, a major diagnostic dilemma is caused by overlapping features of benign reactive astrocytic lesions and low-grade astrocytomas, especially with small biopsies. P53 immunoreactivity in astrocytes could be useful in differentiating benign reactive lesions from malignant astrocytomas. An immunohistochemical study on 110 brain lesions from 108 patients using a monoclonal antibody (DO-7) against p53 protein was conducted. Using the modified Ringertz and World Health Organization system, the specimens included 22 astrocytomas, 12 anaplastic astrocytomas, 42 glioblastoma multiforme tumors, three nonglial tumors, and 56 reactive astrocytic lesions to 25 neoplasms, nine infectious processes, six cerebrovascular disorders,one metabolic disorder, two vascular malformations, eleven degenerative/demyelinating lesions, and two unknown primary lesions. Immunoreactive astrocytic tumors included 12 (54%) astrocytomas, nine (75%) anaplastic astrocytomas, and 38 glioblastoma multiforme tumors (90%). Among the reactive astrocytic lesions, only five (9%) cases of progressive multifocal leukoencephalopathy were immunoreactive. These data demonstrate that p53 immunoreactivity in astrogliosis is unusual but is to be expected in astrocytomas and can help to differentiate reactive from neoplastic astrocytic lesions.

SV40

Case 5



64-year-old man woman with remote h/o breast cancer and recently diagnosed lung mass presenting with left cerebellar lesion



64-year-old man woman with remote h/o breast cancer and recently diagnosed lung mass presenting with left cerebellar lesion

Carcinoma typing (there are only 7)

Carcinoma Type	Useful IHC Markers (in general, expression should be extensive)
Adenocarcinoma (77%)	Site specific transcription factors
Squamous cell carcinoma (12%)	p40 (>95%), high-molecular weight keratin (>99%)
Urothelial carcinoma (7%)	p40 (85%), high-molecular weight keratin (>95%), GATA-3 (80%), uroplakin II (67%), CK20 (50%)
Neuroendocrine tumor/carcinoma (4%)	chromogranin A, synaptophysin, INSM1, POU2F3
Sarcomatoid carcinoma without or with recognizable heterologous elements	SMA, desmin, myogenin (rhabdomyosarcomatous)
Undifferentiated (pure)/ dedifferentiated (concurrent differentiated component) carcinoma	SMARCA4 (BRG1), SMARCB1 (INI1), MMR, EBER, HR-HPV (rare), NUT (rare)
“Mixed” carcinomas composed of two (or more) distinct cell lineages	

I recommended the following panel:

AE1/AE3 (carcinoma)

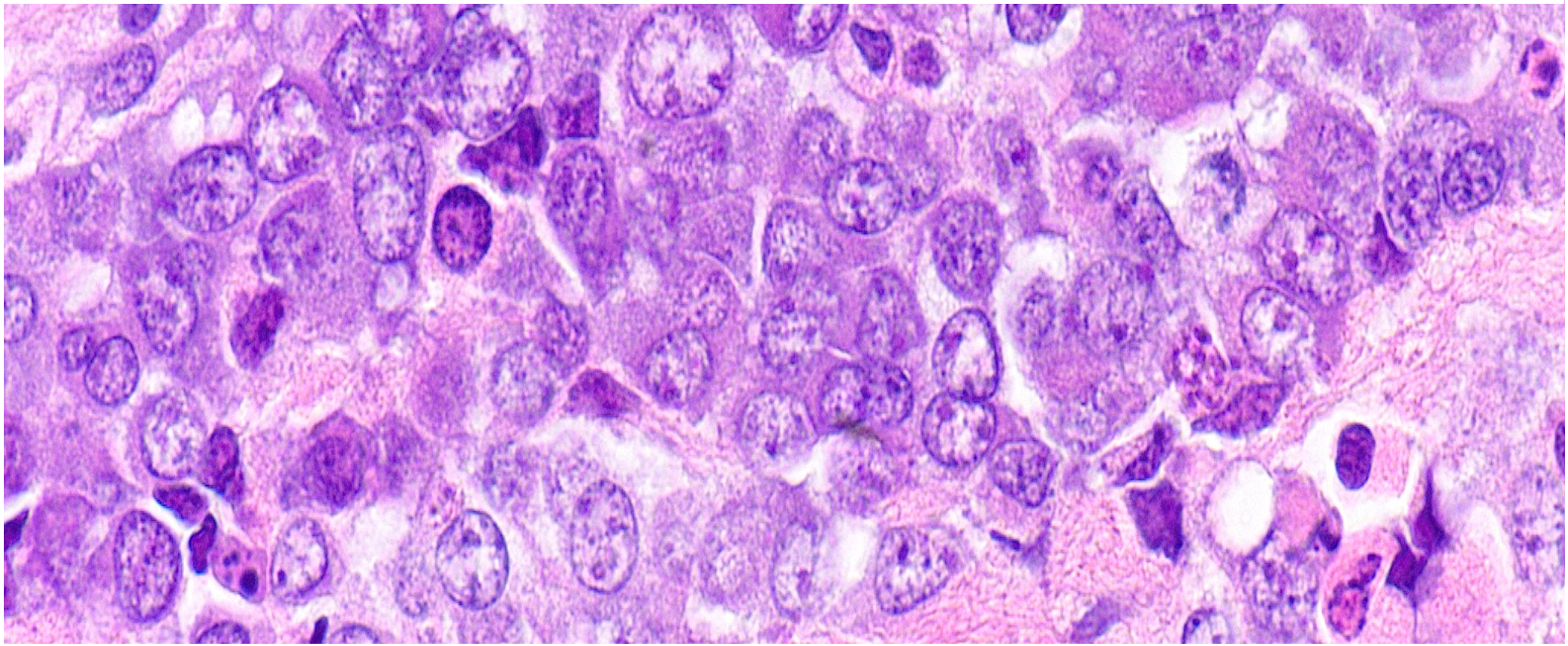
SOX10 (melanoma, TNBC)

Napsin A (lung AdCA)

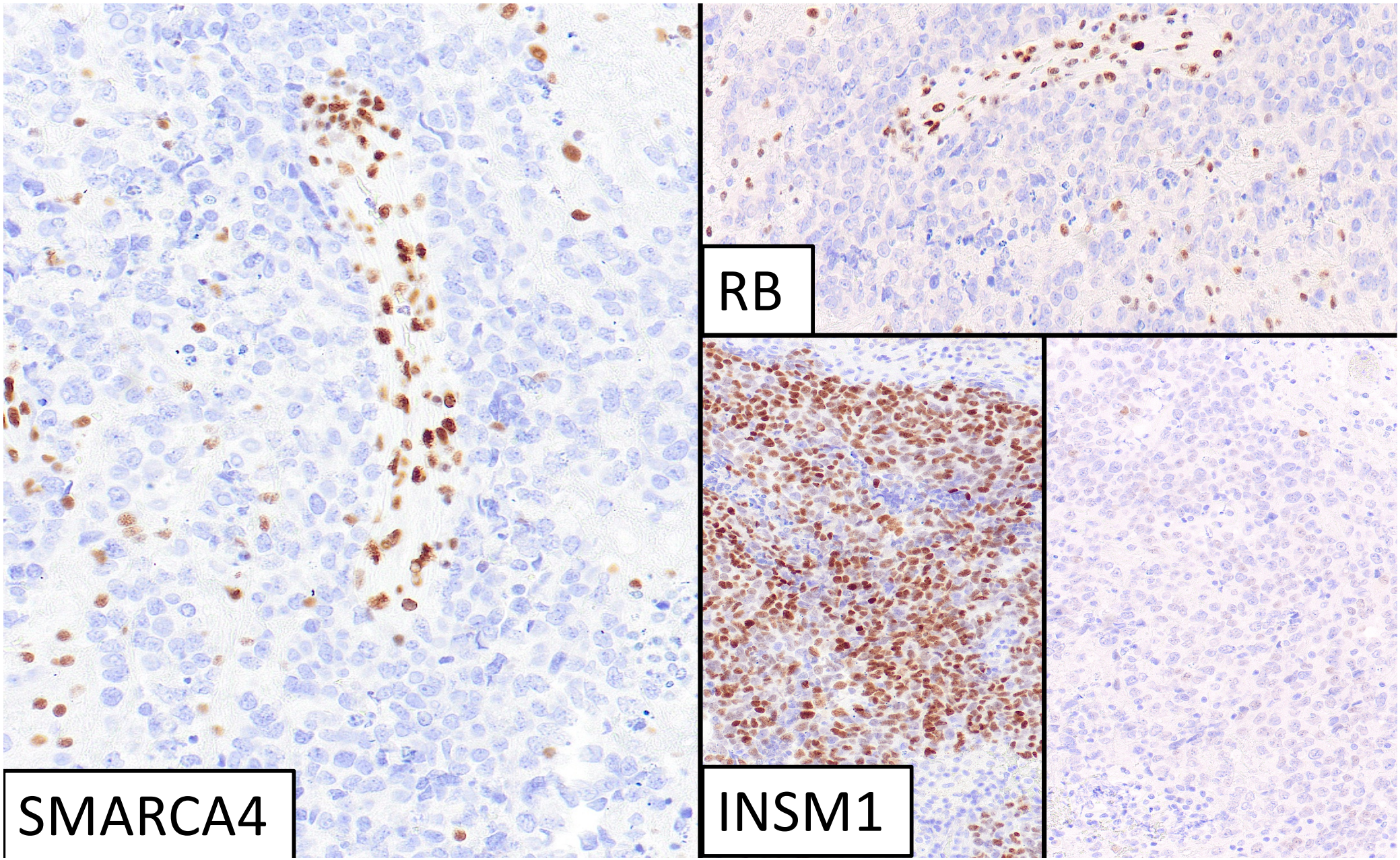
p40, 34βE12 (squamous ca)

INSM1, Rb (NEC)

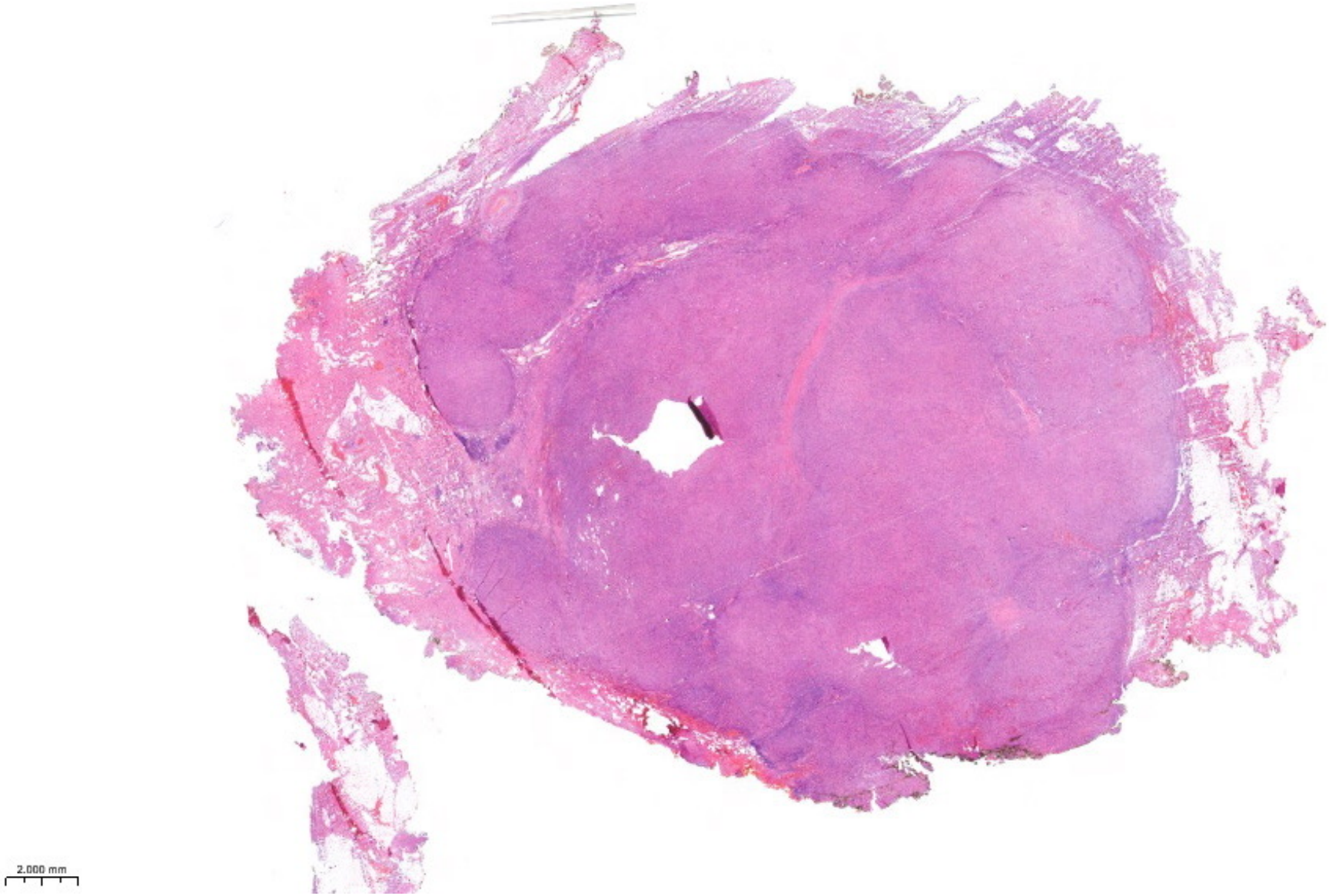
SMARCA4, SMARCB1 (SWI-SNF-deficient undifferentiated ca)



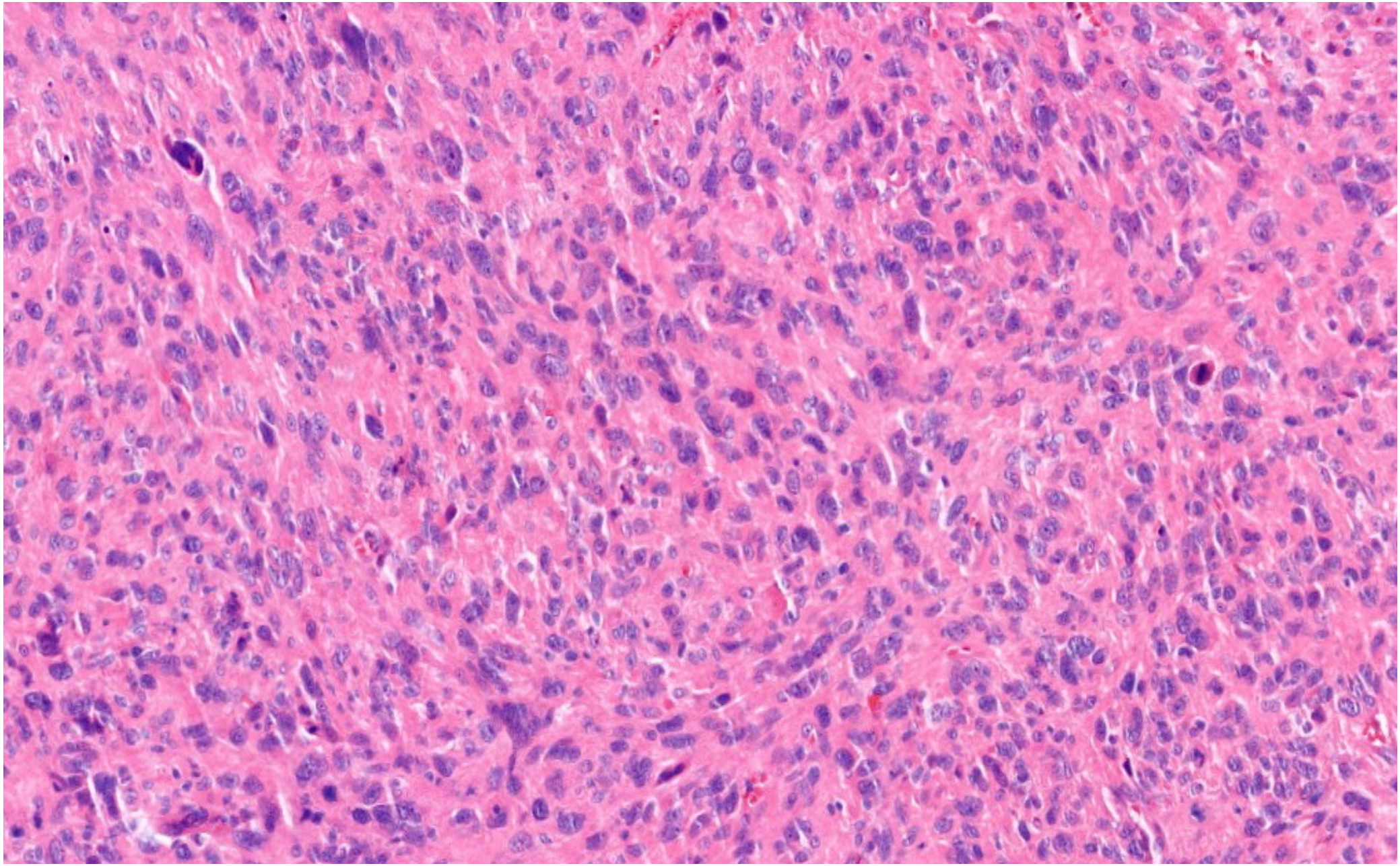
SMARCA4-deficient carcinoma (simultaneously immunophenotypically LCNEC)



Case 6

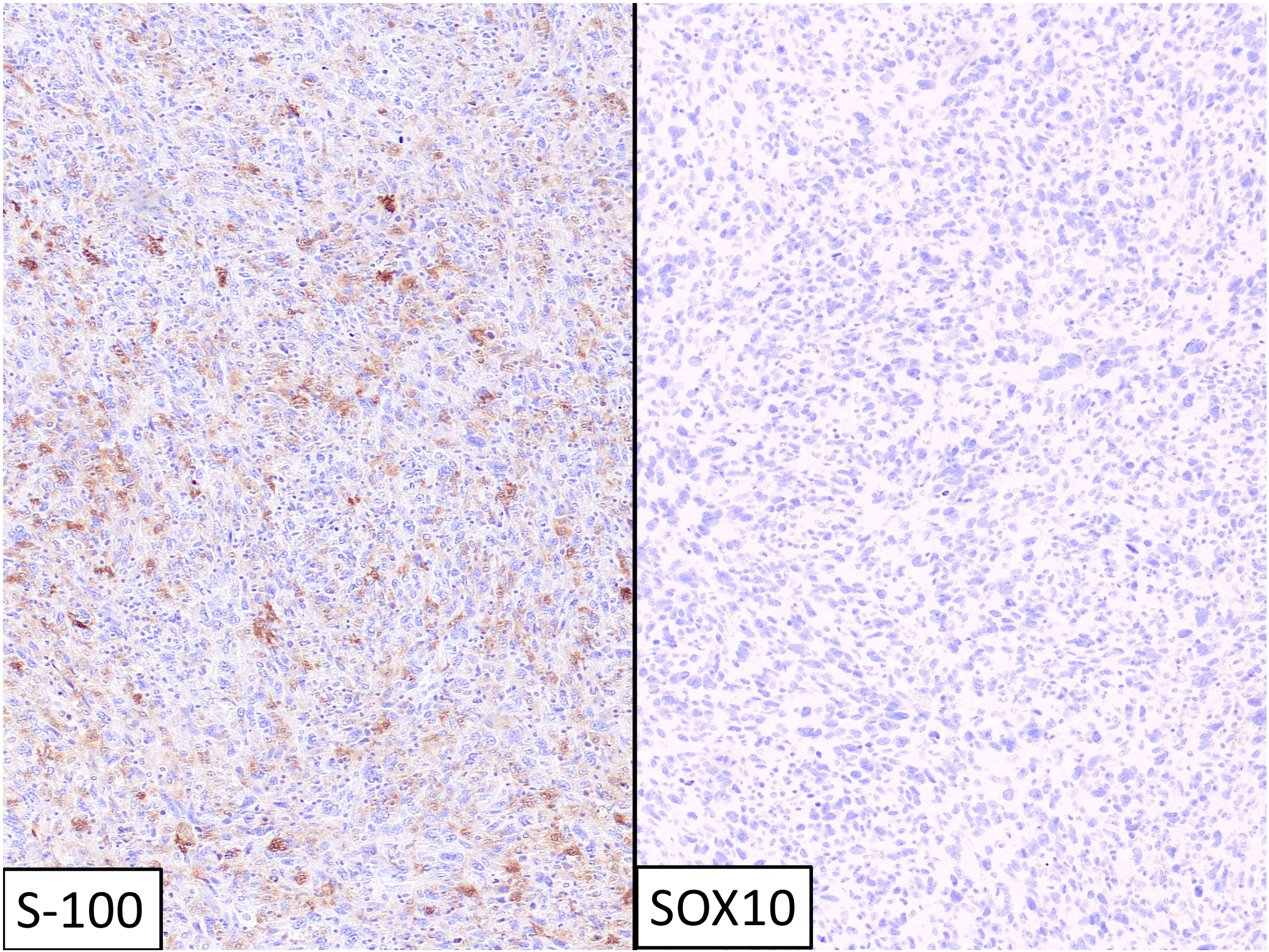


Right postauricular lesion; query LN met; query melanoma



Initial diagnostic panel: AE1/AE3, desmin, actin, S-100, SOX10

Consultants panel: Repeat above plus melan A, HMB-45, MiTF, BRAF V600E, H3K27me3, PD-L1


S-100
SOX10

I recommended the following panel:

CD1a (Langerhans cell)

CD4, CD68, PU.1, lysozyme

CD21, CD23 (follicular dendritic cell)

CD123 (plasmacytoid centric cells)

S-100-, SOX10-

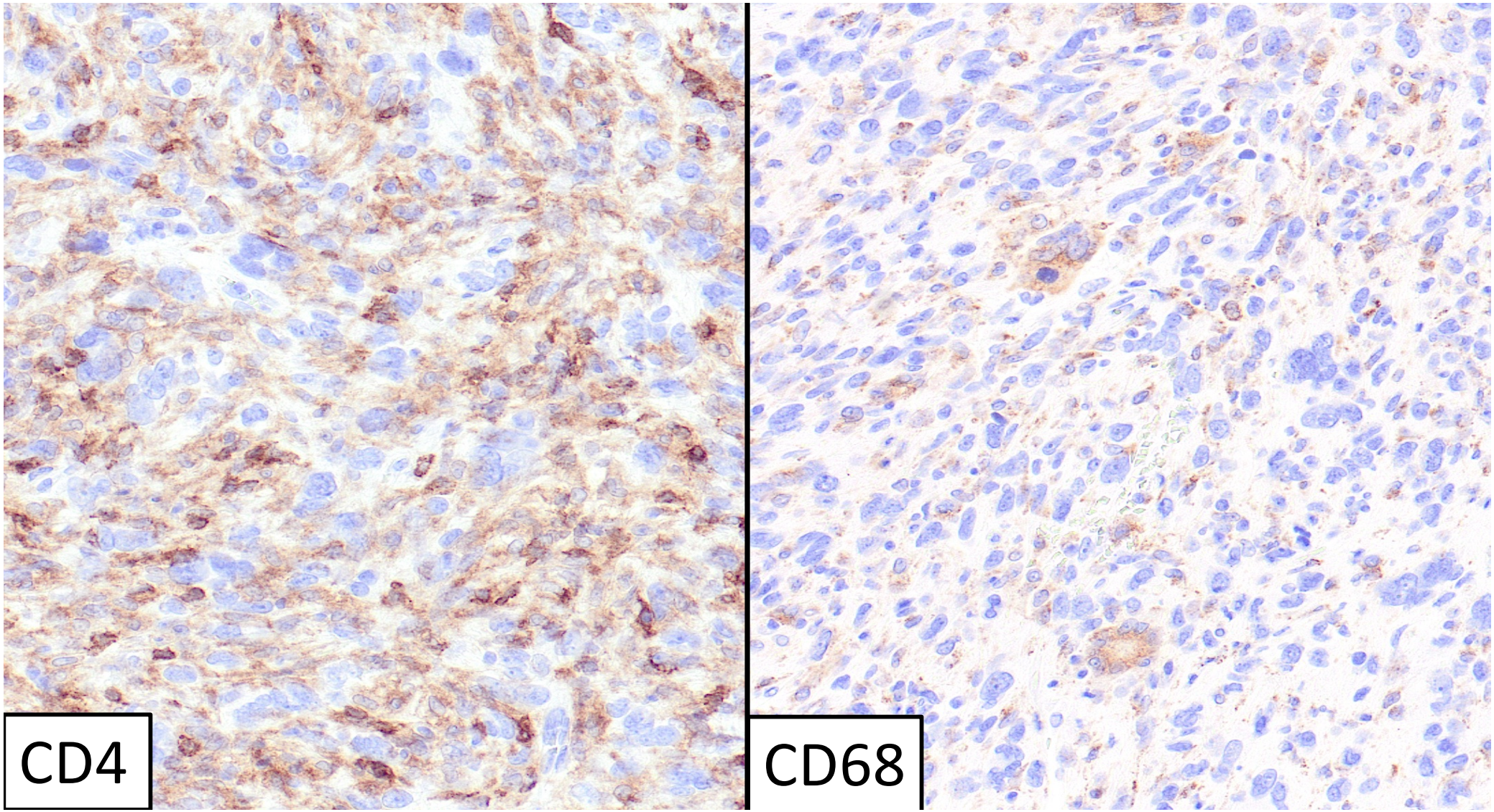
- Most carcinomas, sarcomas, lymphomas
- Mesothelioma
- Germ cell tumor
- Pheochromocytoma/paraganglioma
  (though both expressed by sustentacular cells)

Polyclonal S-100
(S-100B>>S-100A1>>S-100A6)

S-100+, SOX10-

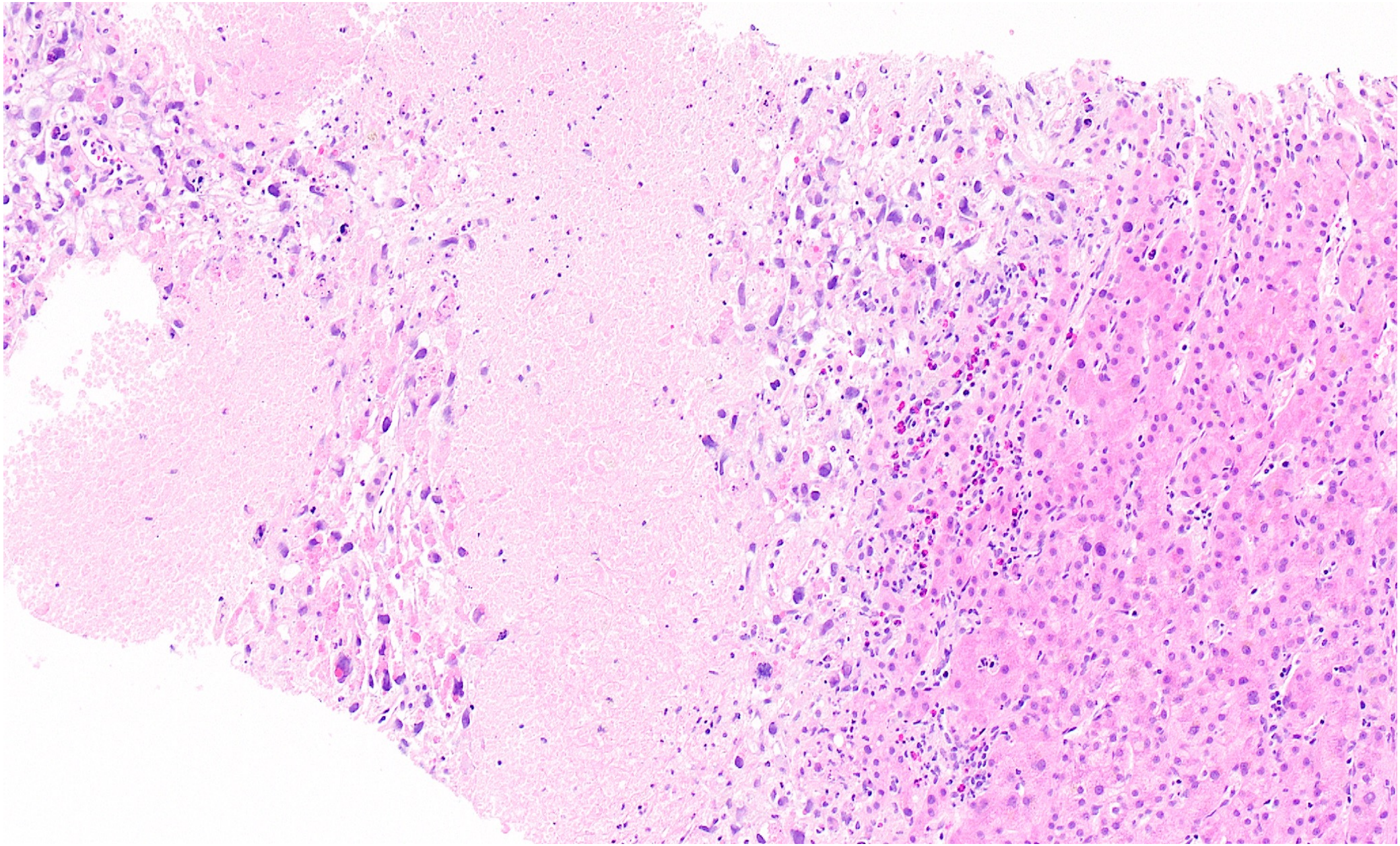
- Tumors of adipocytic/chondroid lineage
- Chordoma
- Ossifying fibromyxoid tumor
- Biphenotypic sinonasal sarcoma
- Lipofibromatosis-like neural tumor
- Infantile fibrosarcoma-like tumor
- Rare cases of Ewing, RMS, SS
- S-100+ carcinomas without myoepithelial differentiation (S-100A1 and/or S-100A6+)
- S-100+ histiocytic/dendritic cell tumors
  (Langerhans cell histiocytosis, Rosai-Dorfman, interdigitating dendritic cell tumor (100%); histiocytic sarcoma, Erdheim-Chester, blastic plamacytoid dendritic cell tumor (30%); follicular dendritic cell sarcoma, juvenile xanthogranuloma (occ.)

Histiocytic of dendritic cell sarcoma, favor interdigitating dendritic cell sarcoma based on the extent of S-100

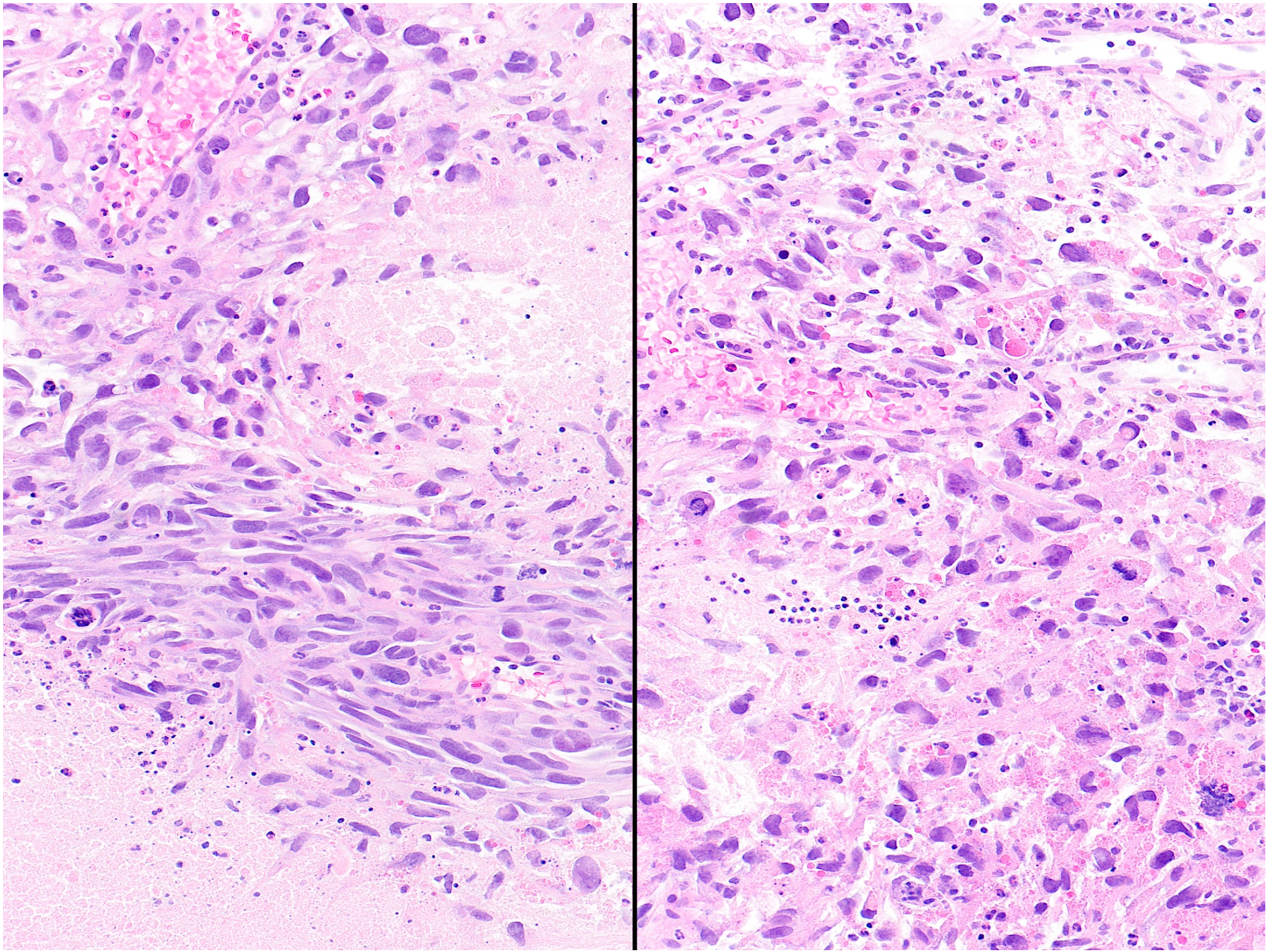


Case 7

Consult from a GI Pathology colleague last week



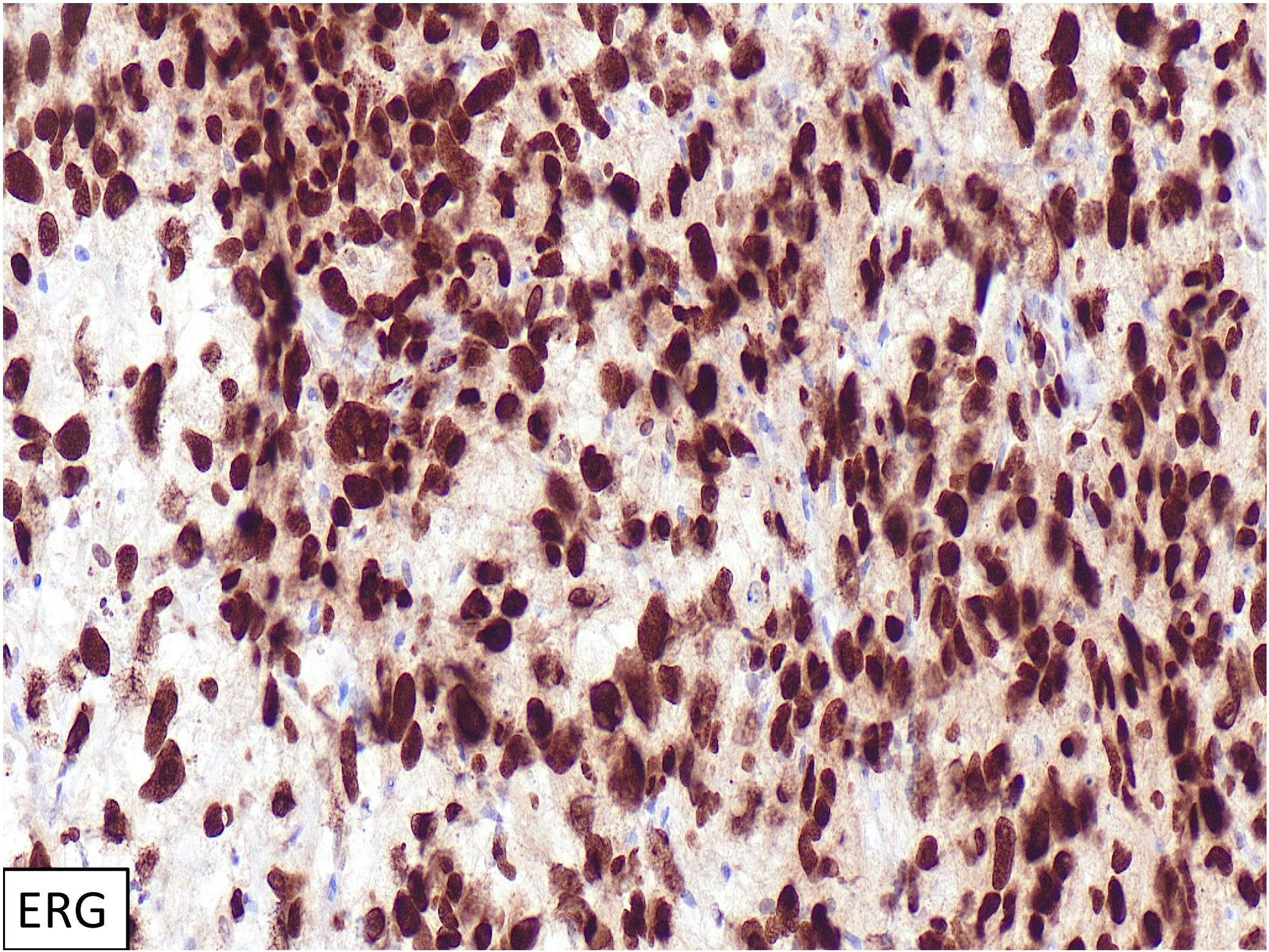
72-year-old man 5-years s/p liver transplant for alcoholic liver disease and large liver mass



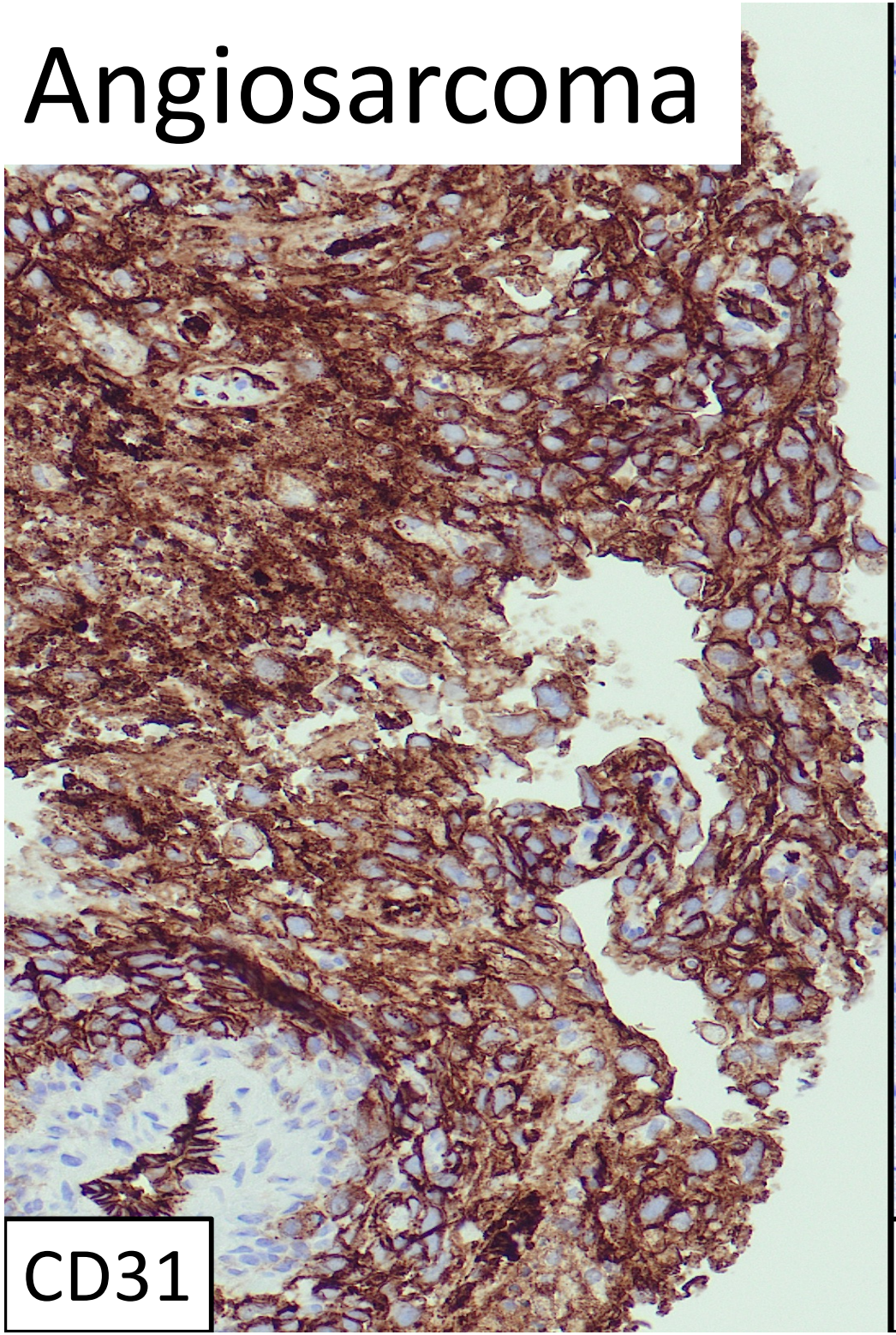
Differential Diagnosis/IHC Panel

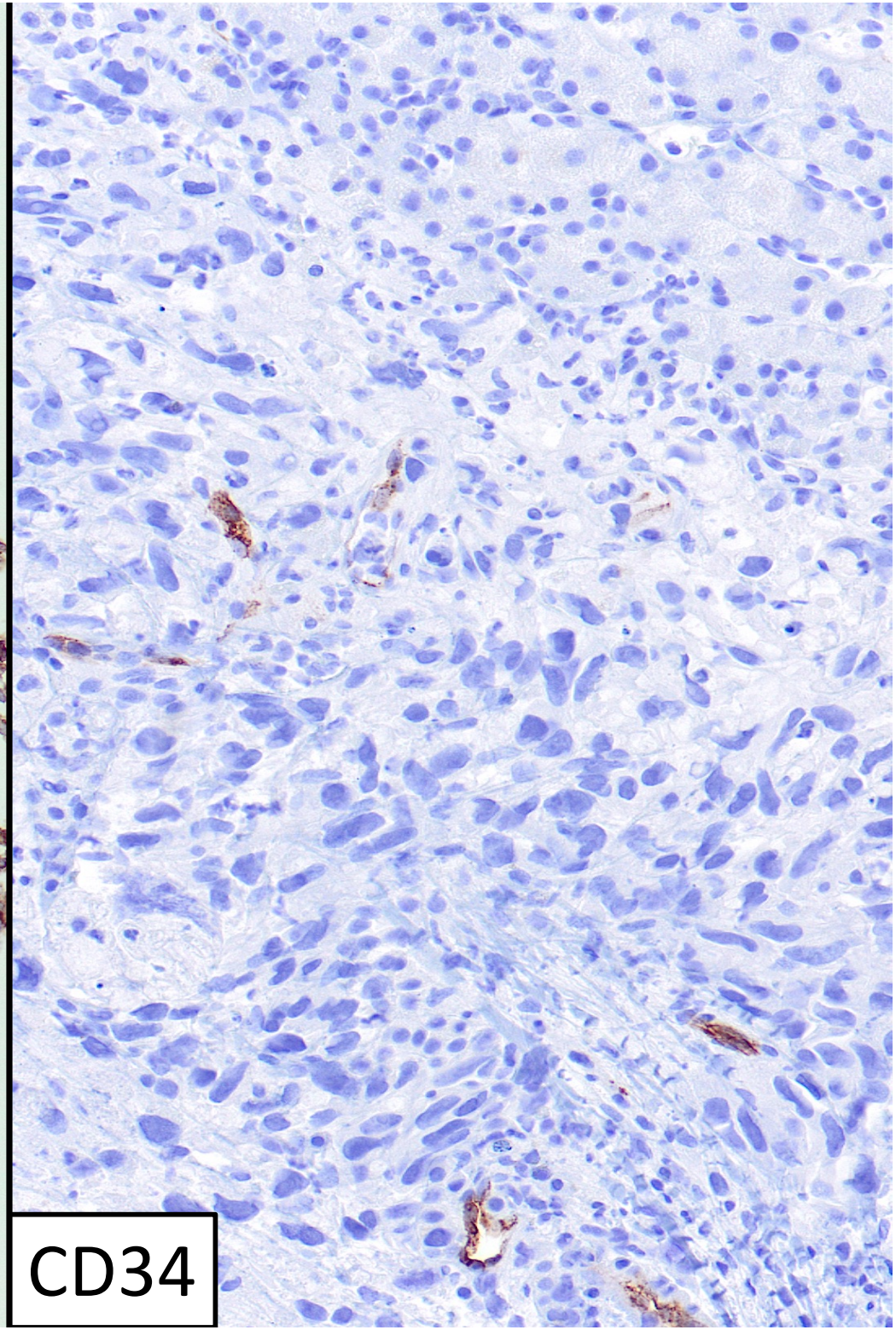
- Sarcomatoid carcinoma
  - AE1/AE3
  - 34βE12
  - EMA
  - p40
  - HepPar1
  - GPC3
- Spindle cell melanoma
  - SOX10

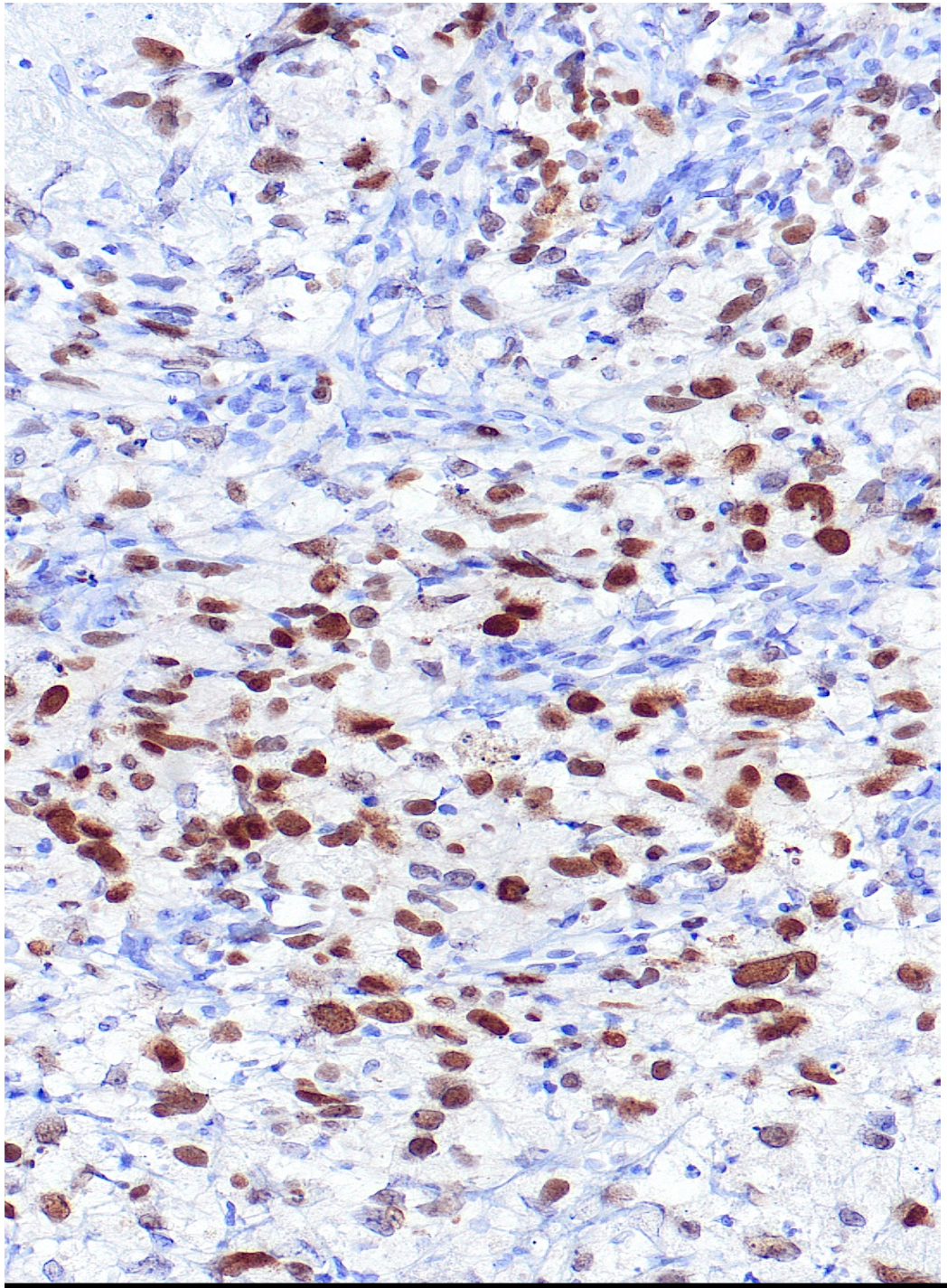
- Spindle cell sarcoma
  - p53
  - EBV-driven LMS
    - EBER
    - SMSA
    - Desmin
    - Caldesmon
  - Angiosarcoma
    - ERG
  - Intimal sarcoma
    - MDM2
  - Embryonal sarcoma
  - GIST
    - KIT
    - DOG1


ERG

Angiosarcoma







Histopathology. 2021 May;78(6):805-813. doi: 10.1111/his.14292. Epub 2021 Feb 14.

p53 immunohistochemical analysis of fusion-positive uterine sarcomas

Nissreen Mohammad [1], Colin J R Stewart [2], Sarah Chiang [3], Gulisa Turashvili [4], Brendan C Dickson [4], Tony L Ng [1], Martin Köbel [5], W Glenn McCluggage [6], Sabrina Croce [7], Cheng-Han Lee [8]

Affiliations + expand

PMID: 33118176 DOI: 10.1111/his.14292

Abstract

Aims: Uterine sarcomas can be grouped into tumours with pathognomonic genetic fusions such as low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), and inflammatory myofibroblastic tumour (IMT), and tumours lacking genetic fusions such as leiomyosarcoma (LMS) and undifferentiated uterine sarcoma (UUS). Members of the latter group frequently harbour TP53 mutations. The aim of this study was to evaluate TP53 mutations by the use of immunohistochemistry in fusion-positive uterine sarcomas.

Methods and results: We performed p53 immunohistochemical staining on 124 uterine sarcomas harbouring genetic fusions and 38 fusion-negative LMSs and UUSs. These included 41 HGESSs with YWHAE, BCOR and BCORL1 fusions/rearrangements, 13 IMTs with ALK fusion, 12 sarcomas with NTRK1/3 fusion, three sarcomas with PDGFB fusion, and 55 LGESSs with JAZF1, SUZ12 and PHF1 fusions/rearrangements. All HGESSs, LGESSs, IMTs and sarcomas with PDGFB fusion showed wild-type p53 expression. Among NTRK1/3-positive sarcomas, a TPR-NTRK1-positive sarcoma with nuclear pleomorphism showed mutation-type p53 expression. The remaining 11 NTRK1/3-positive sarcomas showed wild-type p53 expression, except for the subclonal p53 mutation-type staining in a minor pleomorphic focus of an NTRK3-positive sarcoma. Twenty-one of 27 (78%) LMSs and six of nine (67%) UUSs showed mutation-type p53 expression.

Conclusion: p53 immunohistochemistry may be considered in the initial work-up of a uterine sarcoma, as mutation-type staining would make a fusion-positive sarcoma very unlikely. Mutation-type p53 expression, however, can be seen in a small subset of NTRK1/3-positive sarcomas showing pleomorphic round/ovoid cell histology, which may represent a mechanism of progression in these tumours.

p53: missense-mutation pattern

Pattern-Based Approach to Lymphoma

Is it Lymphoma?	Lymphoma Composed of Small Cells with Diffuse Architecture (MALT v MCL v CLL/SLL)	Lymphoma Composed of Small Cells with Nodular Architecture (I think it's FL)
CD20	CD20	CD20
CD3	CD3	CD3
(CD43)	CD5	CD10
	Cyclin D1	Bcl-6
	LEF1	Bcl-2
	(CD43)	CD21
	(SOX11)	CD5
	(Ki-67 in MCL)	(Ki-67 for FH v FL)