BEYOND GIST: RECENT ADVANCES IN GASTROINTESTINAL MESENCHYMAL TUMORS

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107TH ANNUAL MEETING
GEARED TO LEARN

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PLEASE TURN OFF YOUR CELL PHONES

Tumors Not to be Confused with GIST

Relatively common	Rare
Leiomyoma	Leiomyosarcoma
	Inflammatory fibroid polyp
Desmoid fibromatosis	Inflammatory myofibroblastic tumor
	PEComa
Schwannoma	Glomus tumor
	Gastrointestinal neuroectodermal tumor
	Plexiform fibromyxoma

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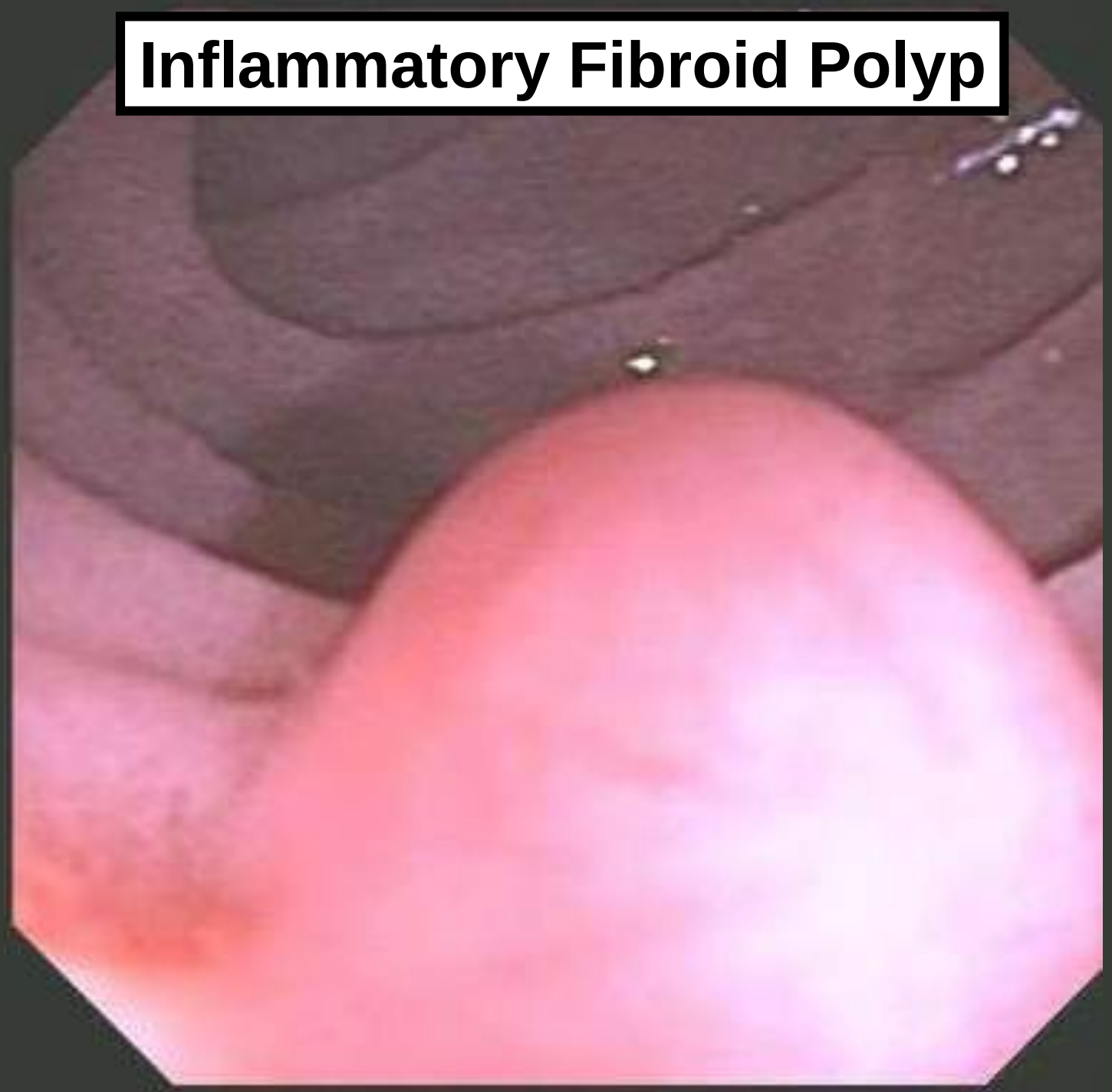
	Plexiform fibromyxoma

Inflammatory Fibroid Polyp

- Most common in antrum and ileum
- Wide age range
- Intussusception (small bowel)
- Polyp > mural mass
- Often ulcerated
- Most often submucosal
- Ill-defined margins
- Benign – do not recur

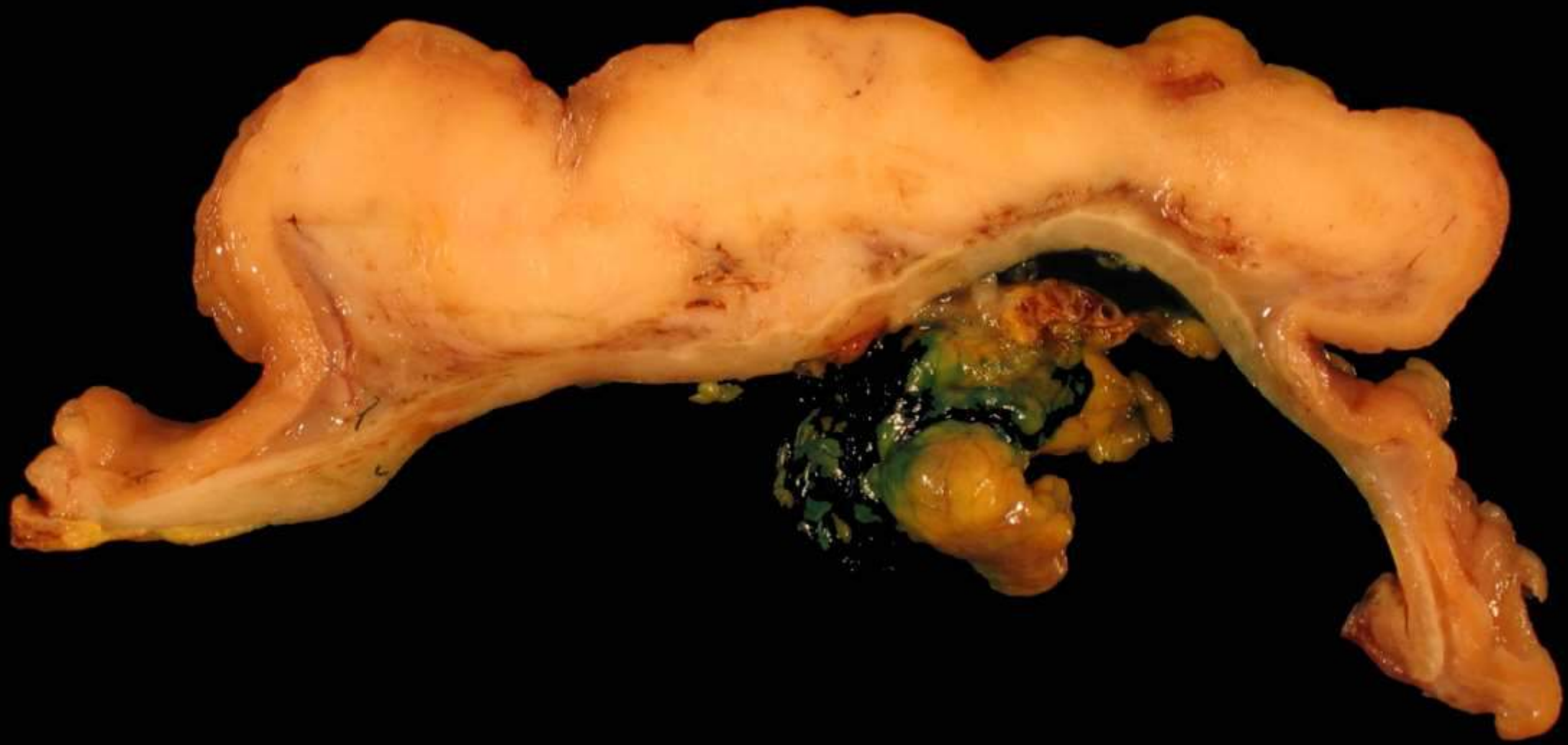
Stomach

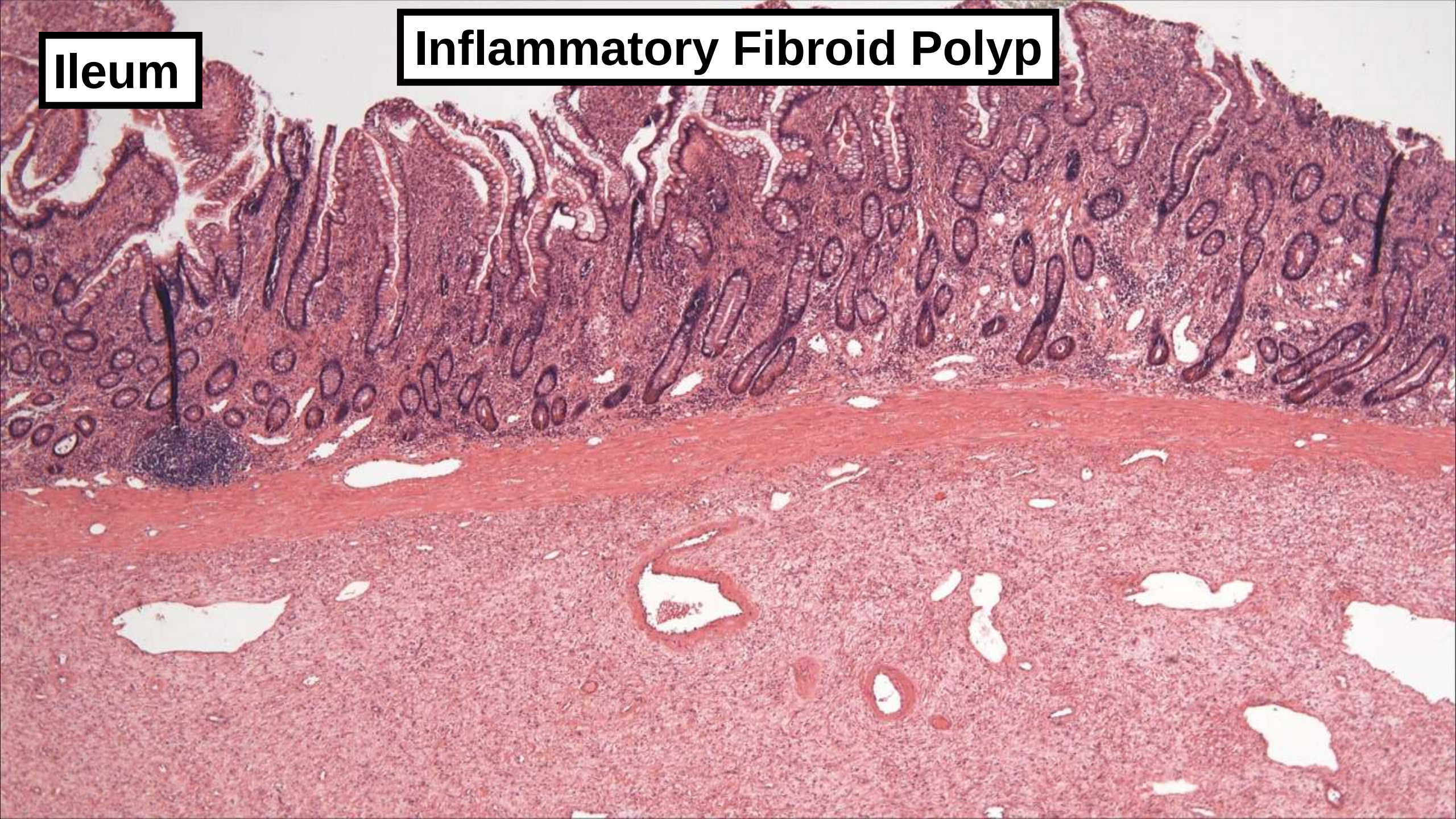
Inflammatory Fibroid Polyp



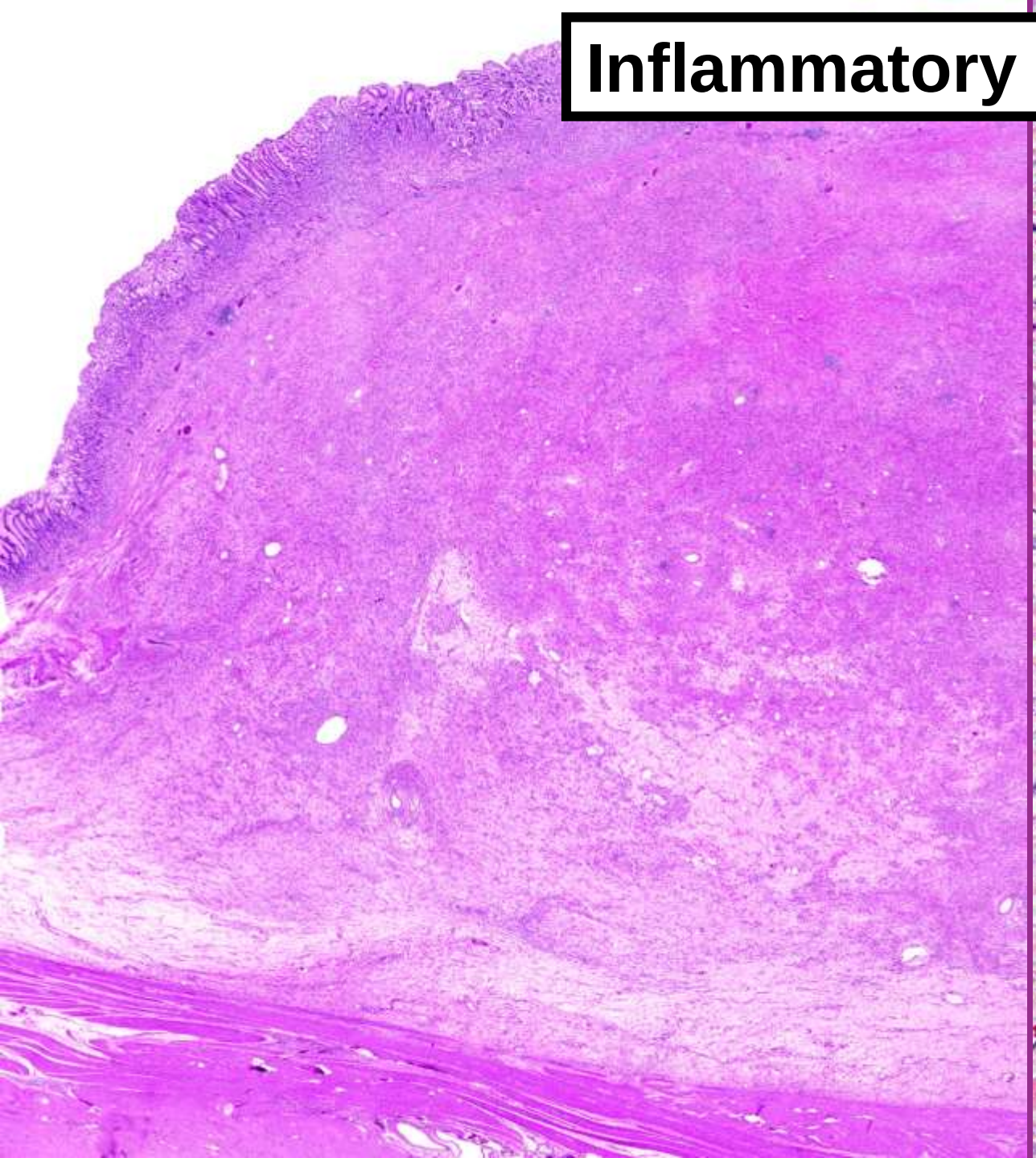
Stomach

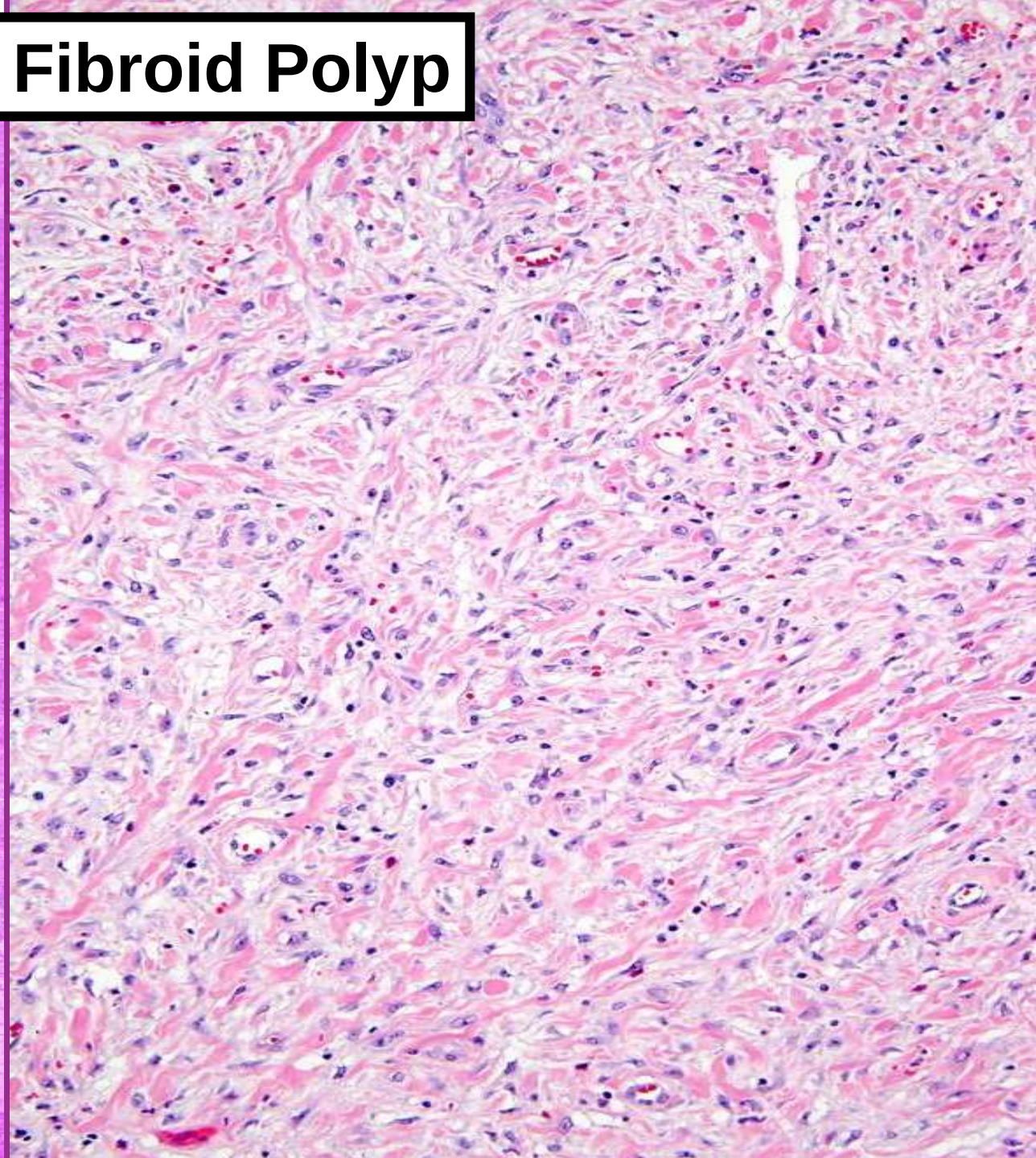
Inflammatory Fibroid Polyp



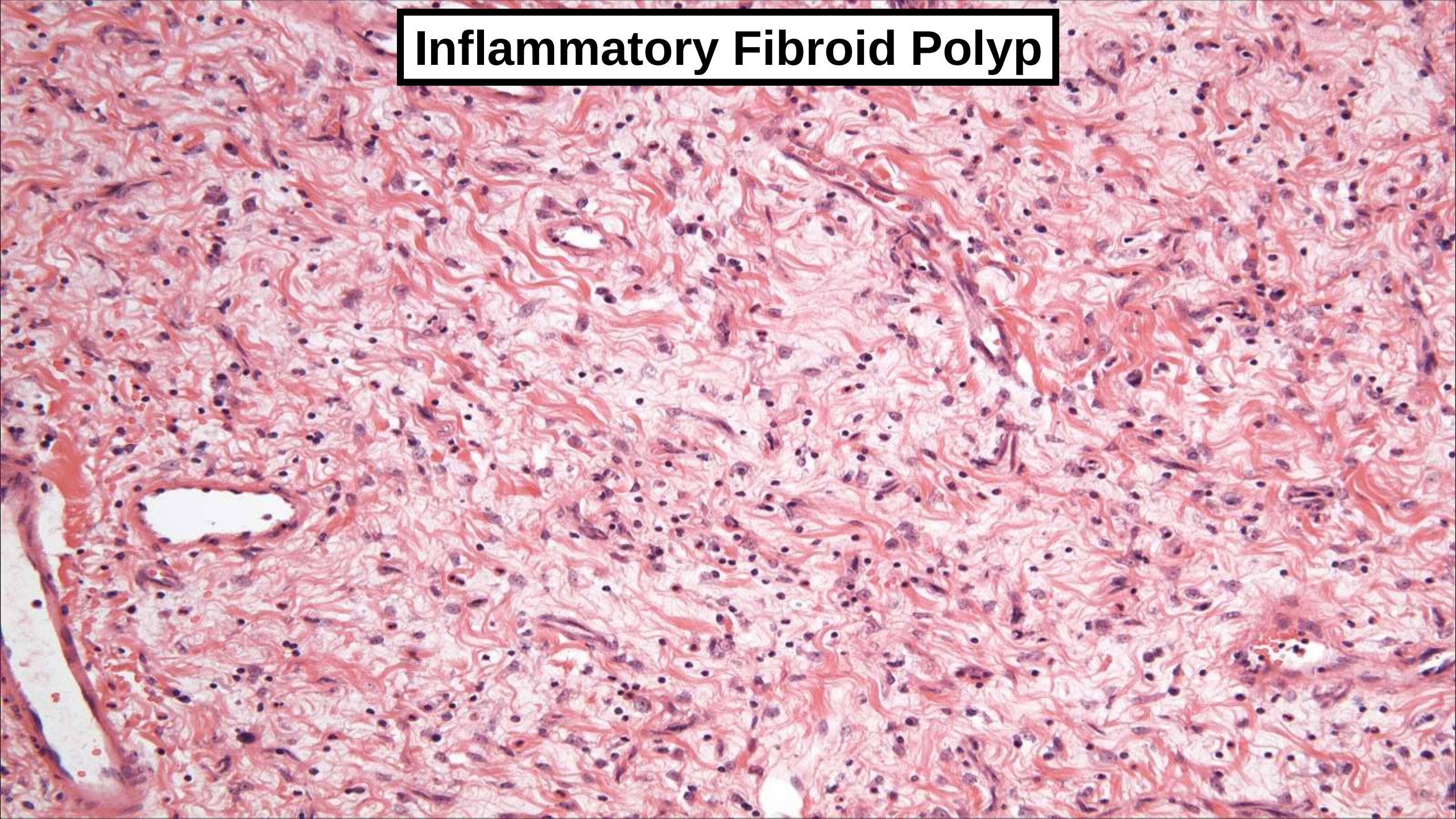

Ileum
Inflammatory Fibroid Polyp

Inflammatory Fibroid Polyp





Inflammatory Fibroid Polyp



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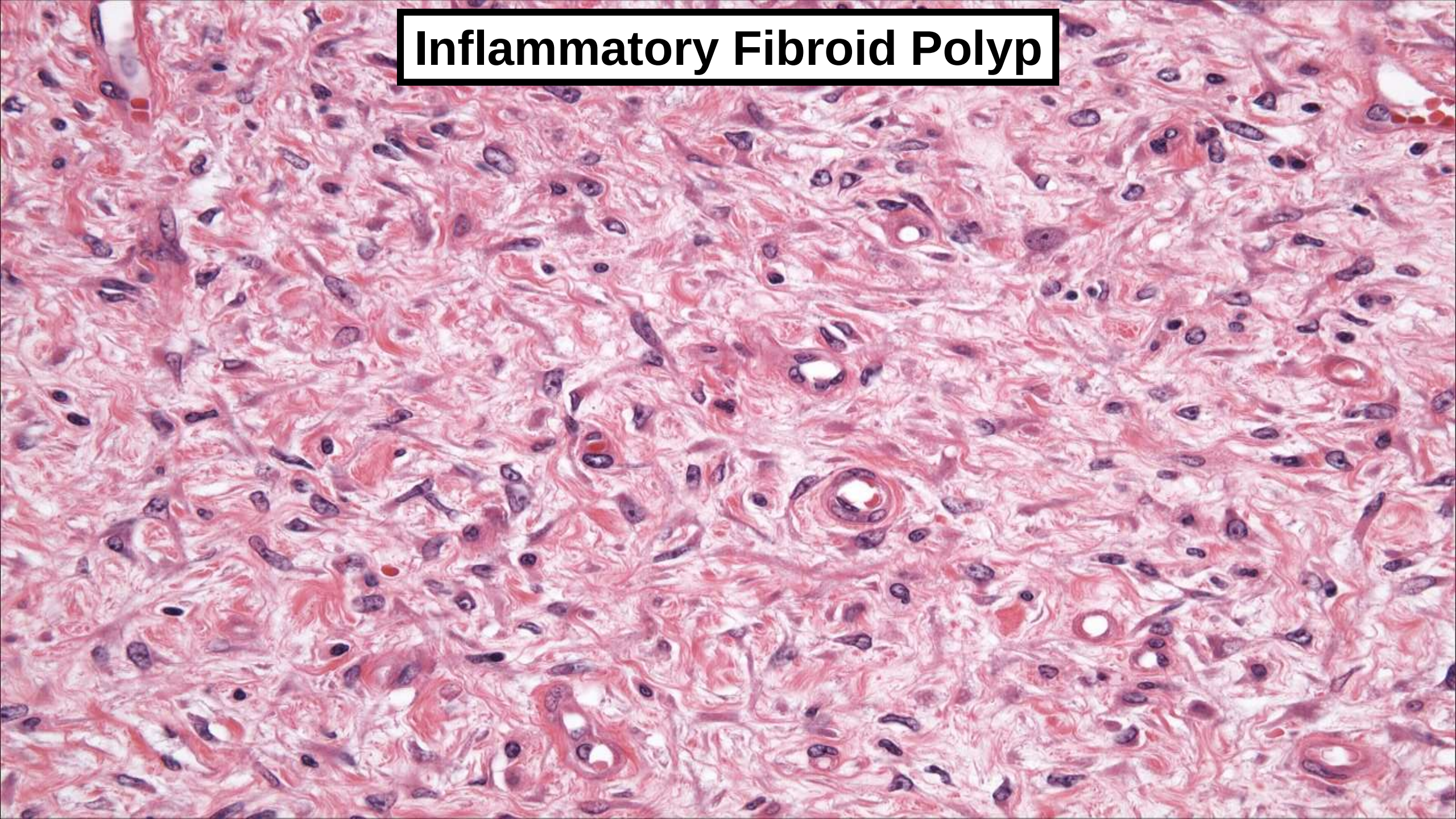
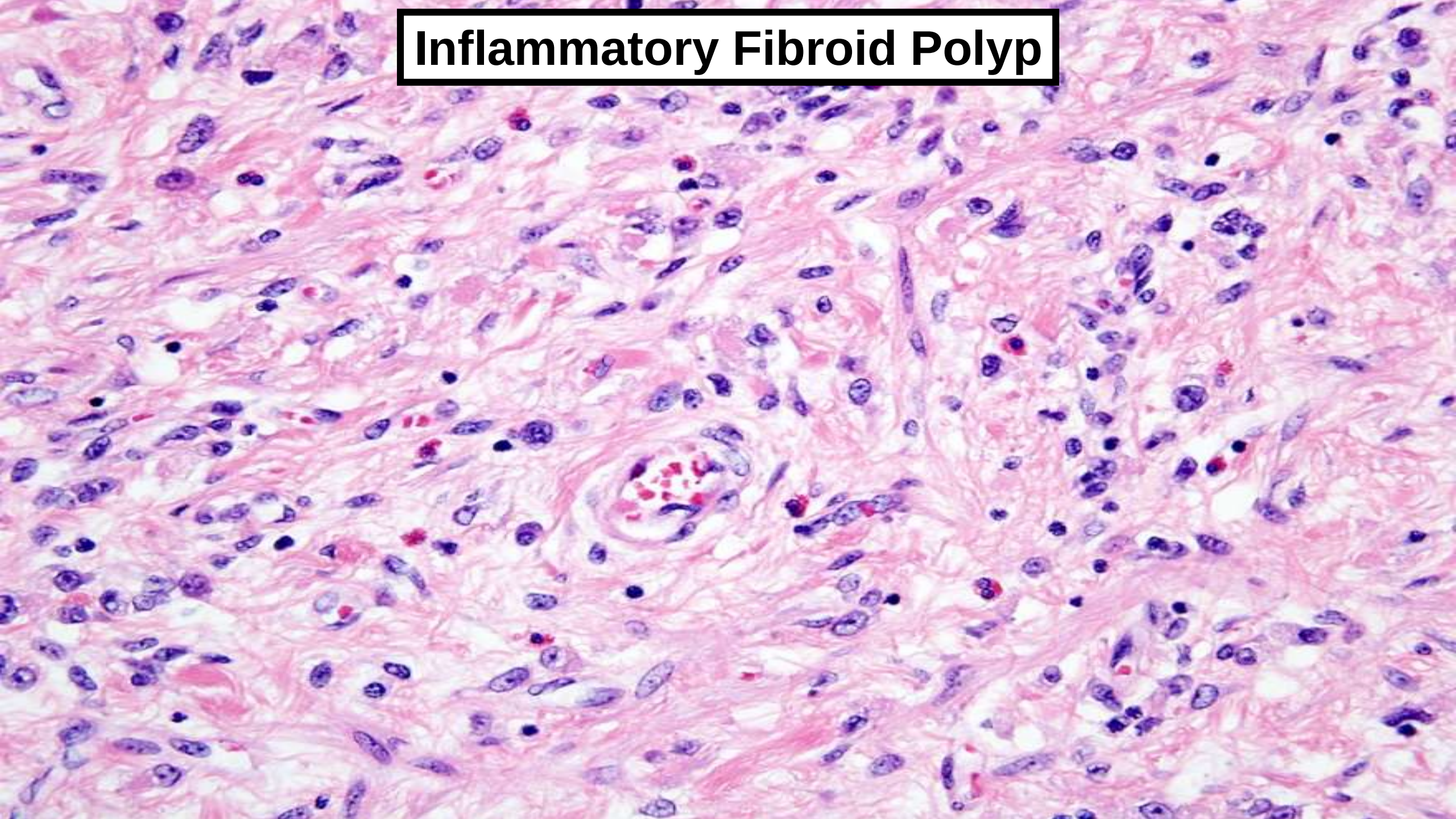
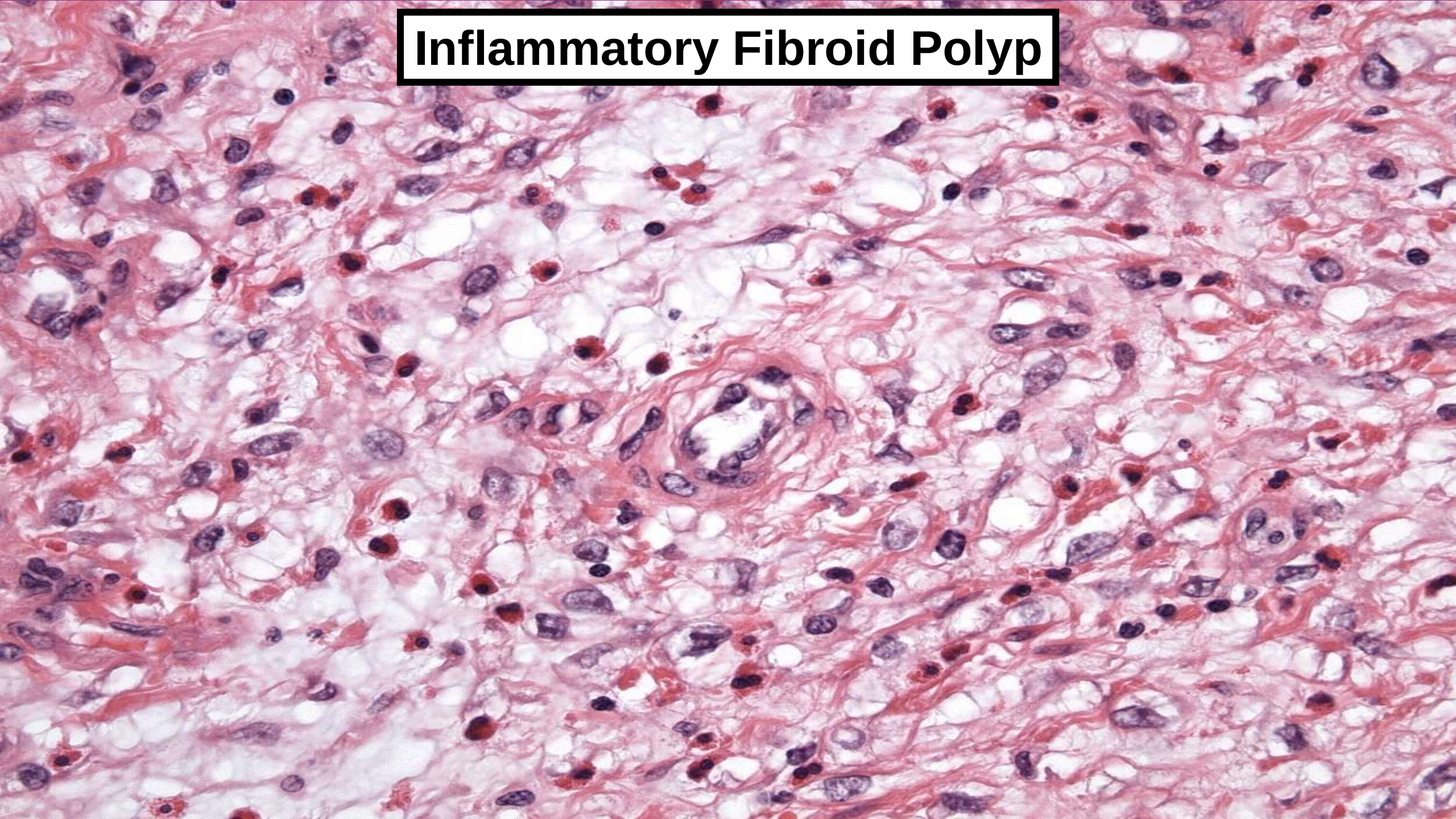
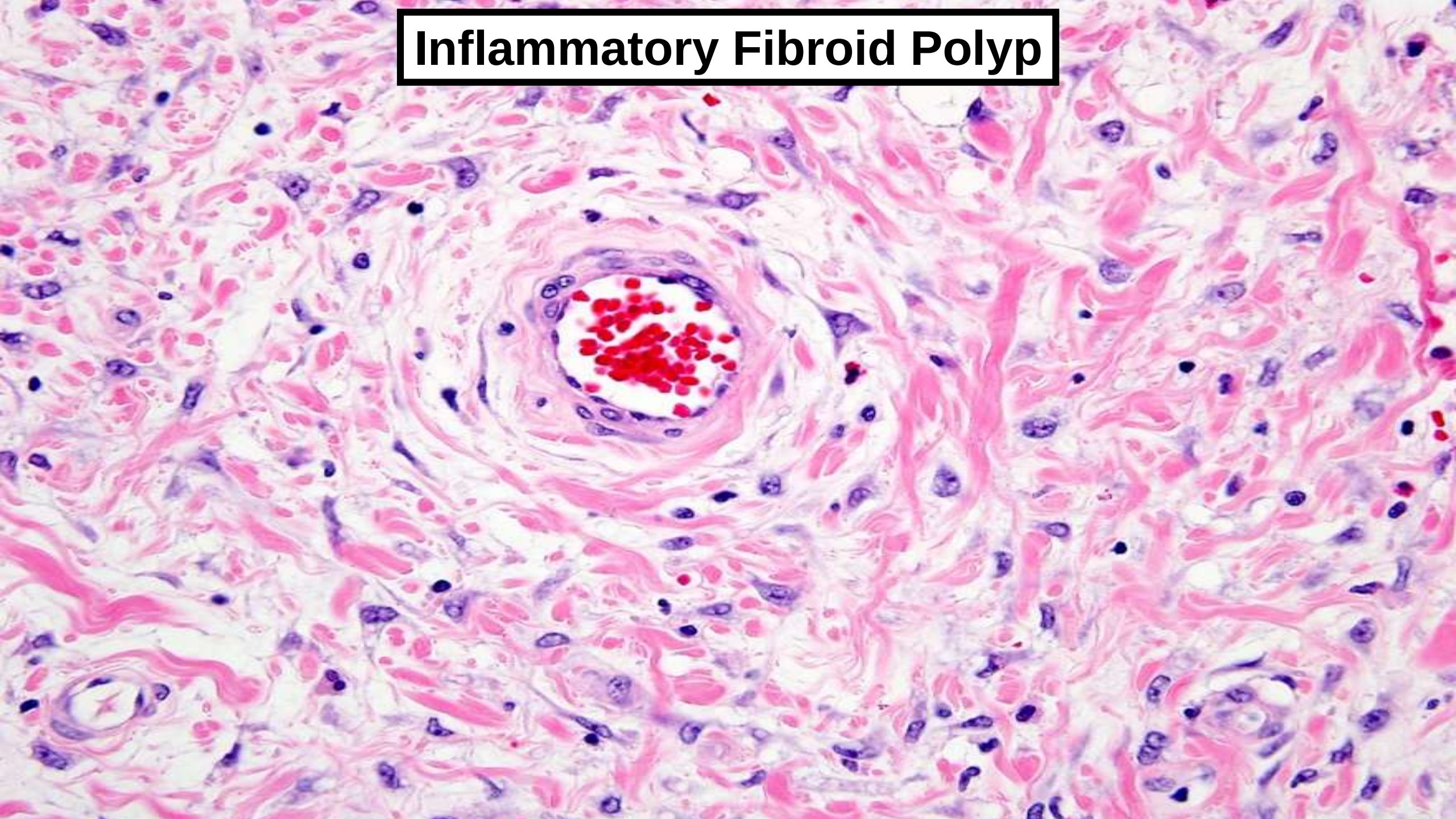


Inflammatory Fibroid Polyp



Inflammatory Fibroid Polyp




Inflammatory Fibroid Polyp

Inflammatory Fibroid Polyp: Molecular Findings

- Long debate: neoplastic or reactive
- Activating mutations in *PDGFRA*

Journal of Pathology
J Pathol 2008; **216**: 176–182
Published online 13 June 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/path.2393

Original Paper

Inflammatory fibroid polyps harbour mutations in the *platelet-derived growth factor receptor alpha (PDGFRA)* gene

H-U Schildhaus, T Cavlar, E Binot, R Büttner, E Wardelmann* and S Merkelbach-Bruse
Institute of Pathology, University of Bonn Medical School, Bonn, Germany

Modern Pathology (2009) 22, 1049–1056
© 2009 USCAP, Inc All rights reserved 0893-3952/09 $32.00
www.modernpathology.org

Gain-of-function PDGFRA mutations, earlier reported in gastrointestinal stromal tumors, are common in small intestinal inflammatory fibroid polyps. A study of 60 cases

Jerzy Lasota[1], Zeng-Feng Wang[2], Leslie H Sobin[3] and Markku Miettinen[1]

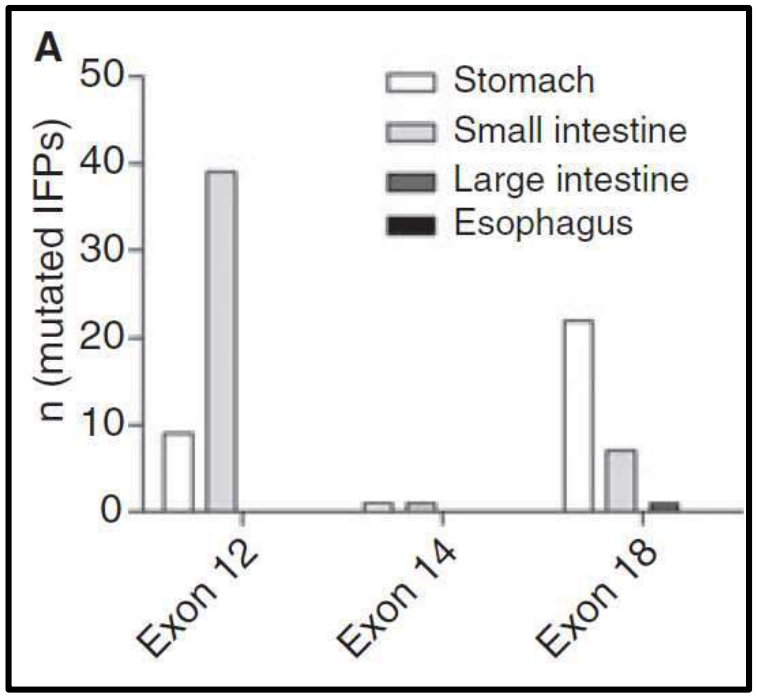
[1]*Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC, USA;*
[2]*Department of Scientific Laboratories, Armed Forces Institute of Pathology, Washington, DC, USA and*
[3]*Division of Gastrointestinal Pathology, Armed Forces Institute of Pathology, Washington, DC, USA*

Histopathology

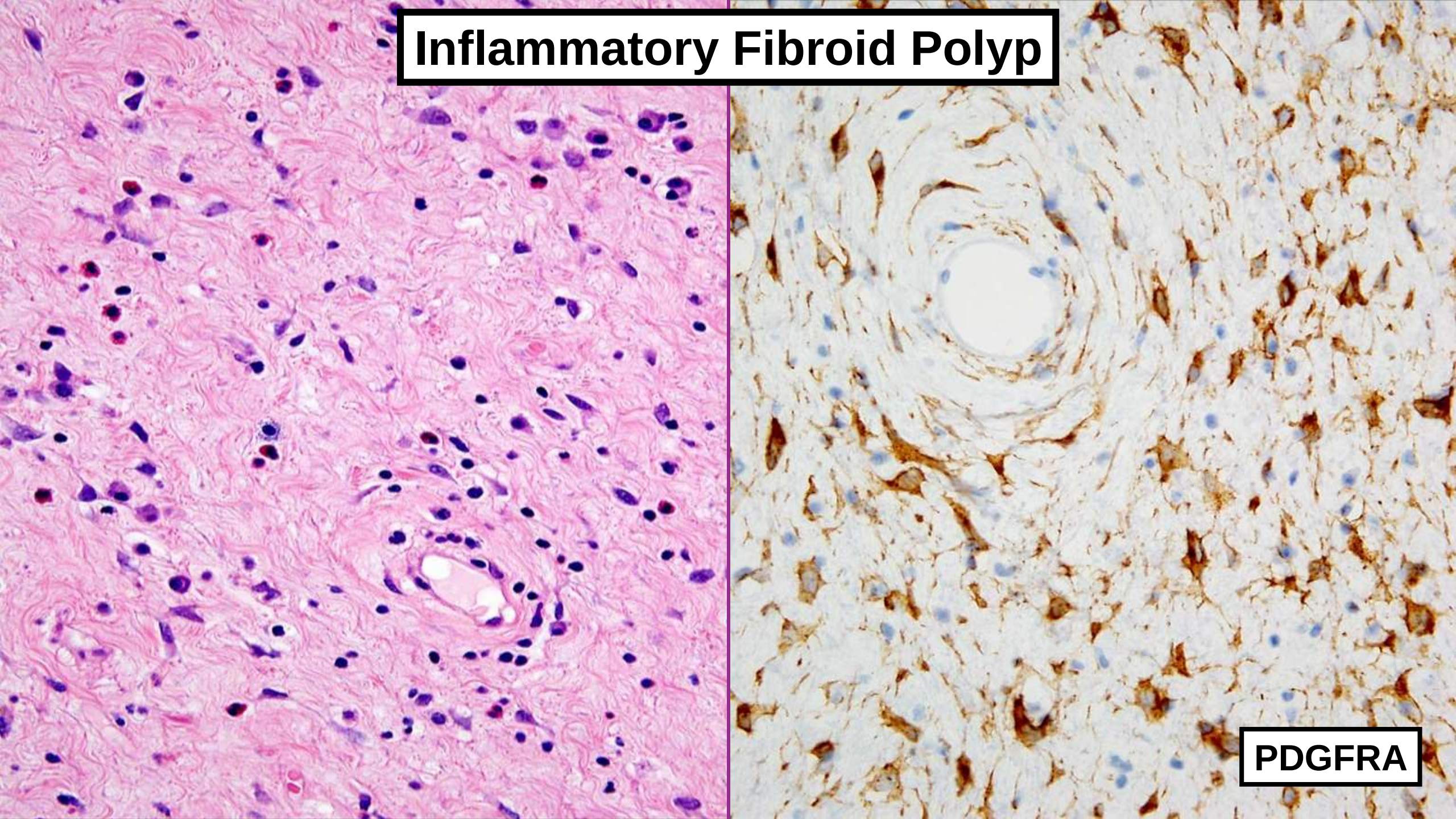
Histopathology 2012, **61**, 59–68. DOI: 10.1111/j.1365-2559.2012.04203.x

Activating *PDGFRA* mutations in inflammatory fibroid polyps occur in exons 12, 14 and 18 and are associated with tumour localization

Sebastian Huss,[1] Eva Wardelmann,[1] Diane Goltz,[2] Elke Binot,[1] Wolfgang Hartmann,[1] Sabine Merkelbach-Bruse,[1] Reinhard Büttner[1] & Hans-Ulrich Schildhaus[1]
[1]*Institute of Pathology, University of Cologne Medical Center, Cologne, Germany, and* [2]*Institute of Pathology, University of Bonn Medical Center, Bonn, Germany*



Inflammatory Fibroid Polyp



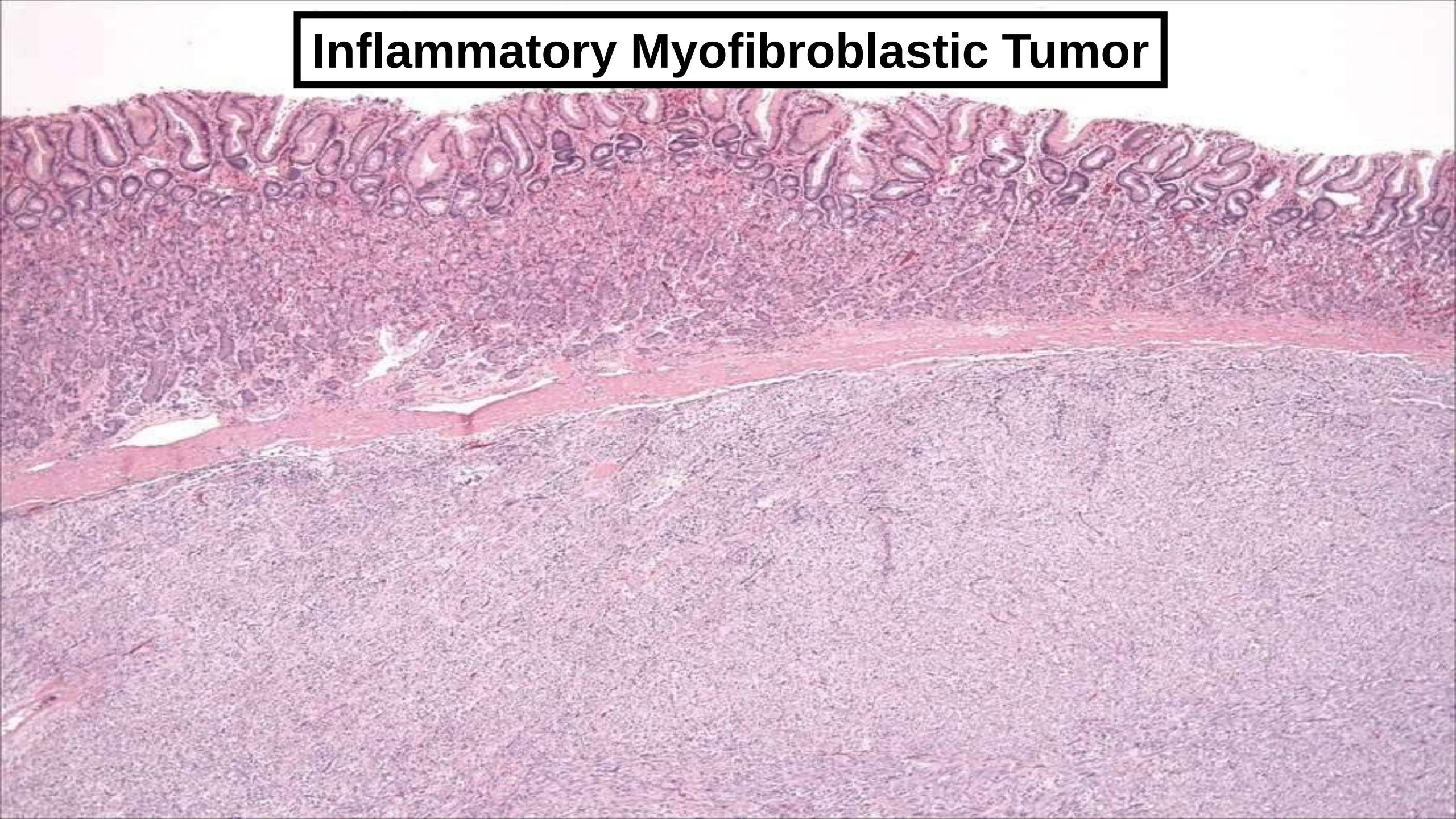
Inflammatory Myofibroblastic Tumor

- Most common in children and young adults
- Outside of lung, most common sites: abdomen (mesentery, GI tract, omentum), pelvis, retroperitoneum
- May be multifocal at presentation in abdominal cavity

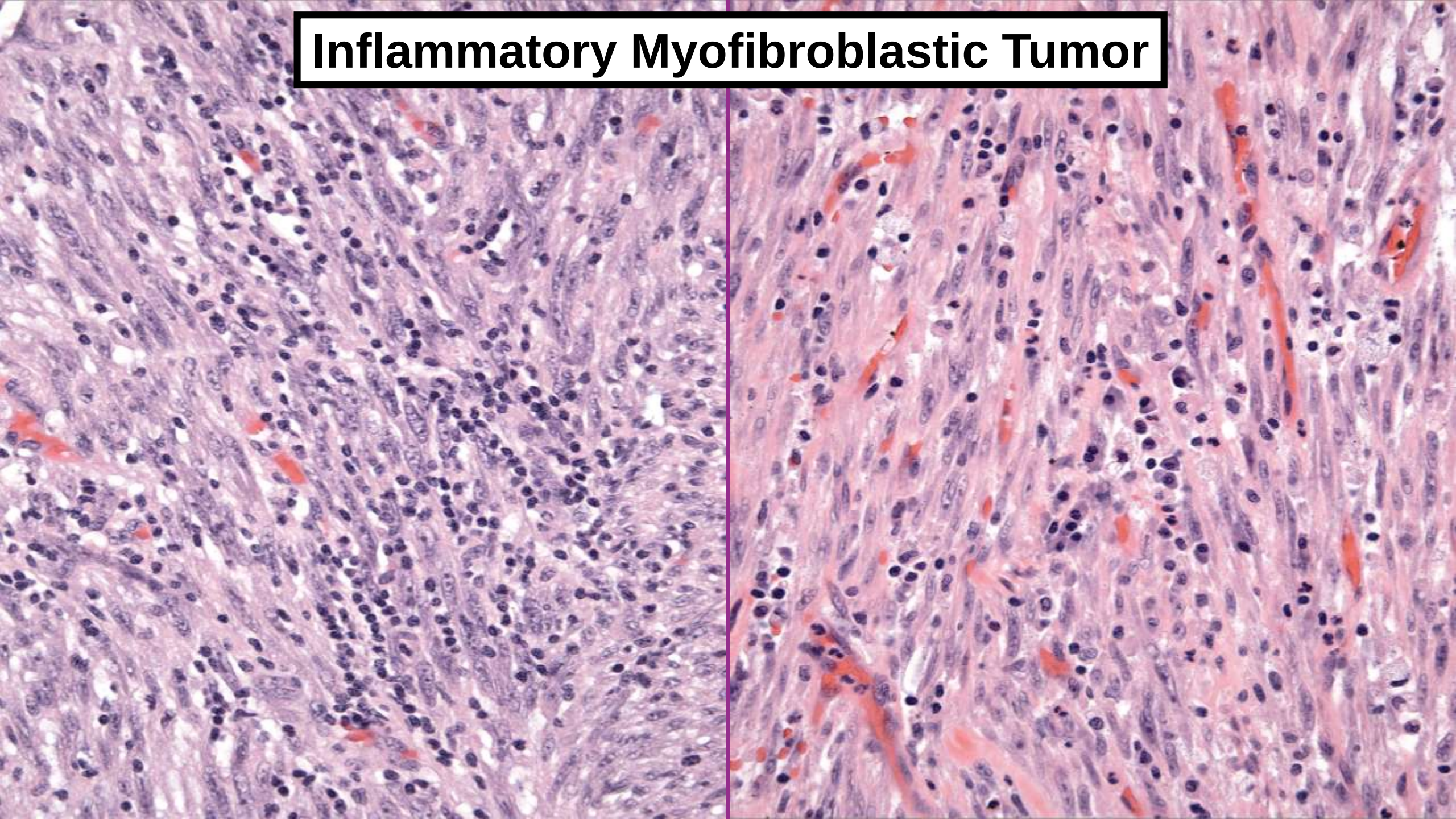
Inflammatory Myofibroblastic Tumor: Prognosis

- **WHO: Intermediate biologic potential, rarely metastasizing**
- **Local recurrence:**
  - **<2% lung**
  - **25% extrapulmonary (intra-abdominal++)**
- **Metastasis:**
  - **1-2% (lung, brain, liver, bone)**
- **In general, poor correlation between histology and behavior**

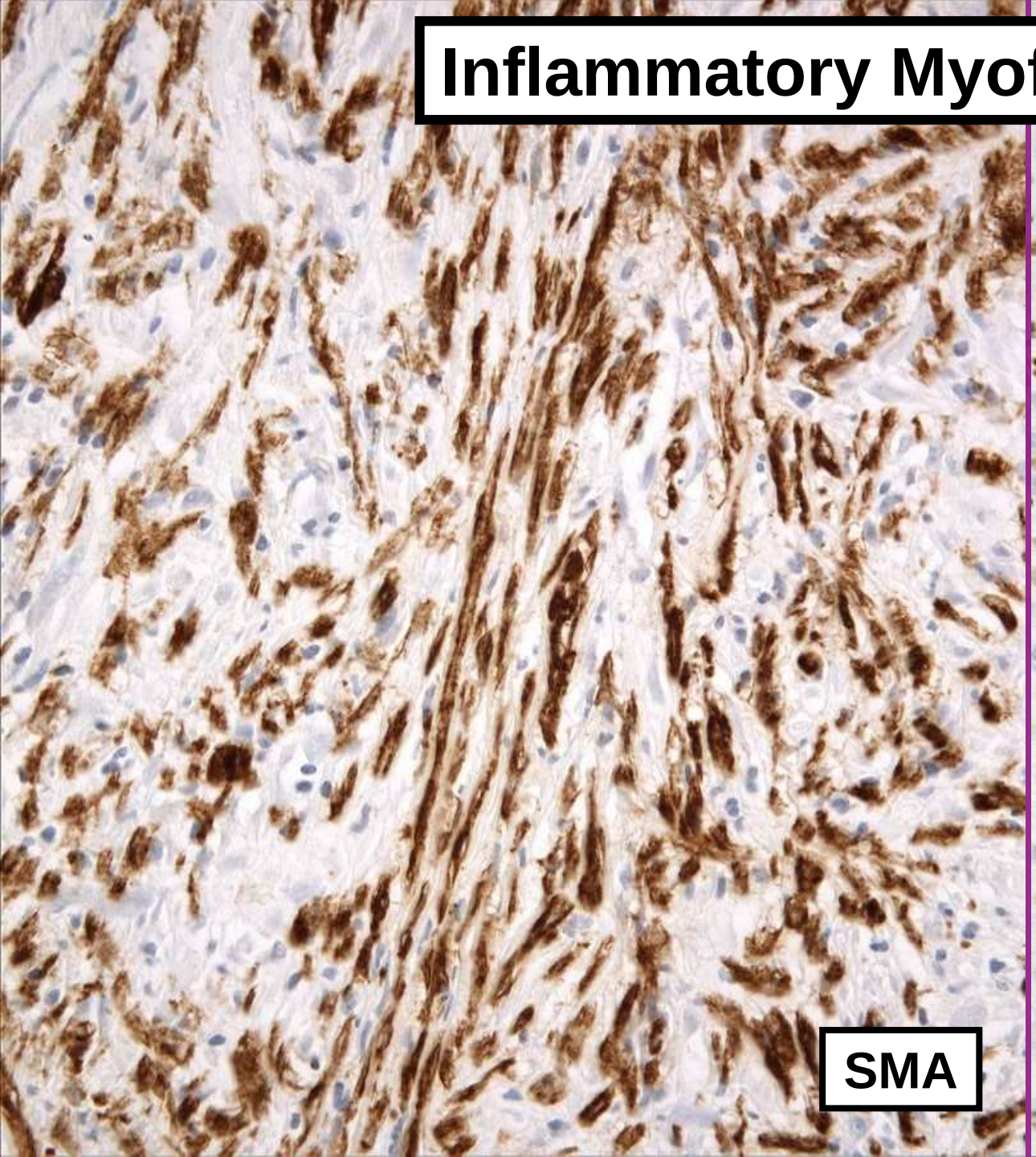
Inflammatory Myofibroblastic Tumor

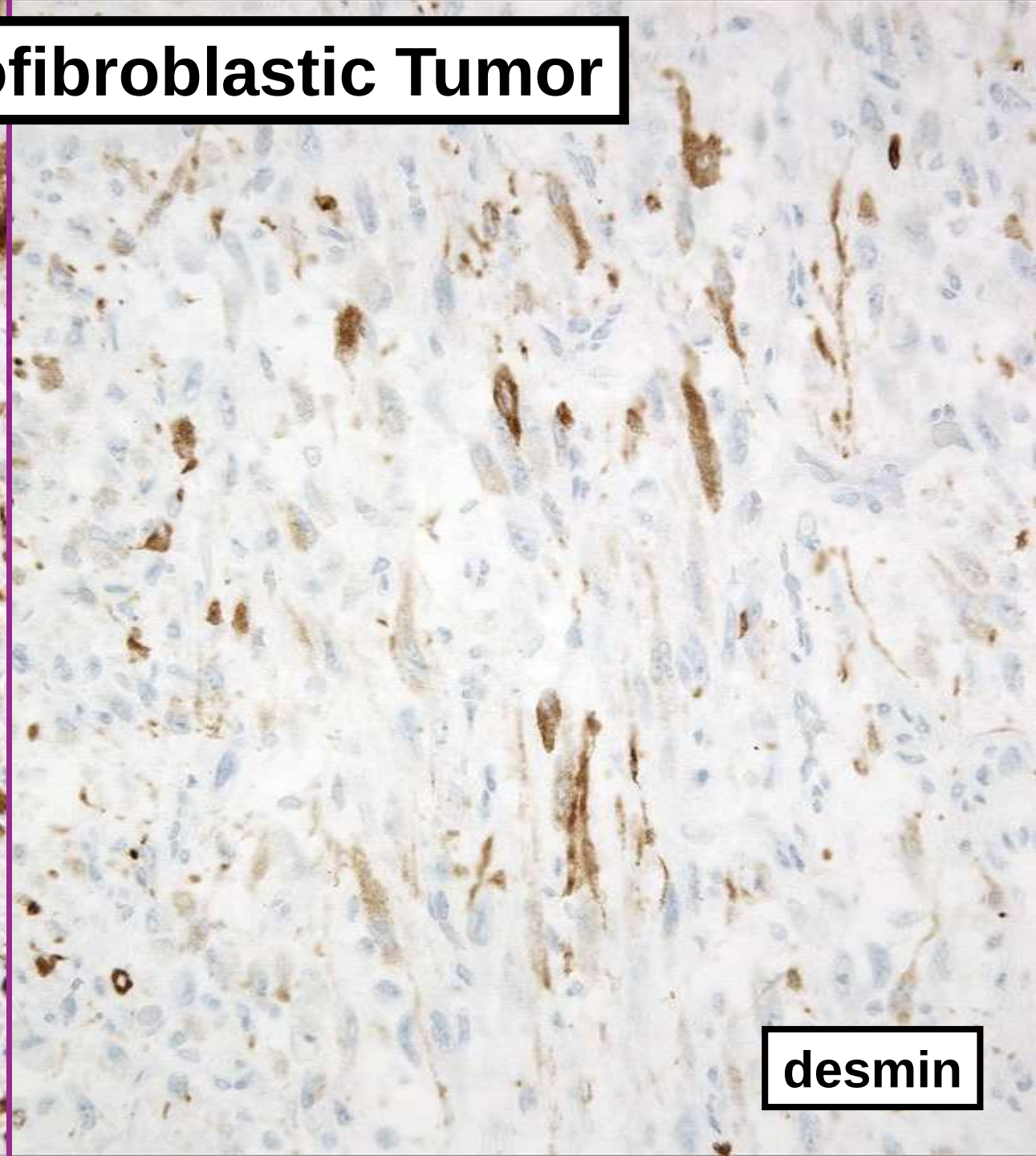


Inflammatory Myofibroblastic Tumor



Inflammatory Myofibroblastic Tumor



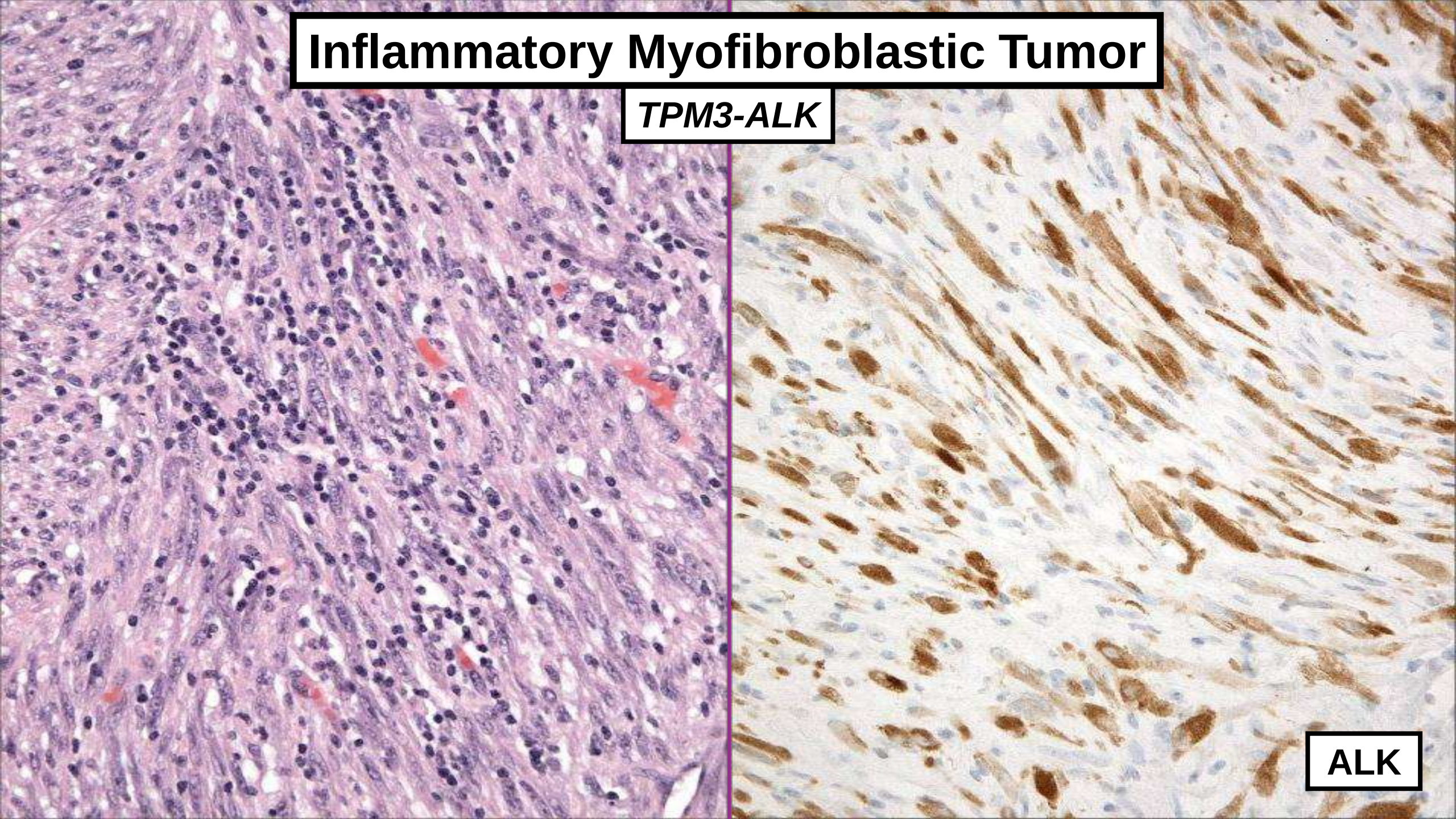


ALK in Inflammatory Myofibroblastic Tumor

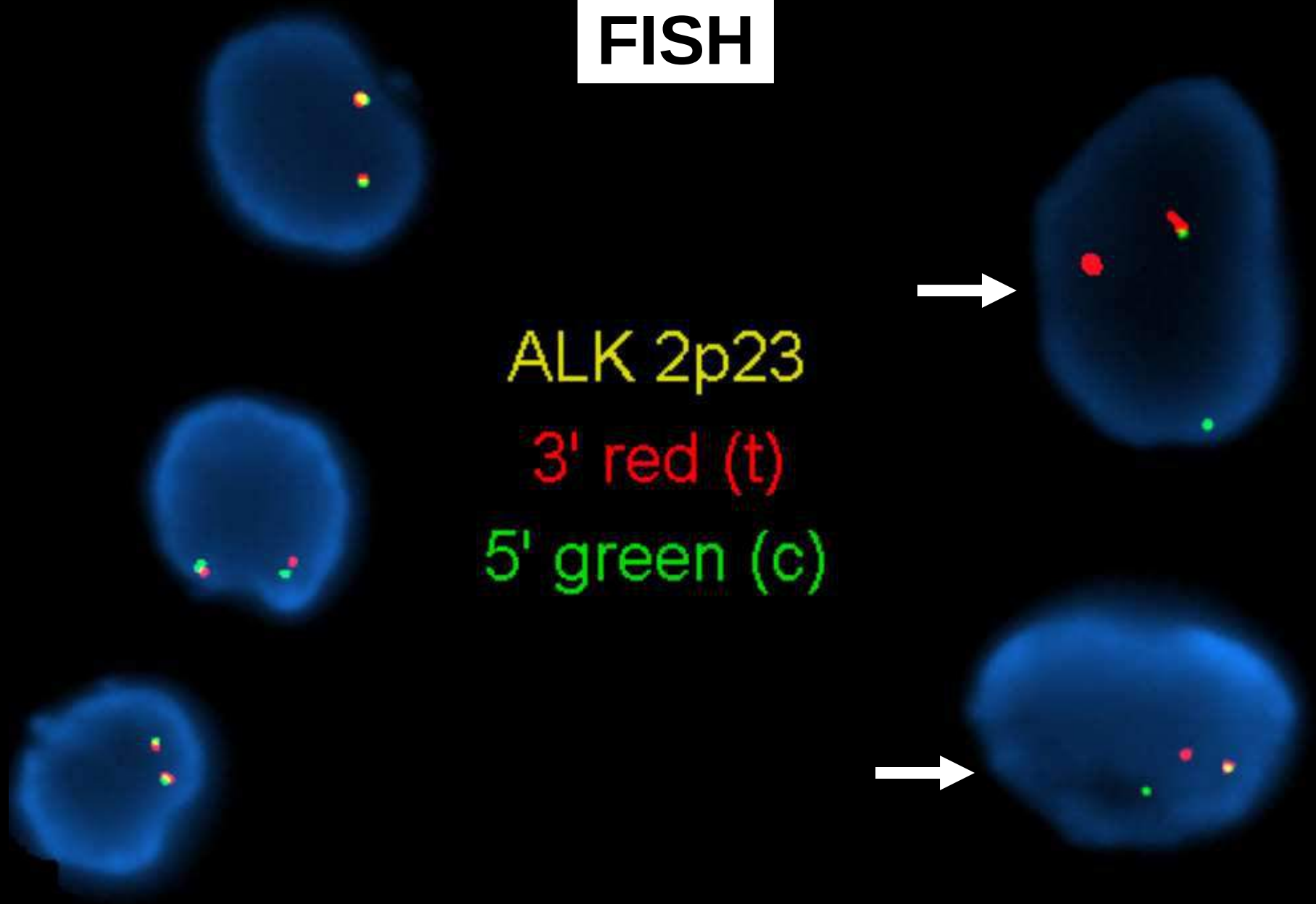
- ***ALK*** **gene rearrangement in 60% IMT**
  <10% in adults >50 yrs
- **Heterogeneous fusion partners**
- **Strong correlation between detection of ALK expression by IHC and *ALK* rearrangement in IMT**
- **ALK negative in other myofibroblastic and smooth muscle tumors, GIST**

Inflammatory Myofibroblastic Tumor

TPM3-ALK



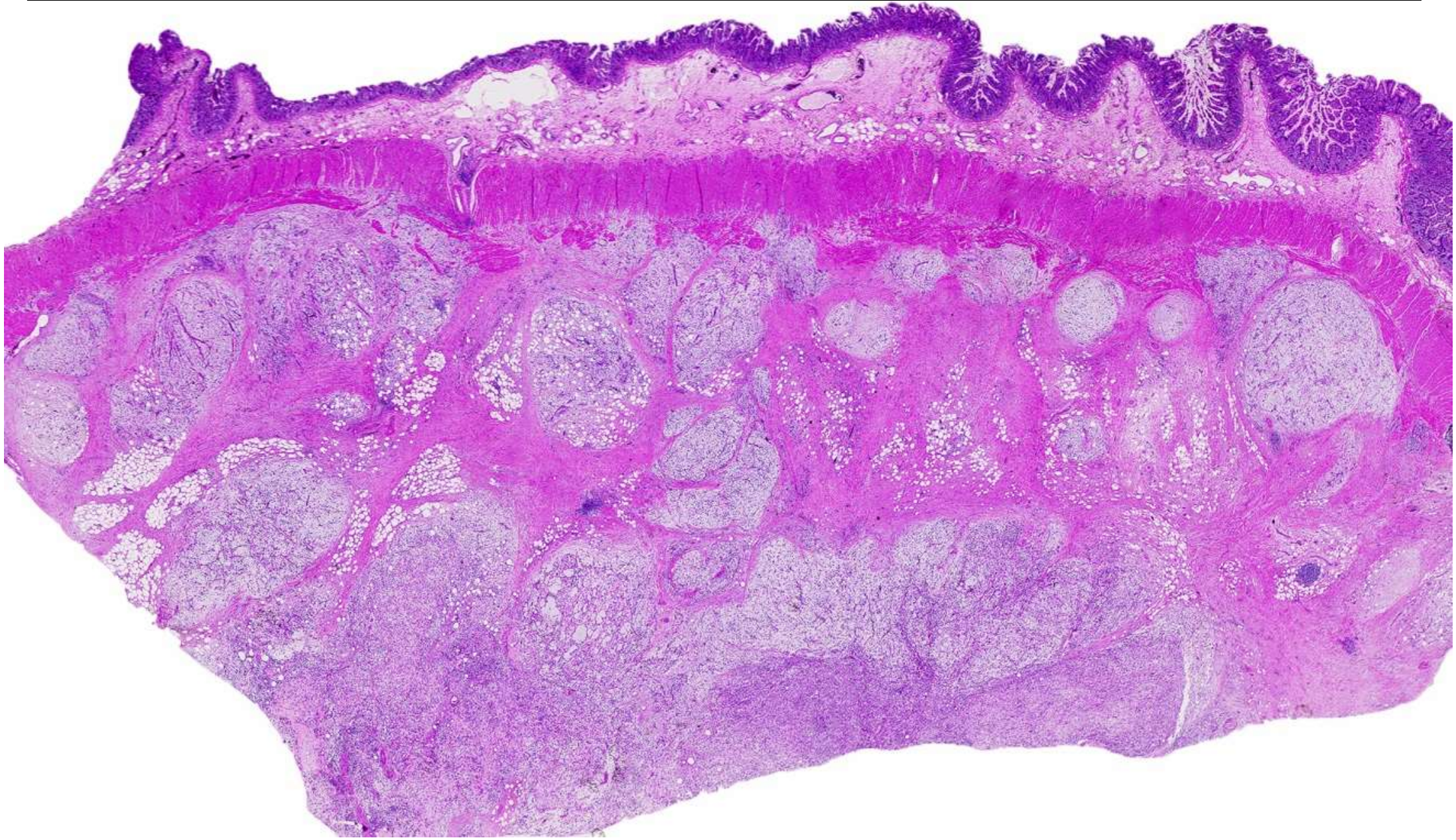
FISH



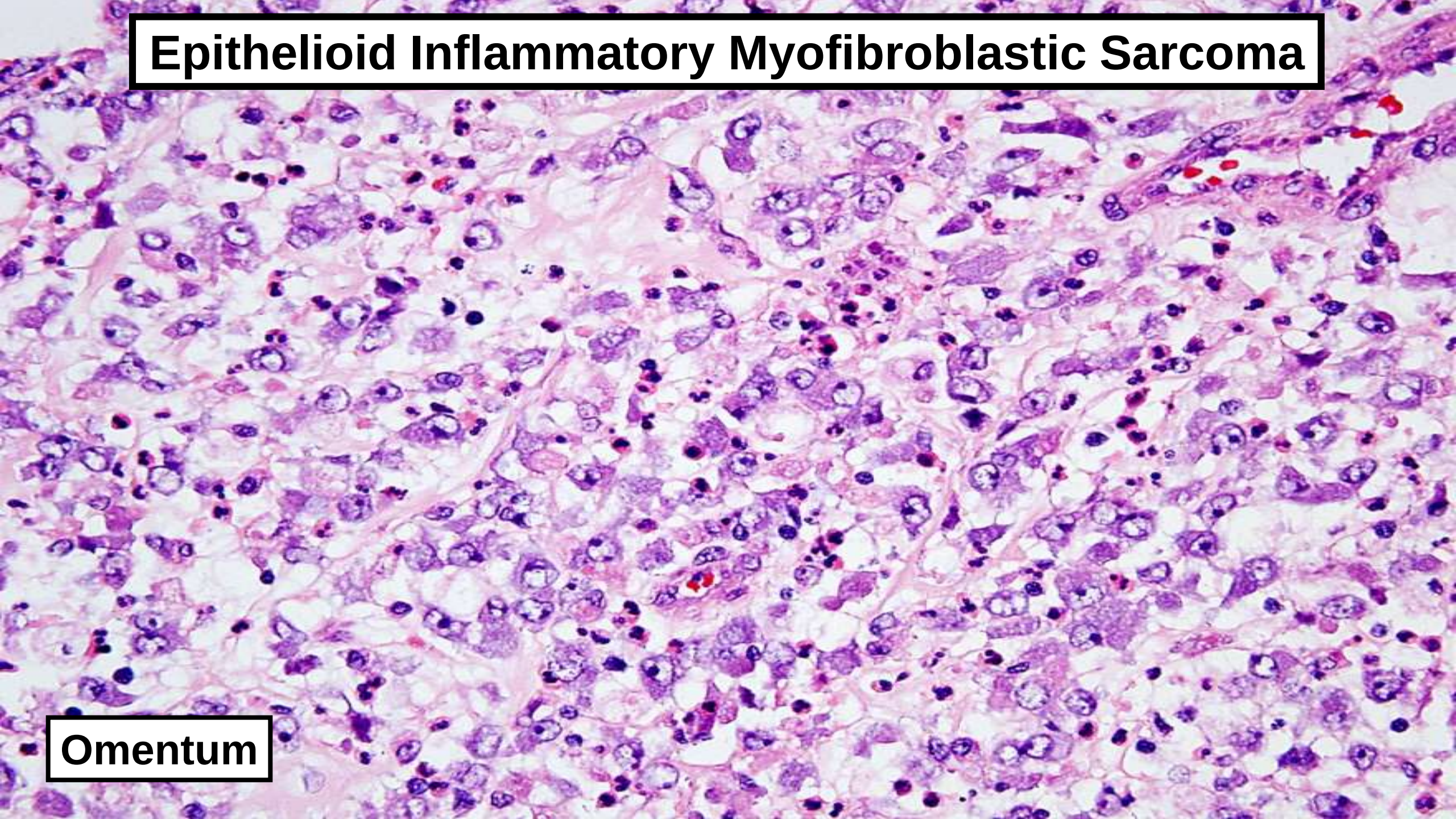
Epithelioid Inflammatory Myofibroblastic Sarcoma

- Distinctive aggressive variant of inflammatory myofibroblastic tumor (rapid recurrences)
- Predilection for young male adults
- Nearly all intra-abdominal (mesentery, omentum)
- Epithelioid morphology
- Often myxoid stroma; prominent neutrophils
- Nuclear membrane >> perinuclear pattern of ALK
- *RANBP2-ALK* >> *RRBP1-ALK* fusion

Epithelioid Inflammatory Myofibroblastic Sarcoma

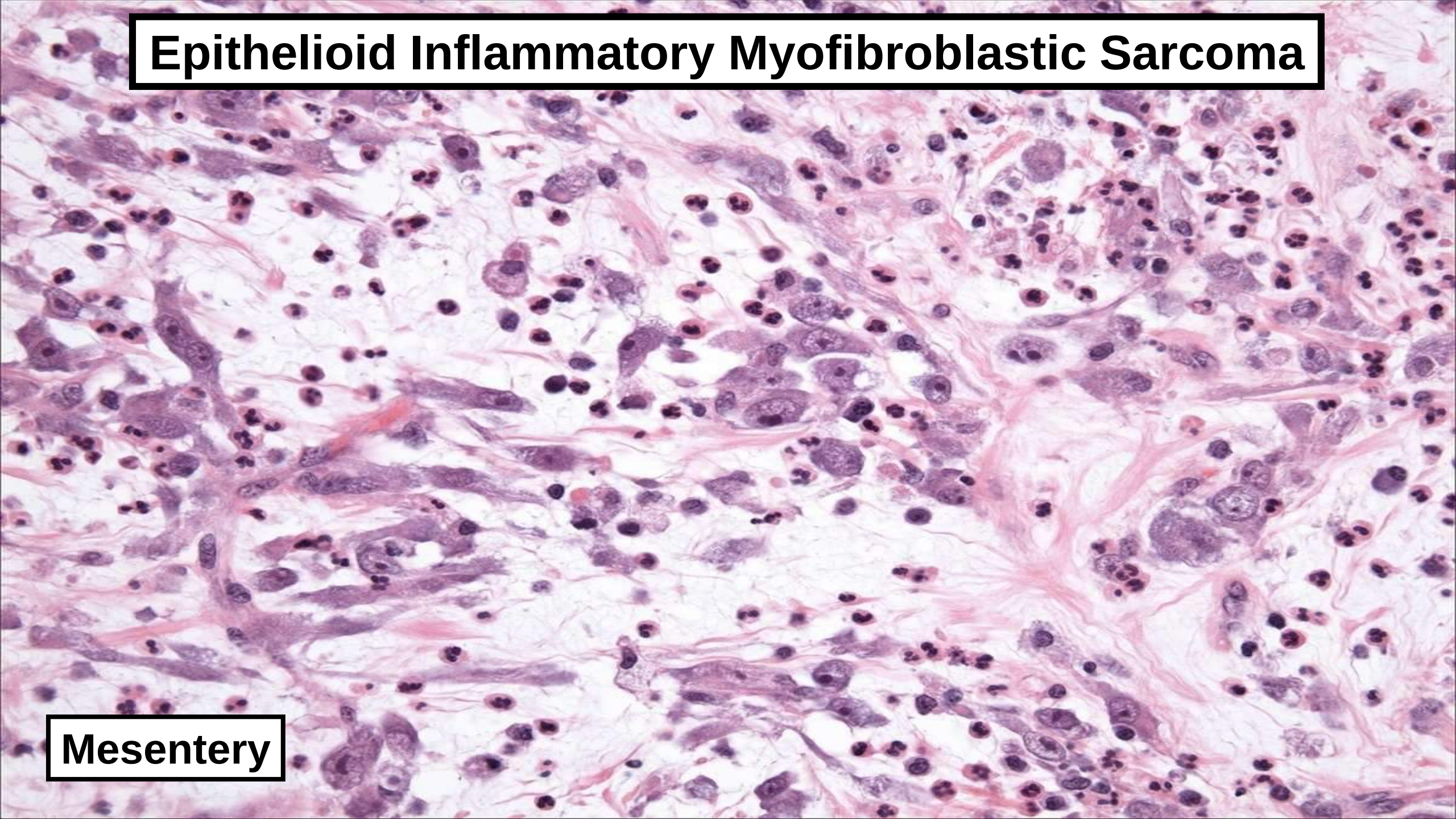


Epithelioid Inflammatory Myofibroblastic Sarcoma



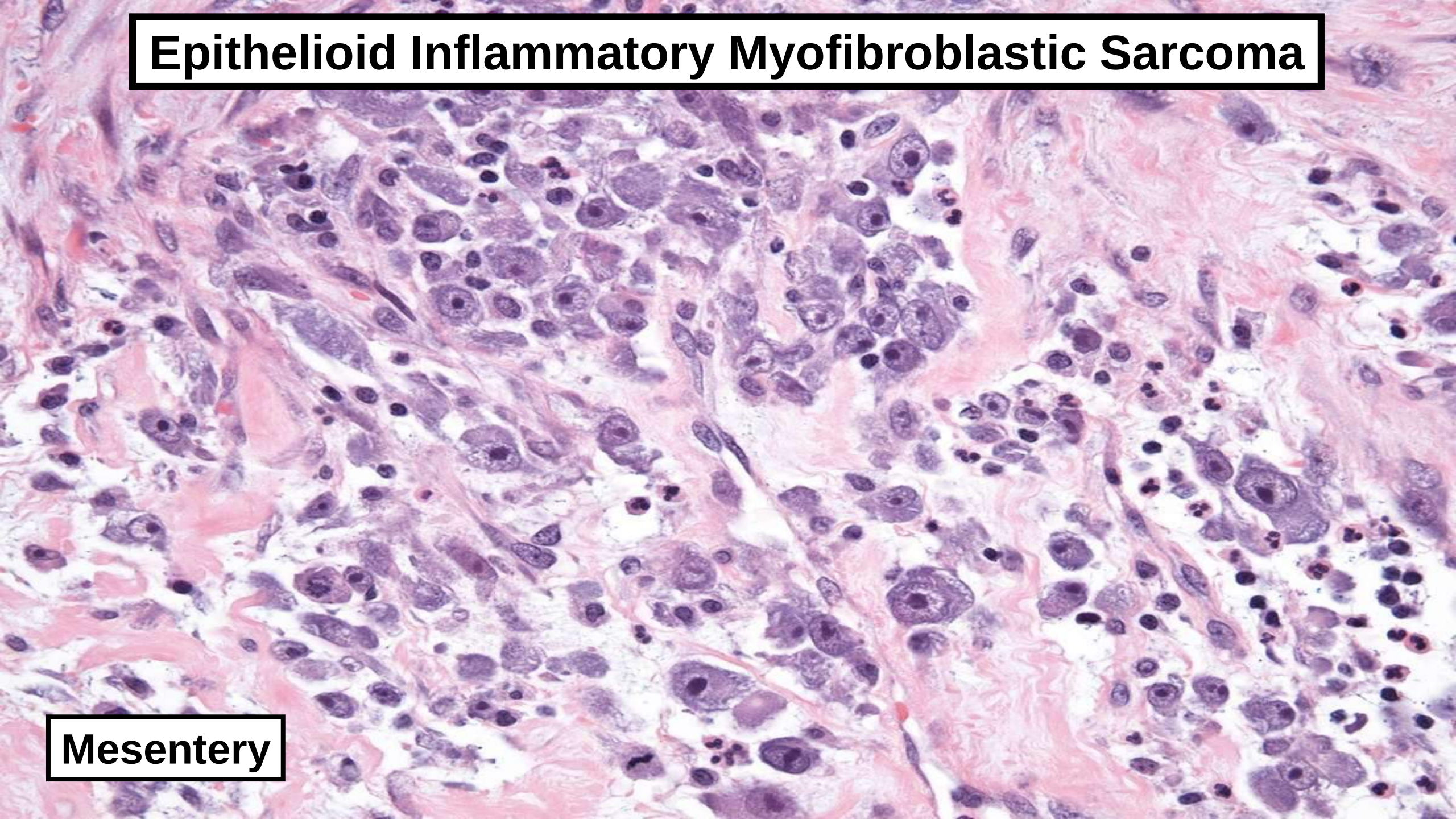
Omentum

Epithelioid Inflammatory Myofibroblastic Sarcoma



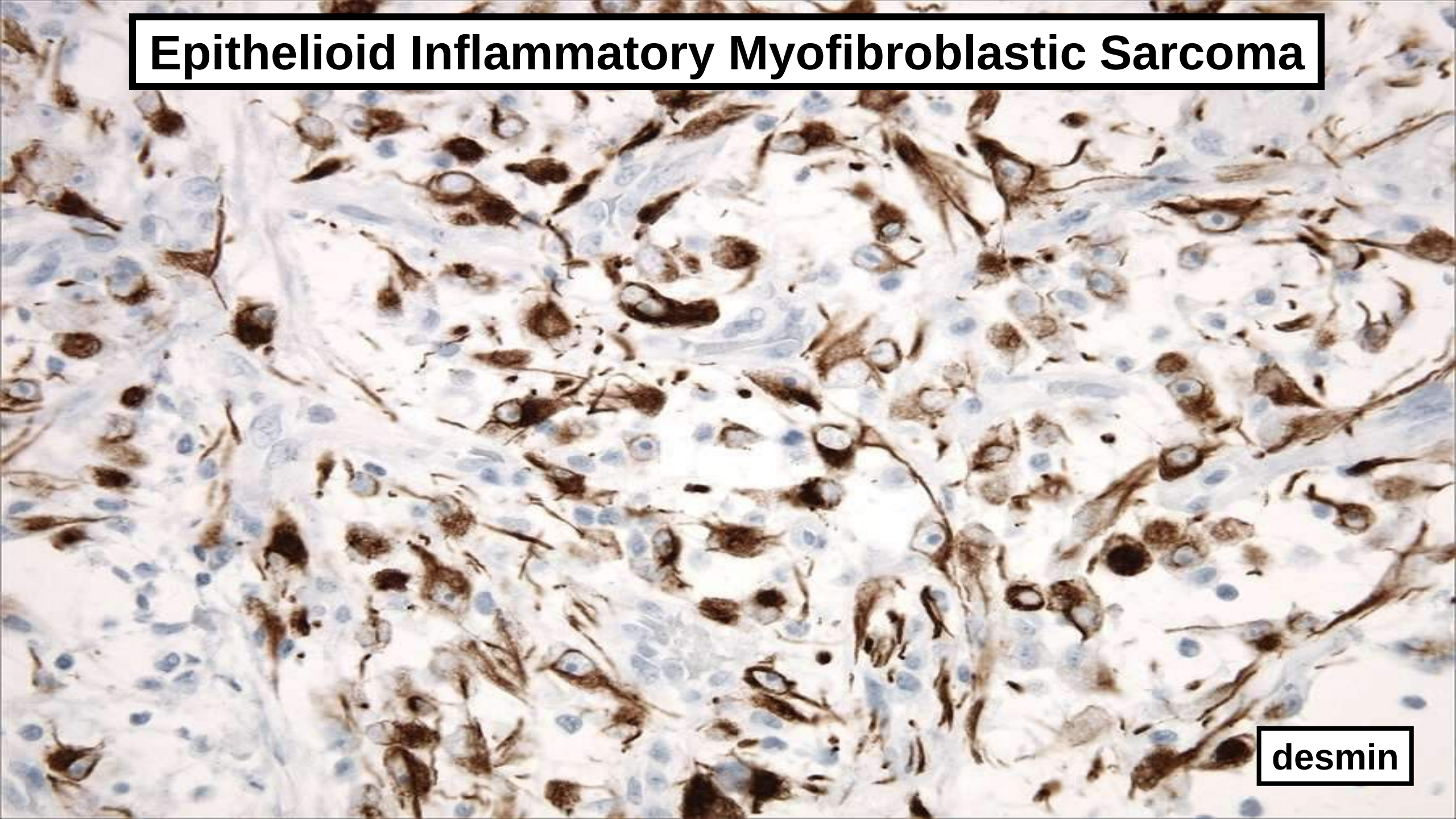
Mesentery

Epithelioid Inflammatory Myofibroblastic Sarcoma



Mesentery

Epithelioid Inflammatory Myofibroblastic Sarcoma

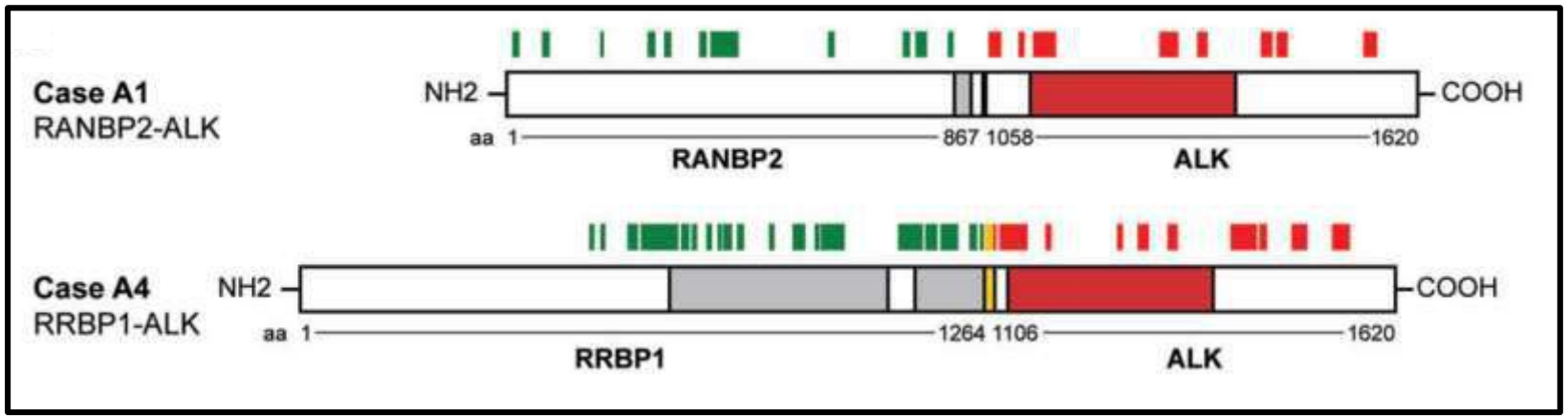


Journal of Pathology
J Pathol 2017; **241**: 316–323
Published online 15 December 2016 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4836

BRIEF DEFINITIVE REPORT

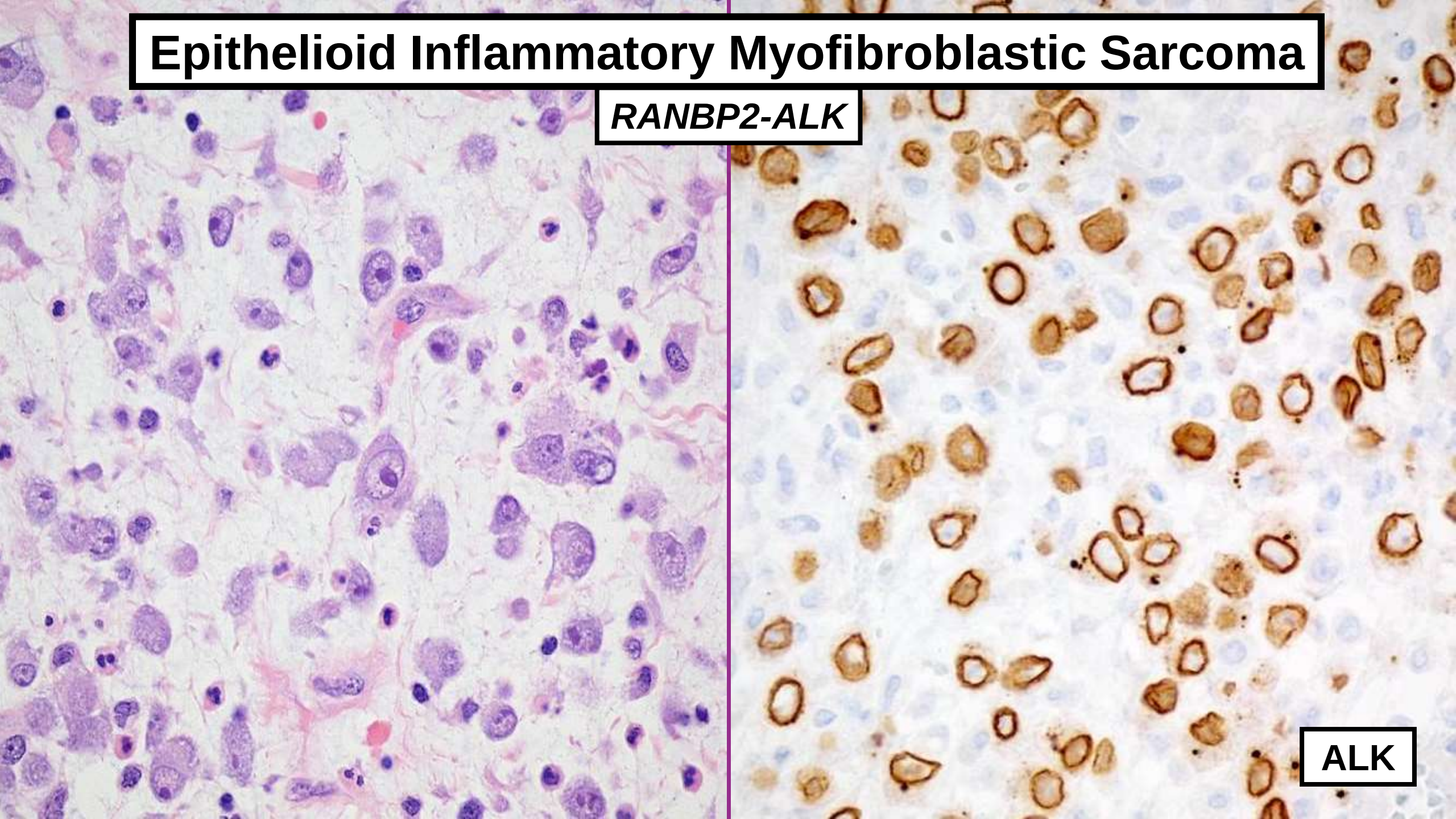
ALK oncoproteins in atypical inflammatory myofibroblastic tumours: novel RRBP1–ALK fusions in epithelioid inflammatory myofibroblastic sarcoma

Jen-Chieh Lee,[1,2*] Chien-Feng Li,[2,3†] Hsuan-Ying Huang,[2,4†] Mei-Jun Zhu,[5†] Adrián Mariño-Enríquez,[5] Chung-Ta Lee,[6] Wen-Bin Ou,[5,7,8] Jason L Hornick[5] and Jonathan A Fletcher[5*]

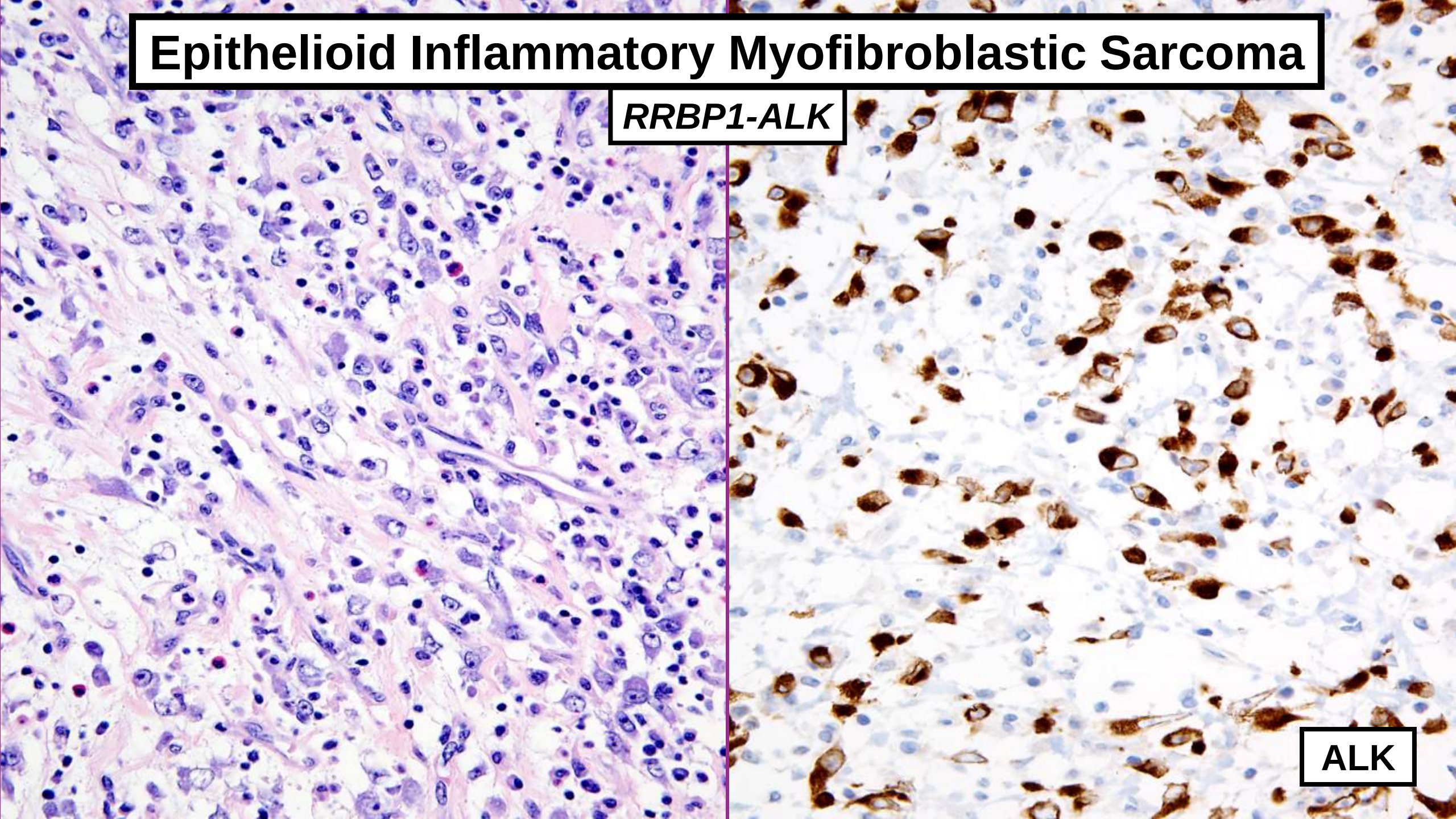


Epithelioid Inflammatory Myofibroblastic Sarcoma

RANBP2-ALK



Epithelioid Inflammatory Myofibroblastic Sarcoma



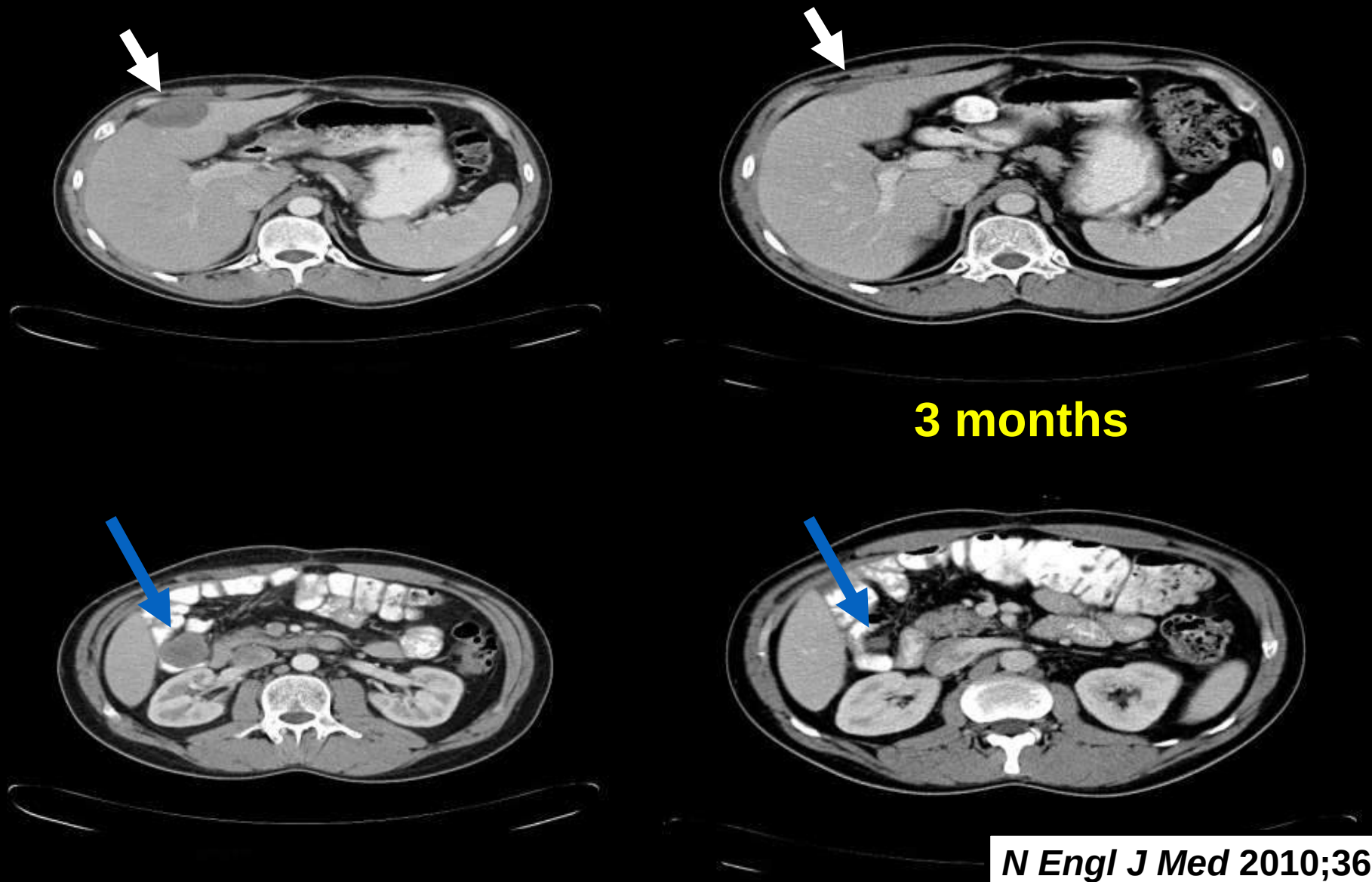
The NEW ENGLAND JOURNAL of MEDICINE

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

N Engl J Med 2010;363:1727-33.

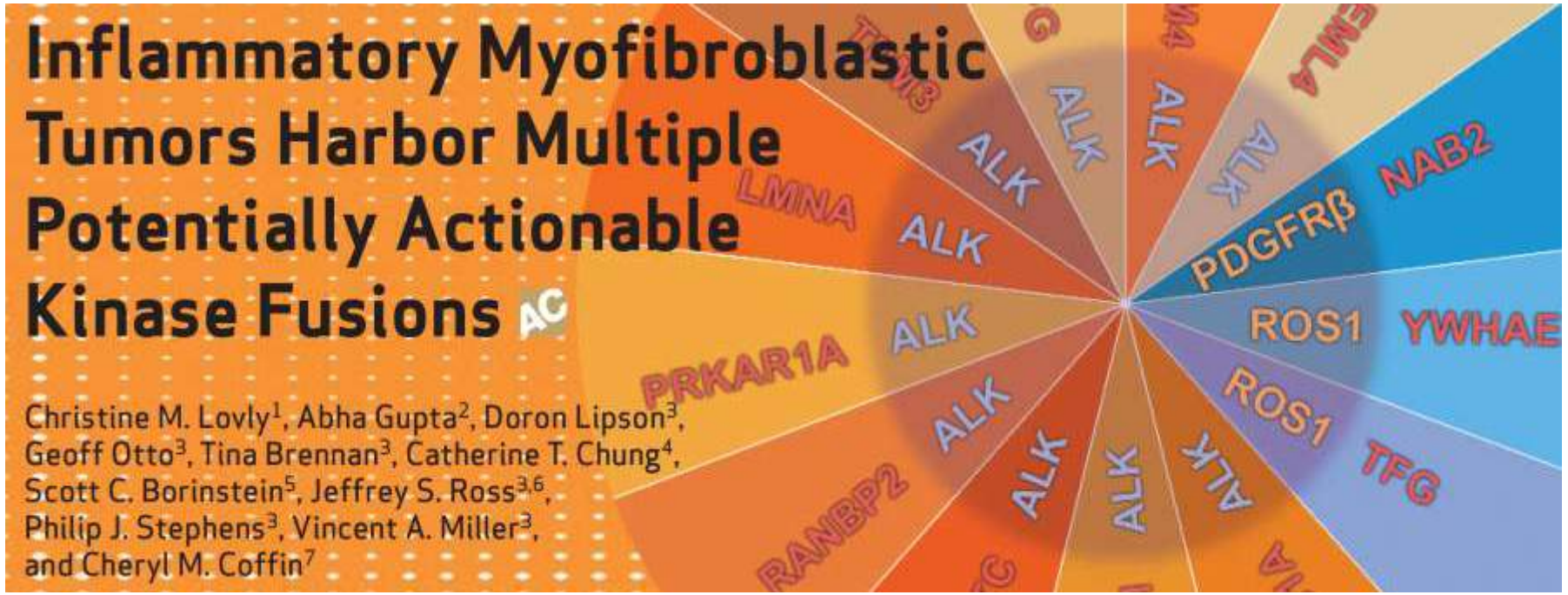
Multifocal Recurrent EIMS Treated with Crizotinib



N Engl J Med 2010;363:1727-33.

ALK-Negative Inflammatory Myofibroblastic Tumors?

- Until recently, molecular pathogenesis unknown
- Recent reports identified fusions involving receptor tyrosine kinase genes other than *ALK*



Cancer Discovery 2014;4:889-895.

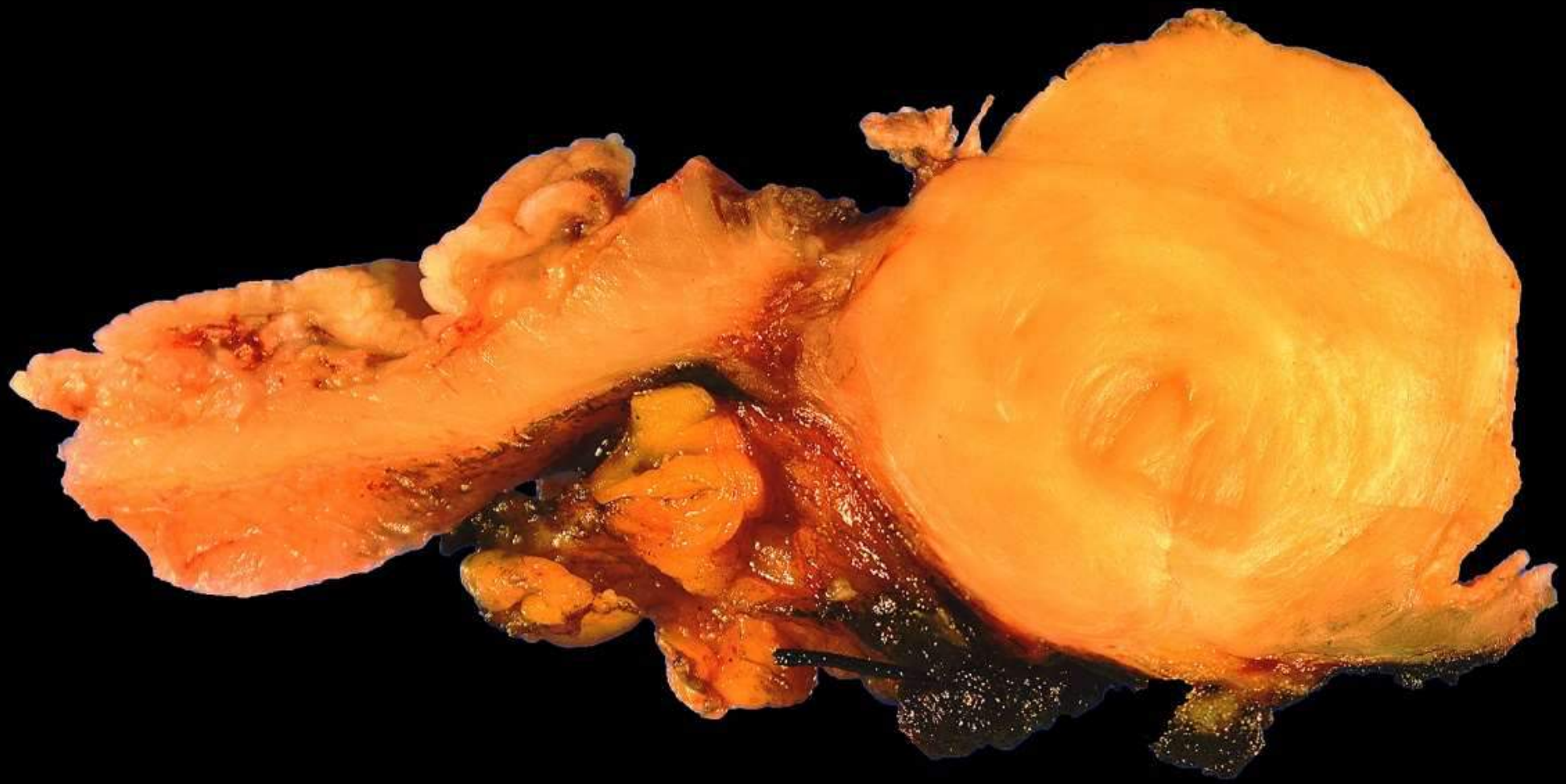
Molecular Characterization of Inflammatory Myofibroblastic Tumors With Frequent *ALK* and *ROS1* Gene Fusions and Rare Novel *RET* Rearrangement

Cristina R. Antonescu, MD, Albert J.H. Suurmeijer, MD,† Lei Zhang, MSc,* Yun-Shao Sung, MSc,* Achim A. Jungbluth, MD,* William D. Travis, MD,* Hikmat Al-Ahmadie, MD,* Christopher D.M. Fletcher, MD,‡ and Rita Alaggio, MD§*

Am J Surg Pathol • Volume 39, Number 7, July 2015

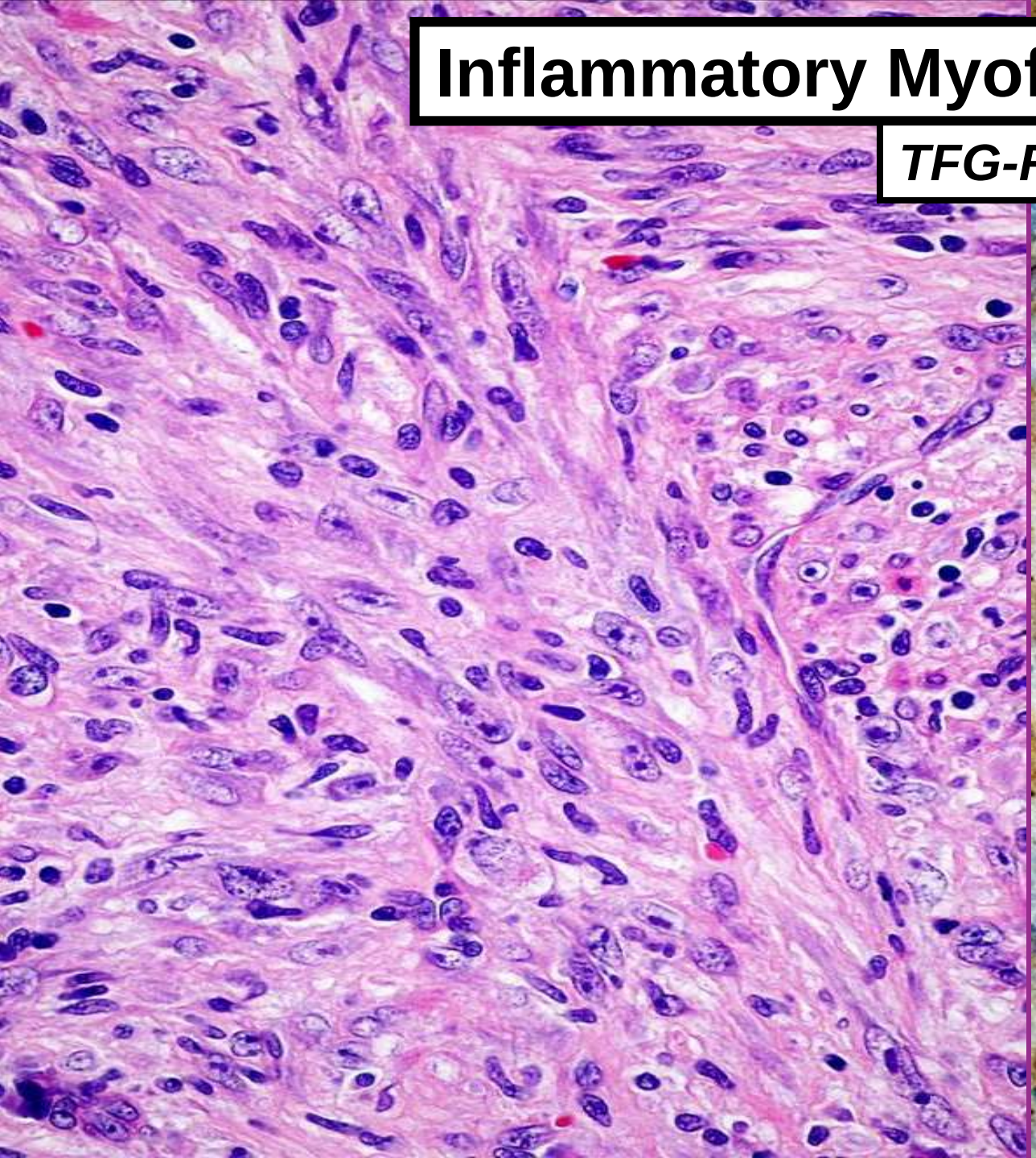
Inflammatory Myofibroblastic Tumor

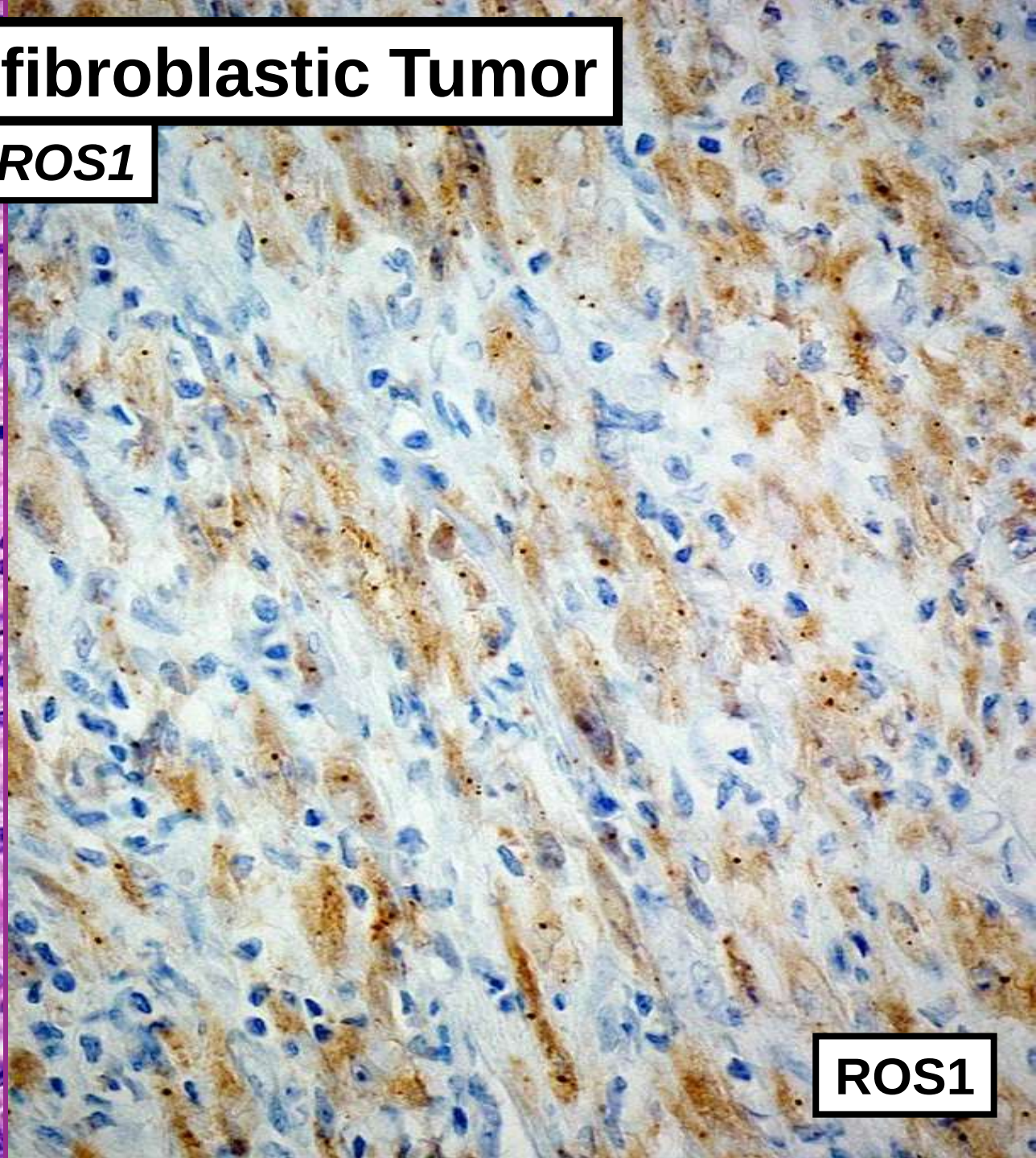
TFG-ROS1



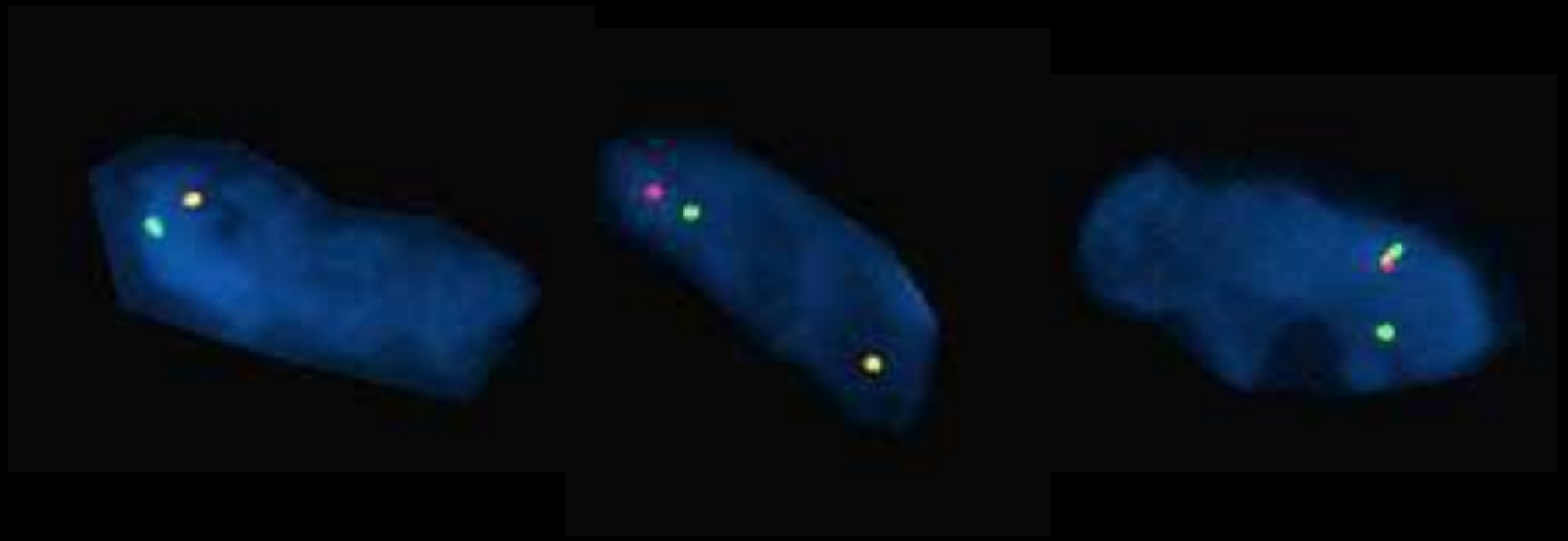
Inflammatory Myofibroblastic Tumor

TFG-ROS1





Inflammatory Myofibroblastic Tumor



ROS1 - 6q22
3' (c)
5' (t)

Histopathology

Histopathology 2016, **69**, 72–83. DOI: 10.1111/his.12910

ALK, *ROS1* and *NTRK3* gene rearrangements in inflammatory myofibroblastic tumours

Hidetaka Yamamoto, Akihiko Yoshida,[1] Kenichi Taguchi,[2] Kenichi Kohashi, Yui Hatanaka, Atsushi Yamashita,[3] Daisuke Mori[4] & Yoshinao Oda

ETV6-NTRK3 Is Expressed in a Subset of ALK-Negative Inflammatory Myofibroblastic Tumors

Ali H. Alassiri, MD,† Rola H. Ali, MD,‡ Yaoqing Shen, PhD,§ Amy Lum, BSc,‖ Caron Strahlendorf, MD,¶ Rebecca Deyell, MD,¶ Rod Rassekh, MD,¶ Poul H. Sorensen, MD, PhD,# Janessa Laskin, MD,‖ Marco Marra, PhD,§ Stephen Yip, MD, PhD,# Cheng-Han Lee, MD, PhD,** and Tony L. Ng, MD, PhD*#*

Am J Surg Pathol • Volume 40, Number 8, August 2016

Gastrointestinal Neuroectodermal Tumor

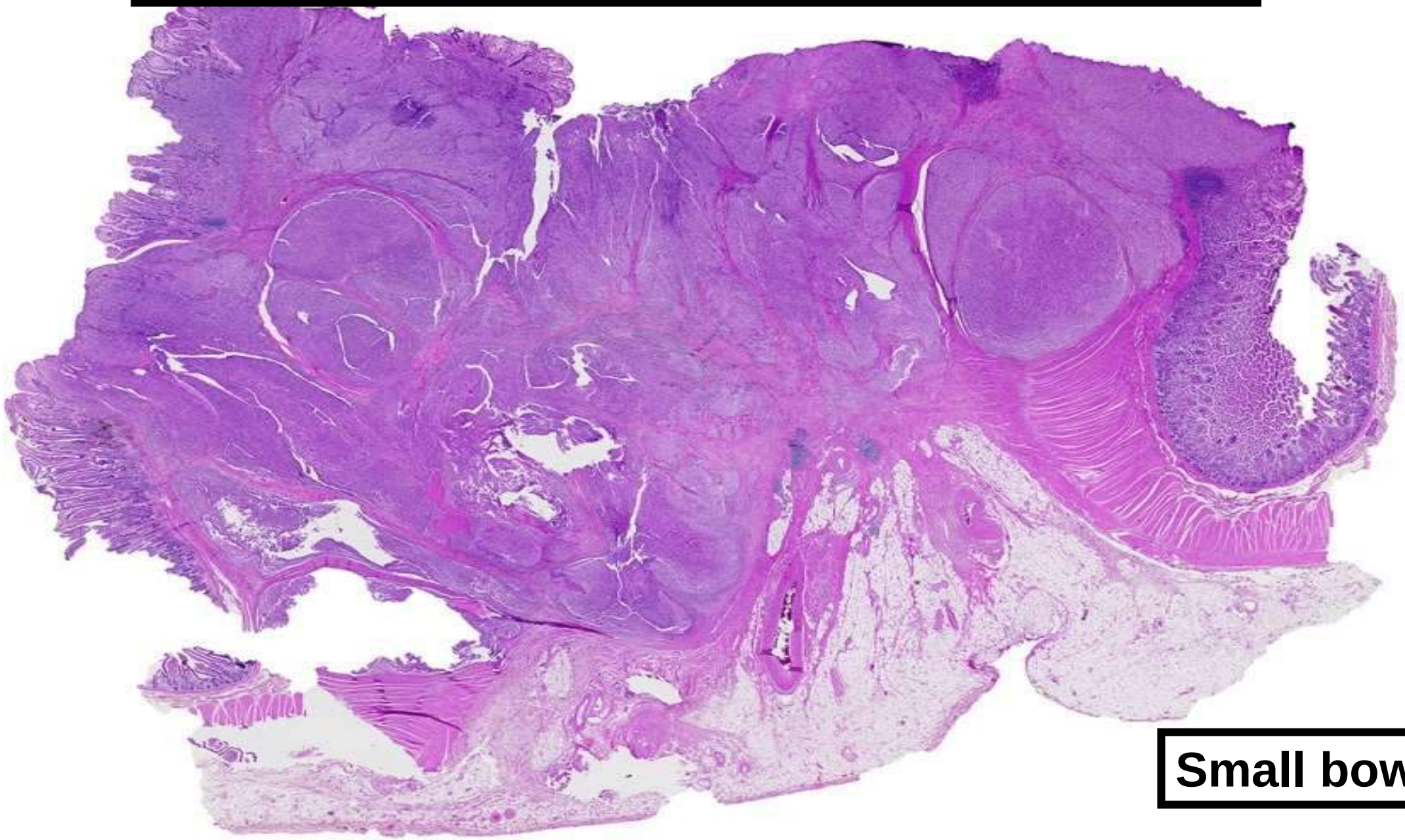
- Also known as clear cell sarcoma-like tumor
- ~50 reported cases, increasingly recognized
- Young to middle-aged adults
- Mean age 40 years
- Small bowel (70%), stomach, colon
- Large infiltrative masses
- May be mistaken for GIST
- Aggressive sarcoma
- Lymph node and liver metastases

Gastrointestinal Neuroectodermal Tumor

Ileum

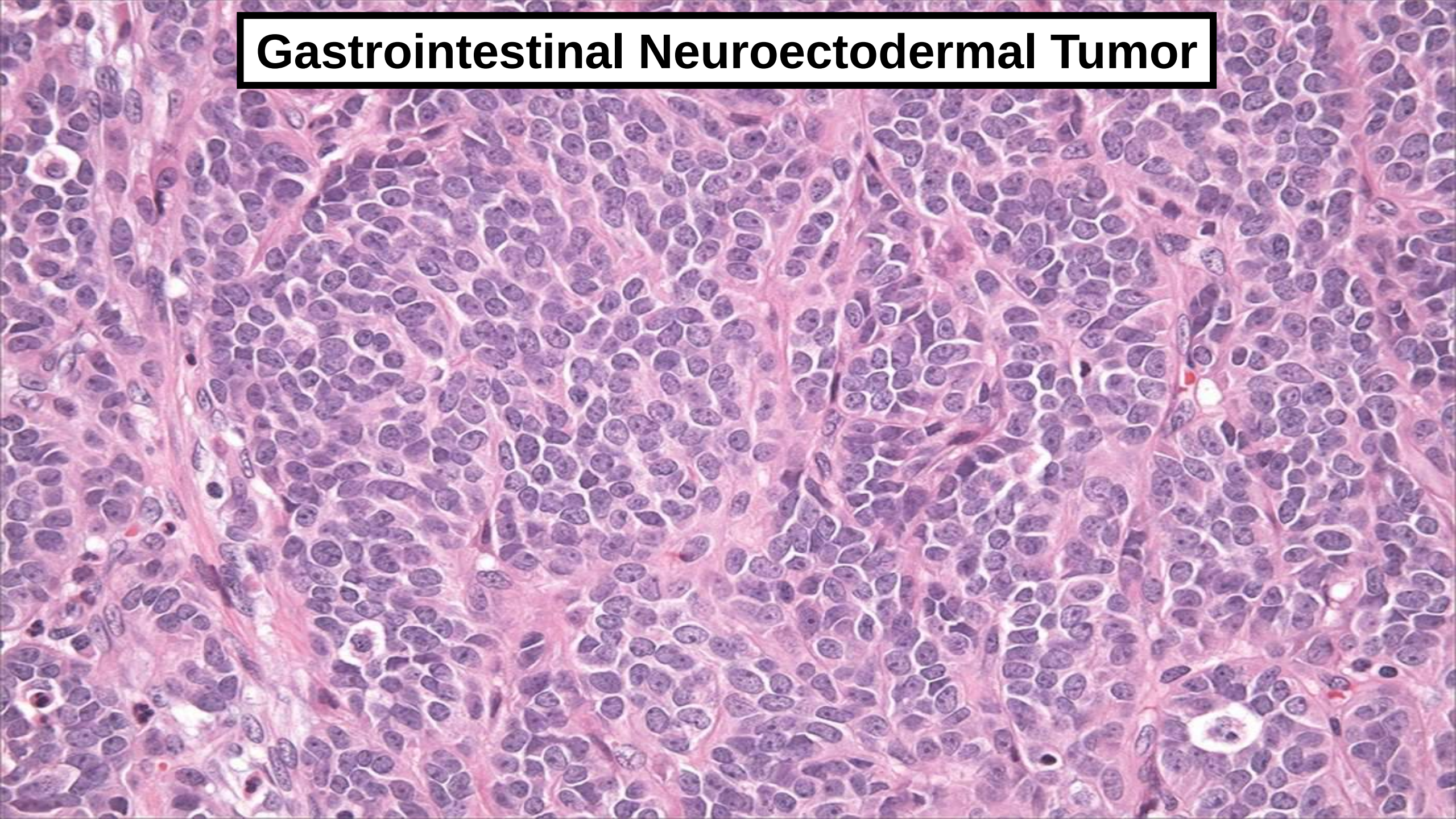
Courtesy of Mee Joo, MD

Gastrointestinal Neuroectodermal Tumor

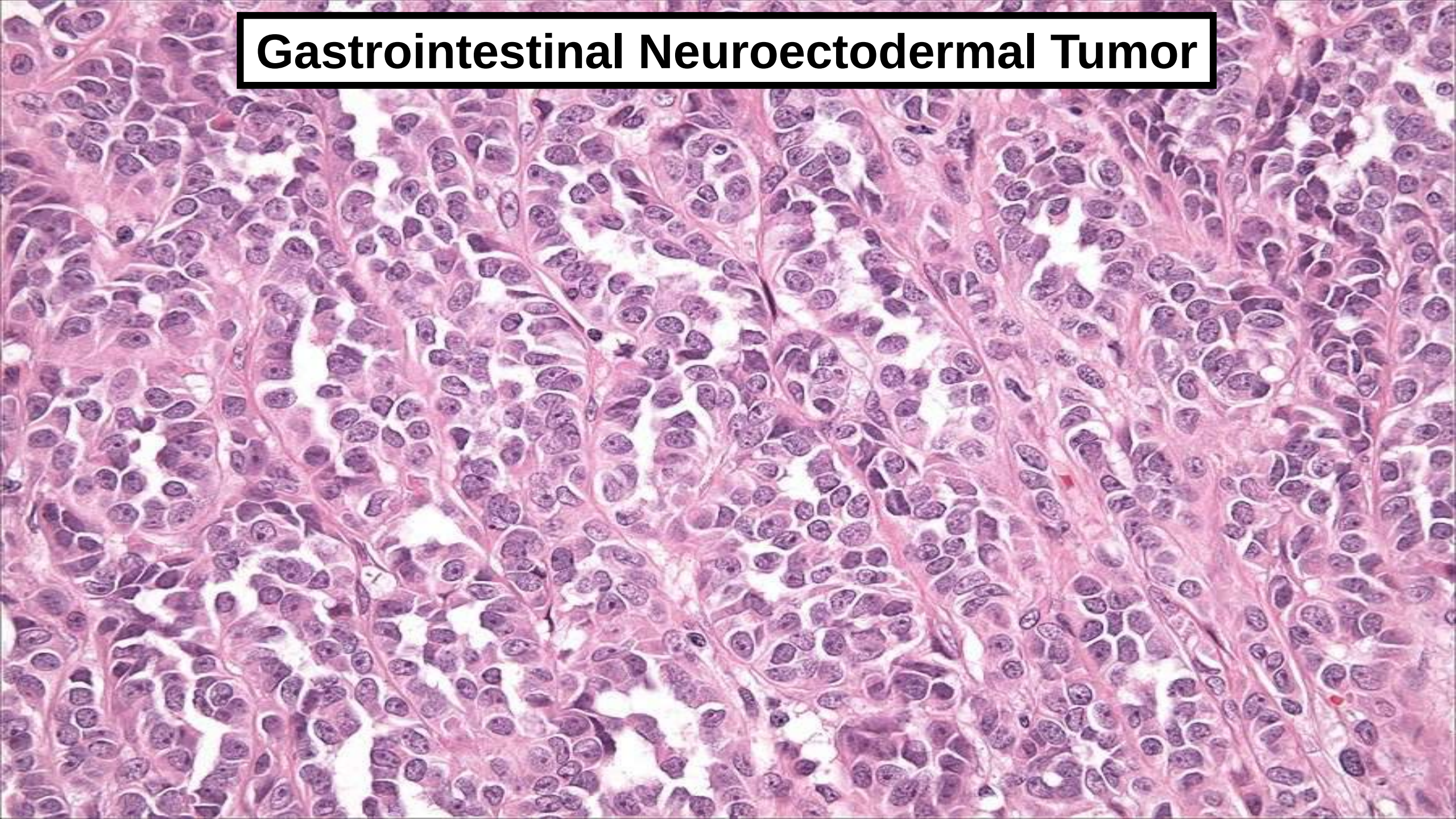


Small bowel

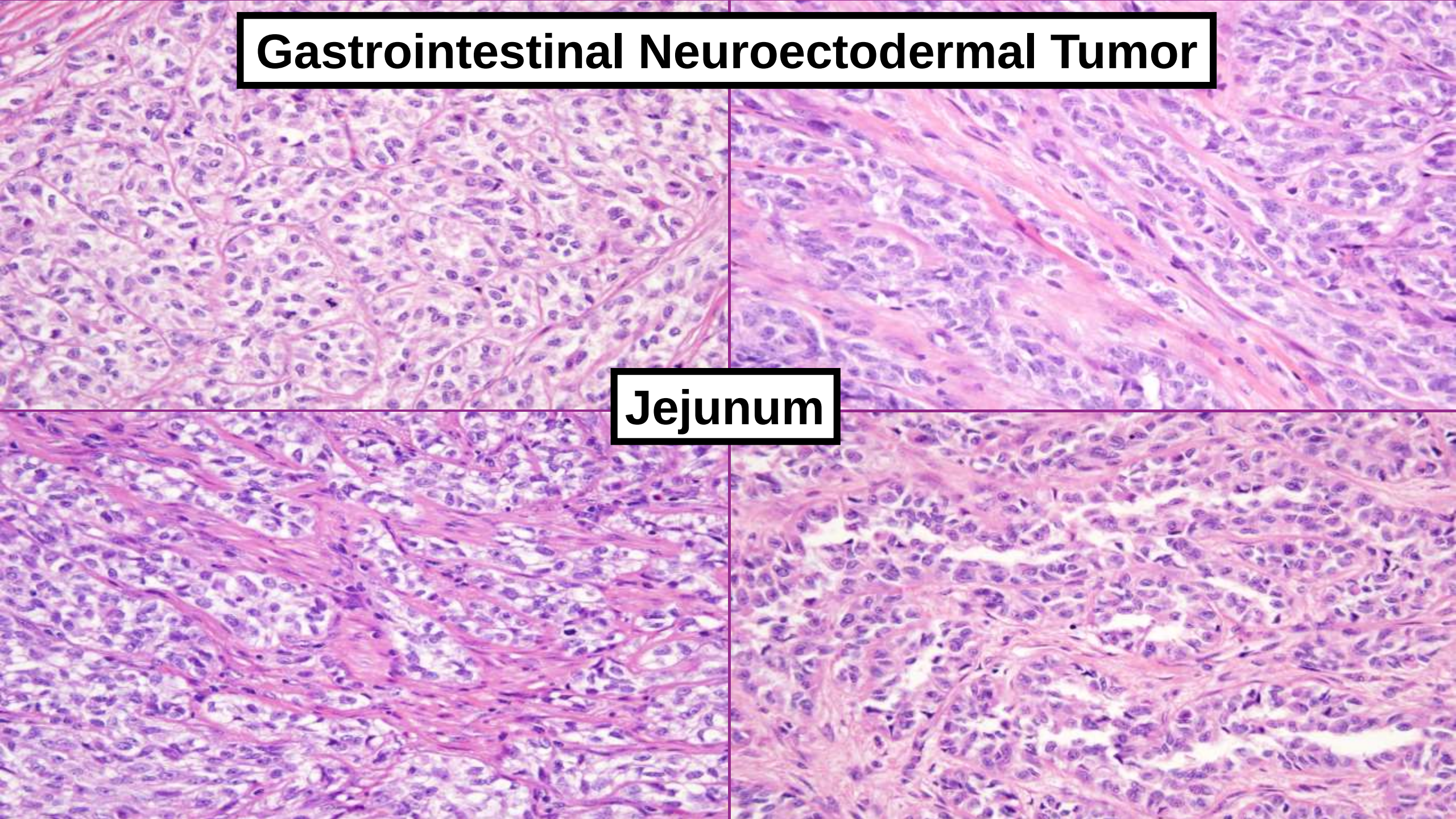
Gastrointestinal Neuroectodermal Tumor

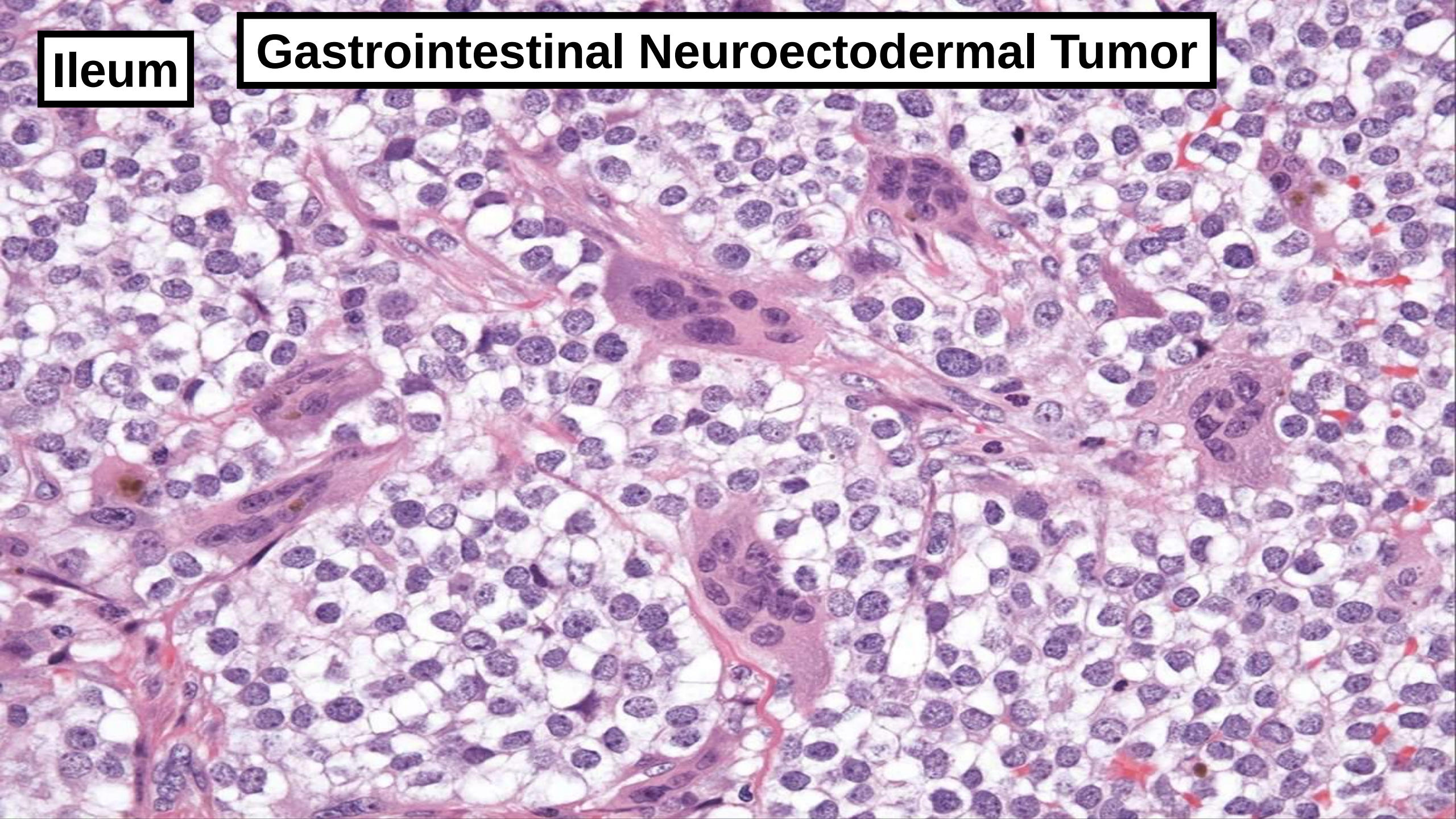


Gastrointestinal Neuroectodermal Tumor



Gastrointestinal Neuroectodermal Tumor




Ileum
Gastrointestinal Neuroectodermal Tumor

Gastrointestinal Neuroectodermal Tumor: Immunophenotype and Molecular Genetics

- Diffuse strong reactivity for S100 protein and SOX10
- Lacks melanocytic markers (HMB-45, melan A, MiTF)
- t(12;22) with *ATF1-EWSR1* or t(2;22) with *CREB1-EWSR1*

EWS-CREB1: A Recurrent Variant Fusion in Clear Cell Sarcoma—Association with Gastrointestinal Location and Absence of Melanocytic Differentiation

Cristina R. Antonescu,[1] Khedoudja Nafa,[1] Neil H. Segal,[2] Paola Dal Cin,[3] and Marc Ladanyi[1]

Clin Cancer Res 2006;12(18) September 15, 2006

Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract

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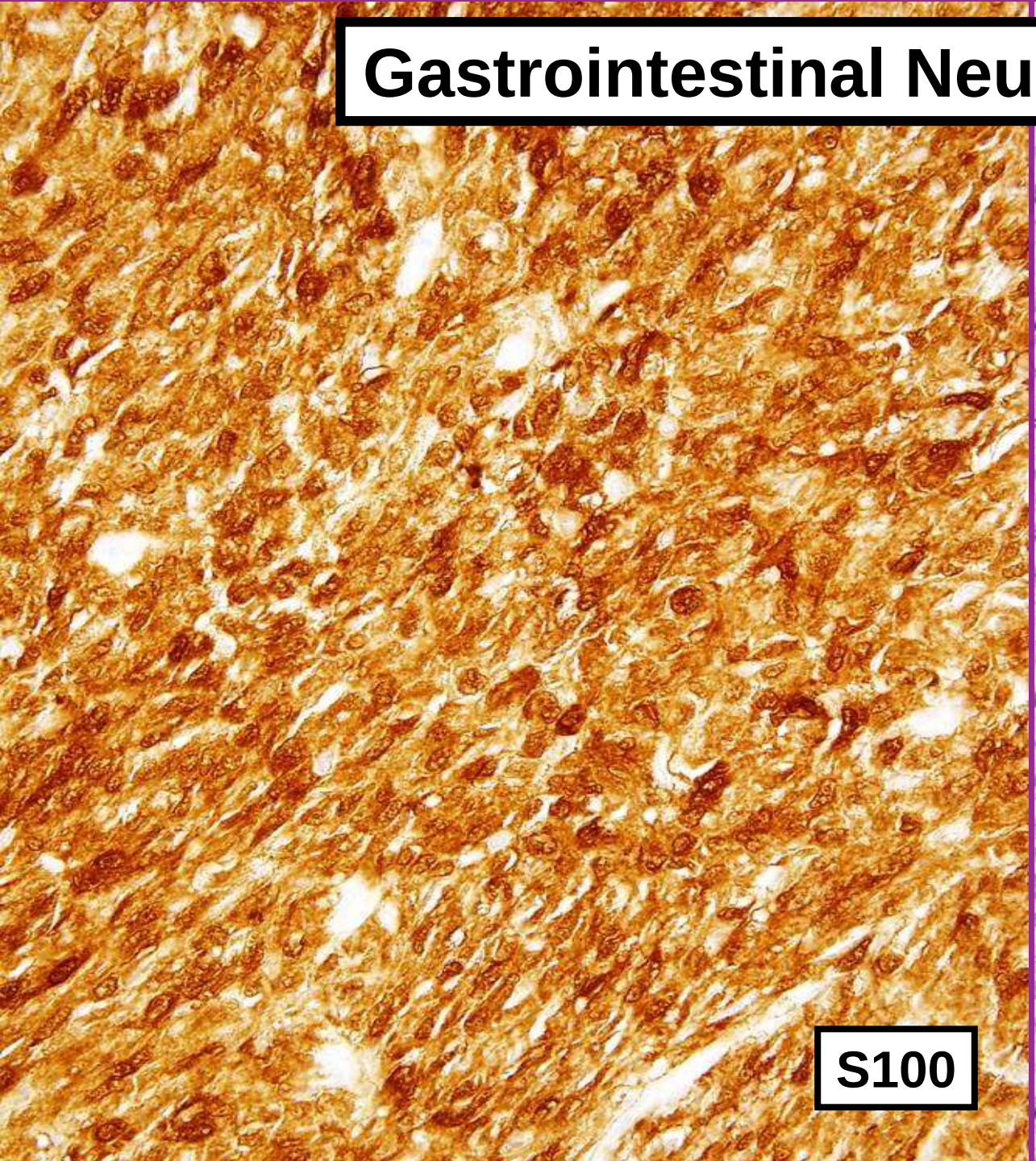
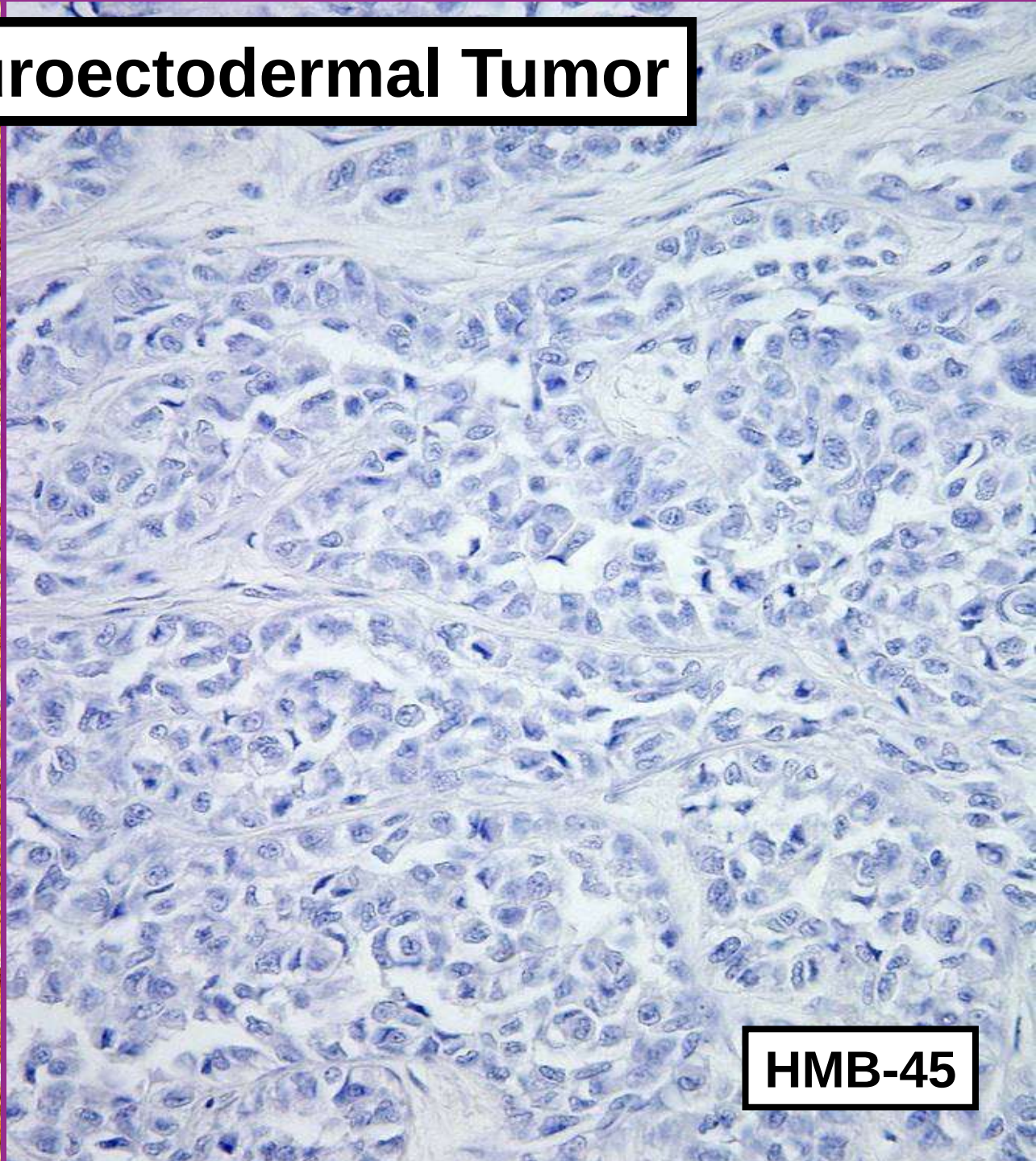
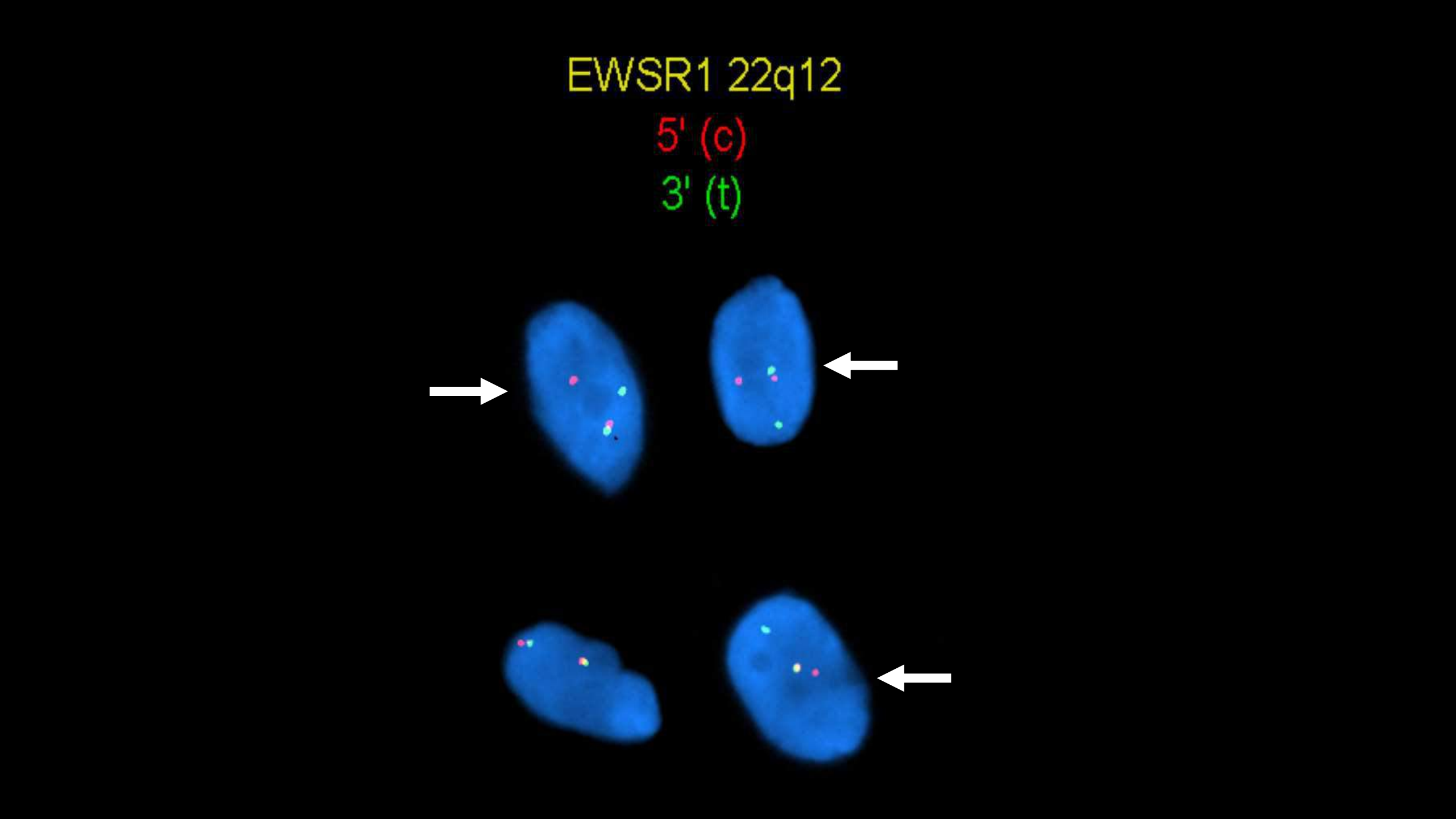
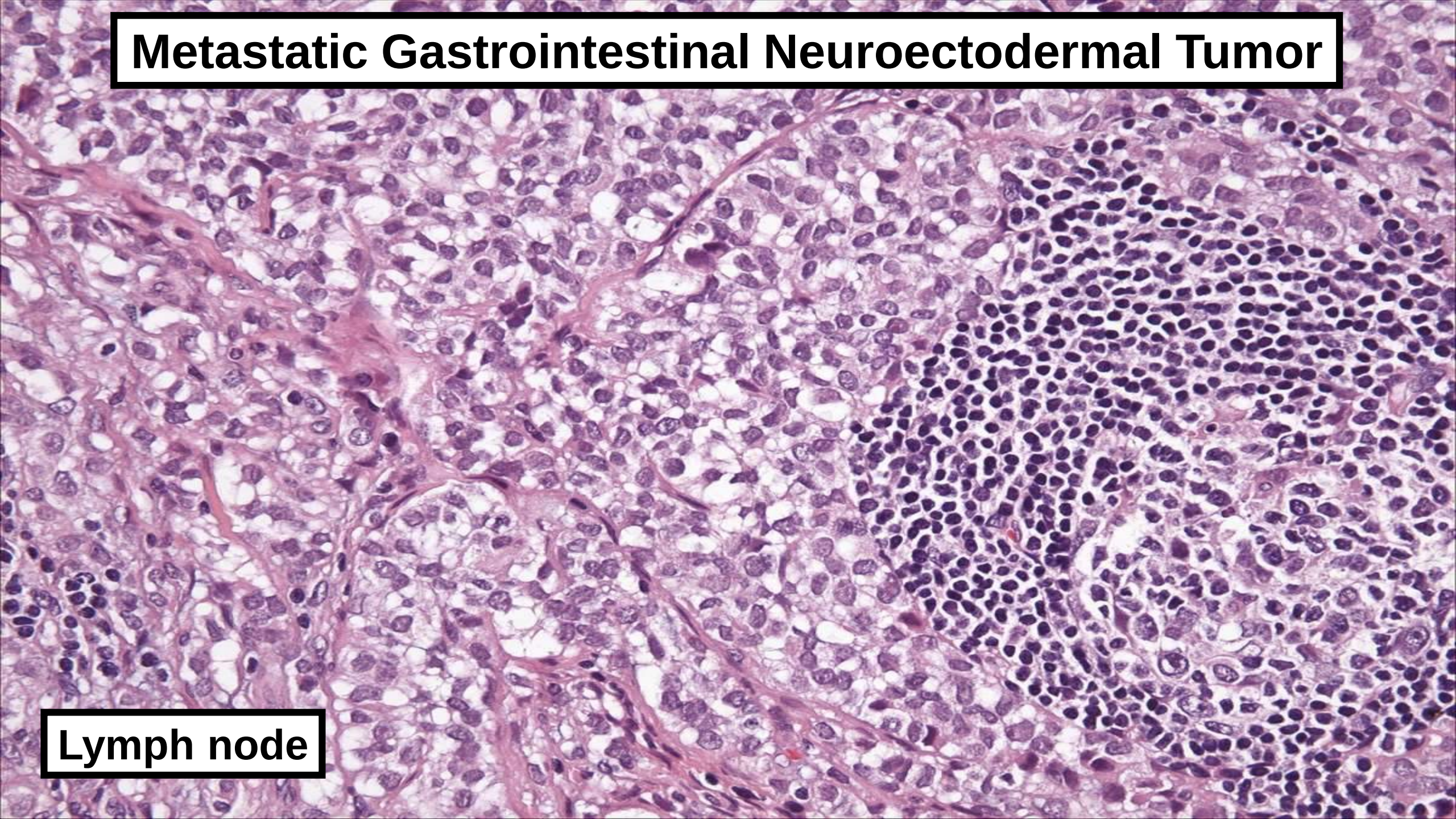
Gastrointestinal Neuroectodermal Tumor






EWSR1 22q12
5' (c)
3' (t)

Metastatic Gastrointestinal Neuroectodermal Tumor



Lymph node

PEComa

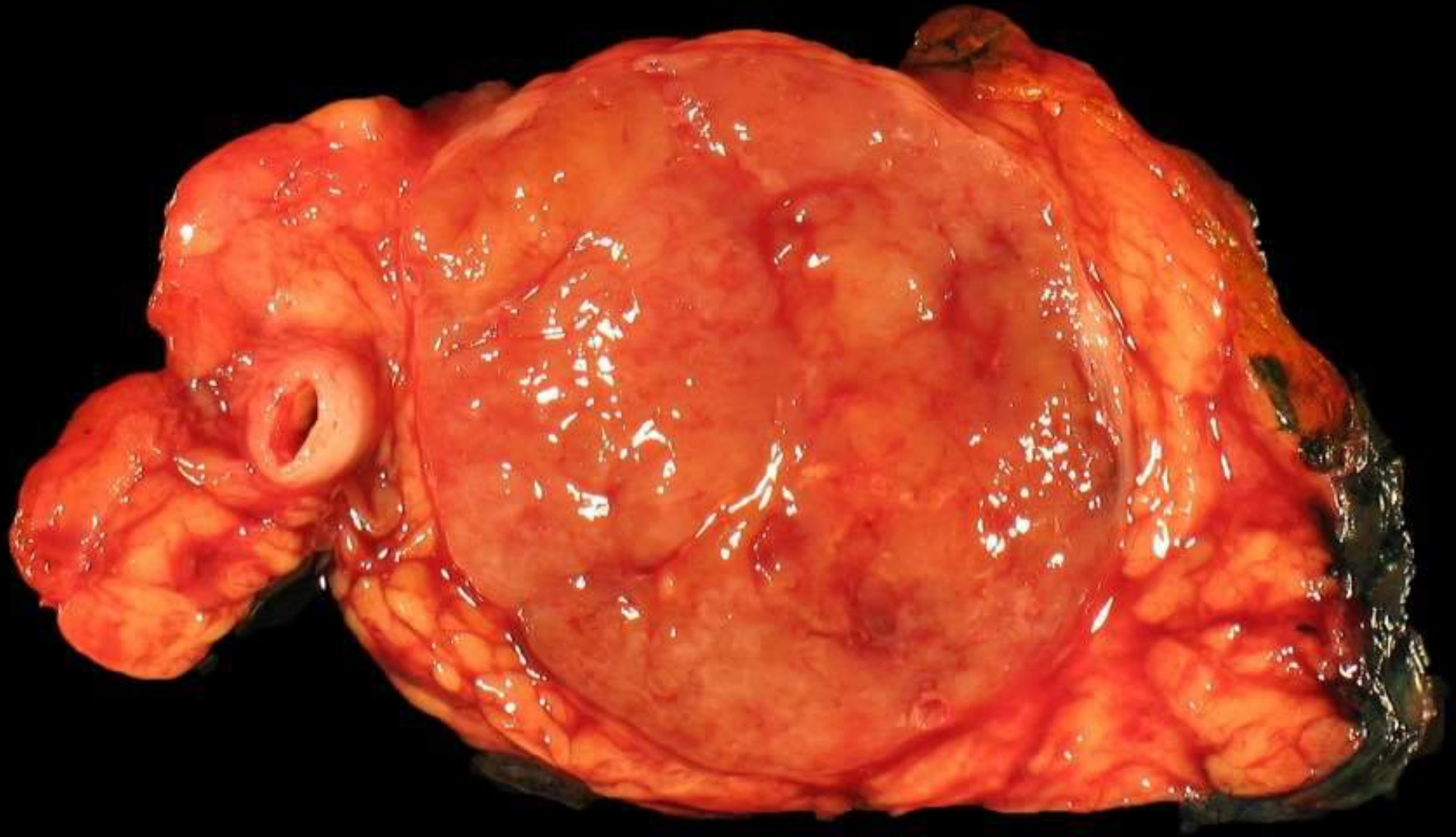
- Family of related mesenchymal lesions:
  - Angiomyolipoma (AML)
  - Lymphangiomyomatosis (LAM)
  - PEComa NOS
- All share distinctive cell type: “perivascular epithelioid cell” (PEC)
- Evidence of myogenic (smooth muscle) and melanocytic differentiation
- No known normal tissue counterpart

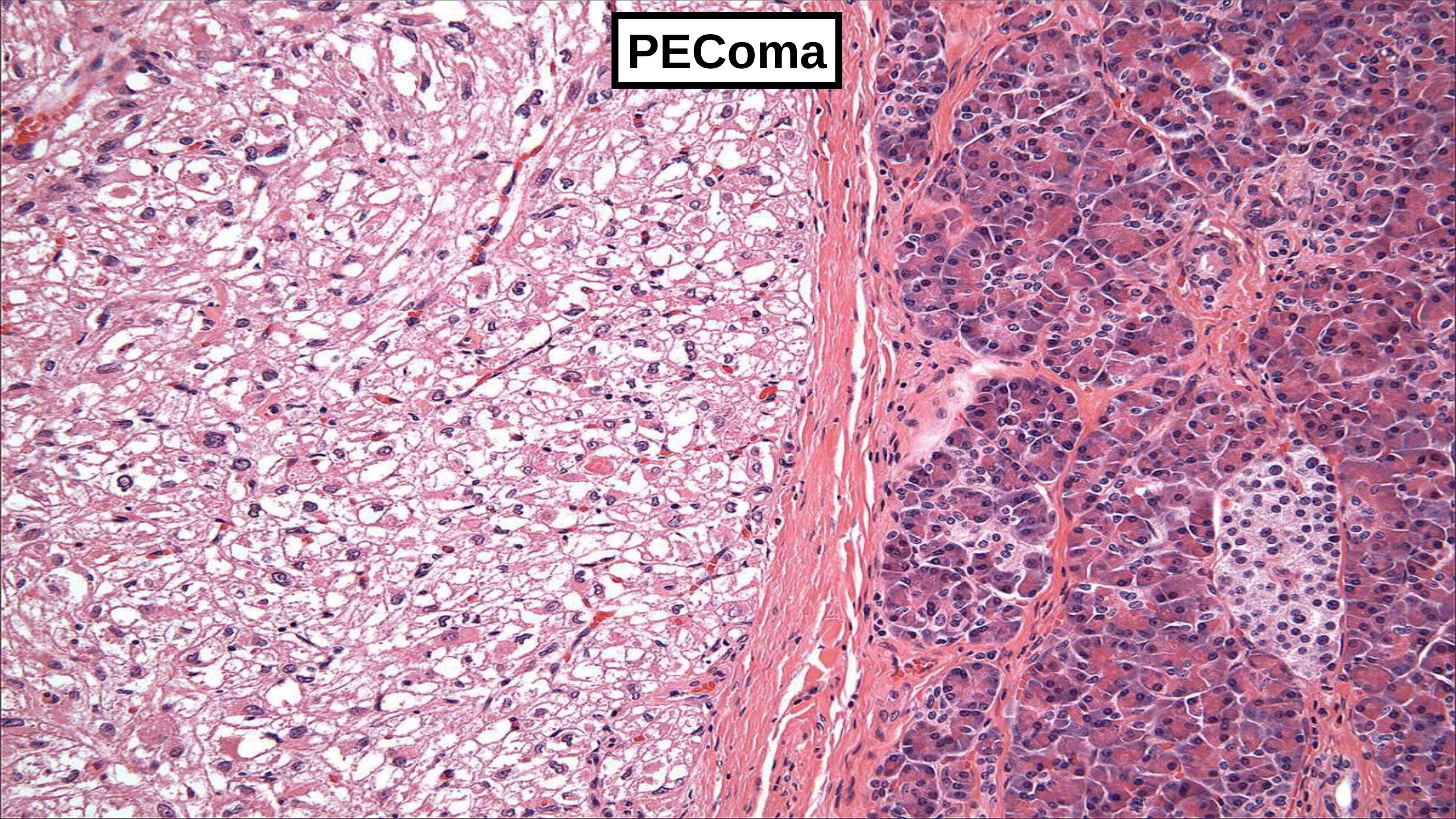
PEComa:
Clinical Features

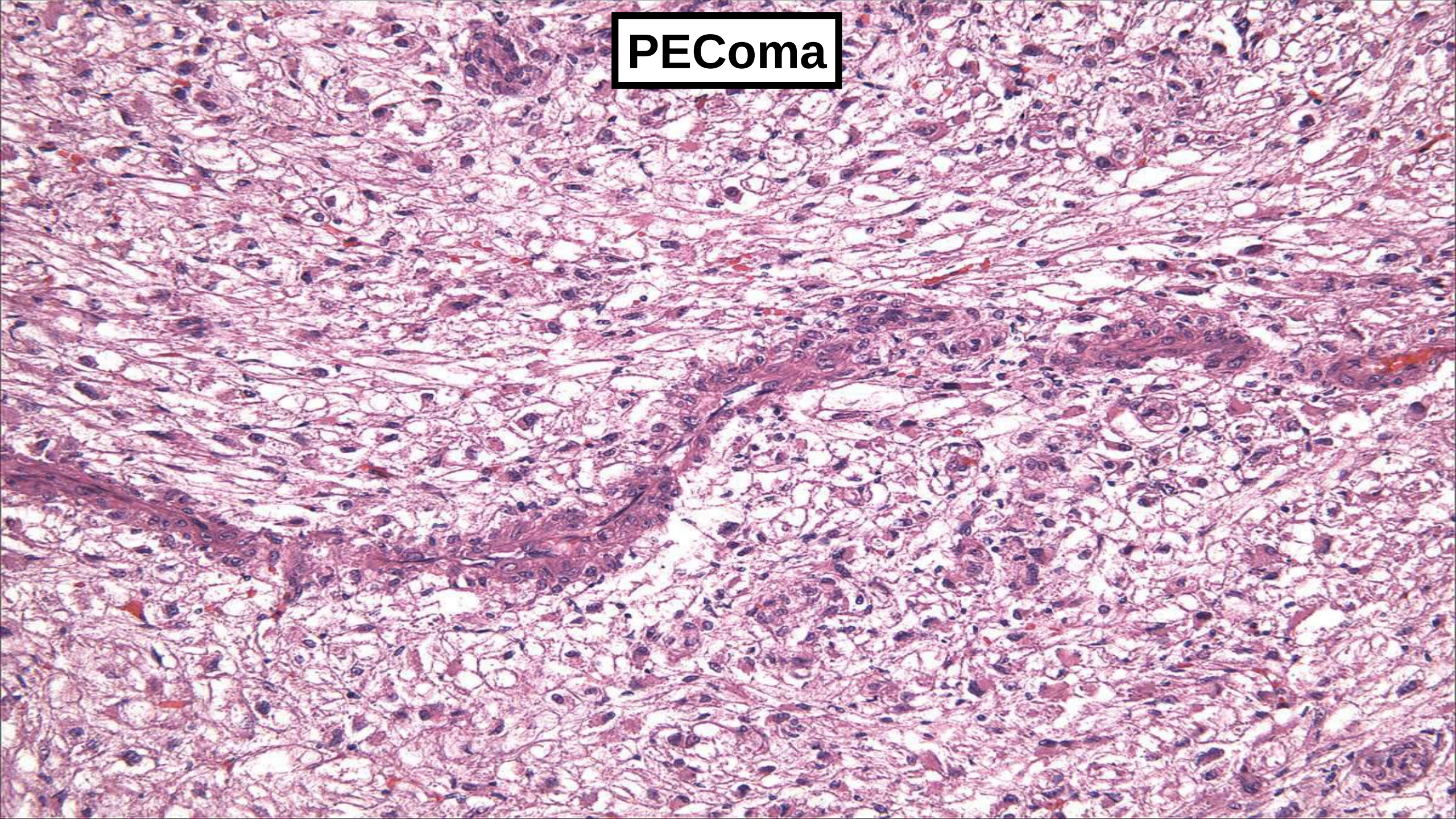
- Female predominance (5:1 overall, but no gender predilection in GI tract)
- Middle-aged adults
- Rarely associated with TSC (unlike AML and LAM)
- Most common sites: abdomen/pelvis, retroperitoneum, visceral sites (especially GI tract and uterus)
- Minority (25%) in somatic soft tissue and skin

Pancreas

PEComa




PEComa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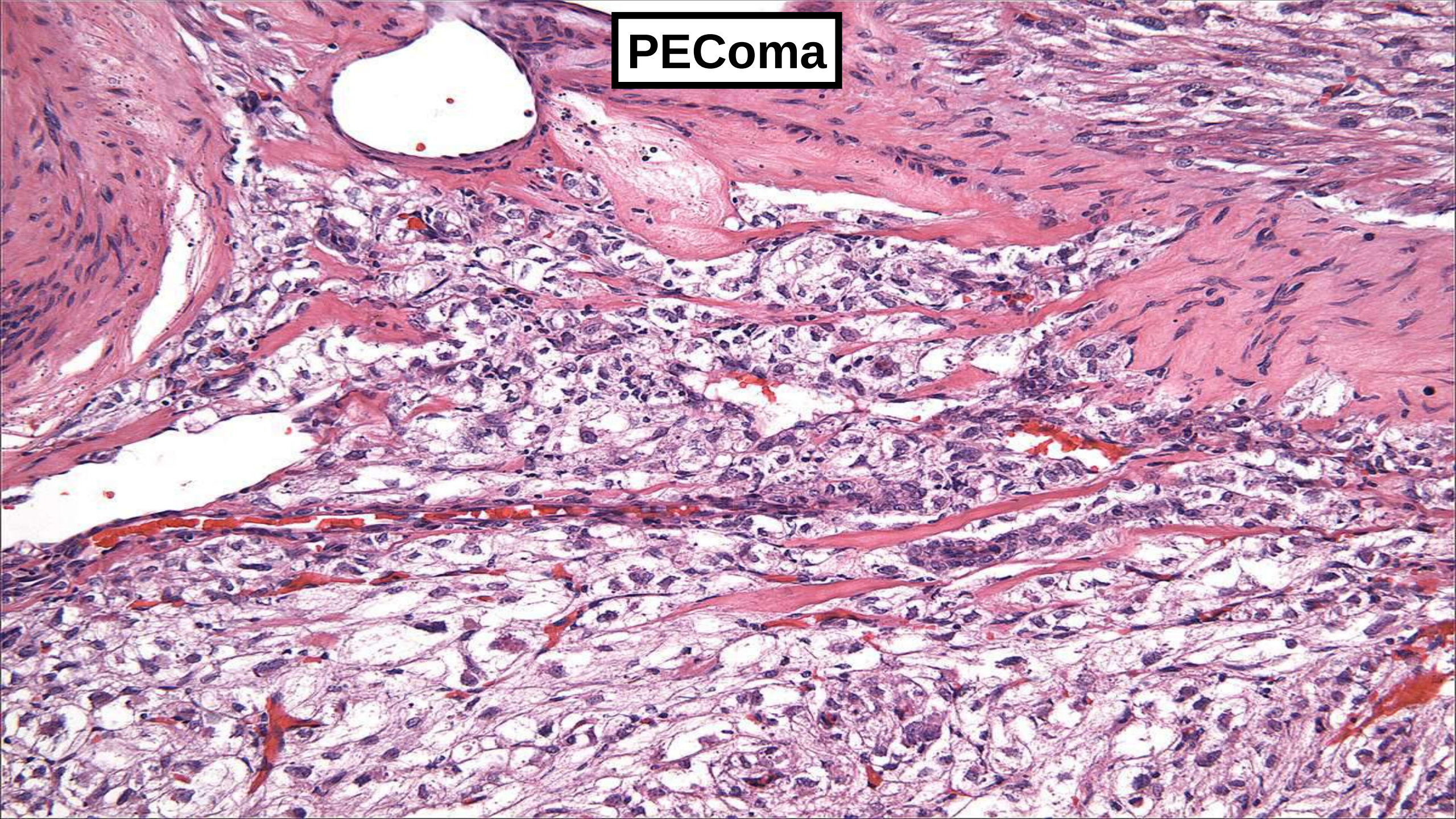
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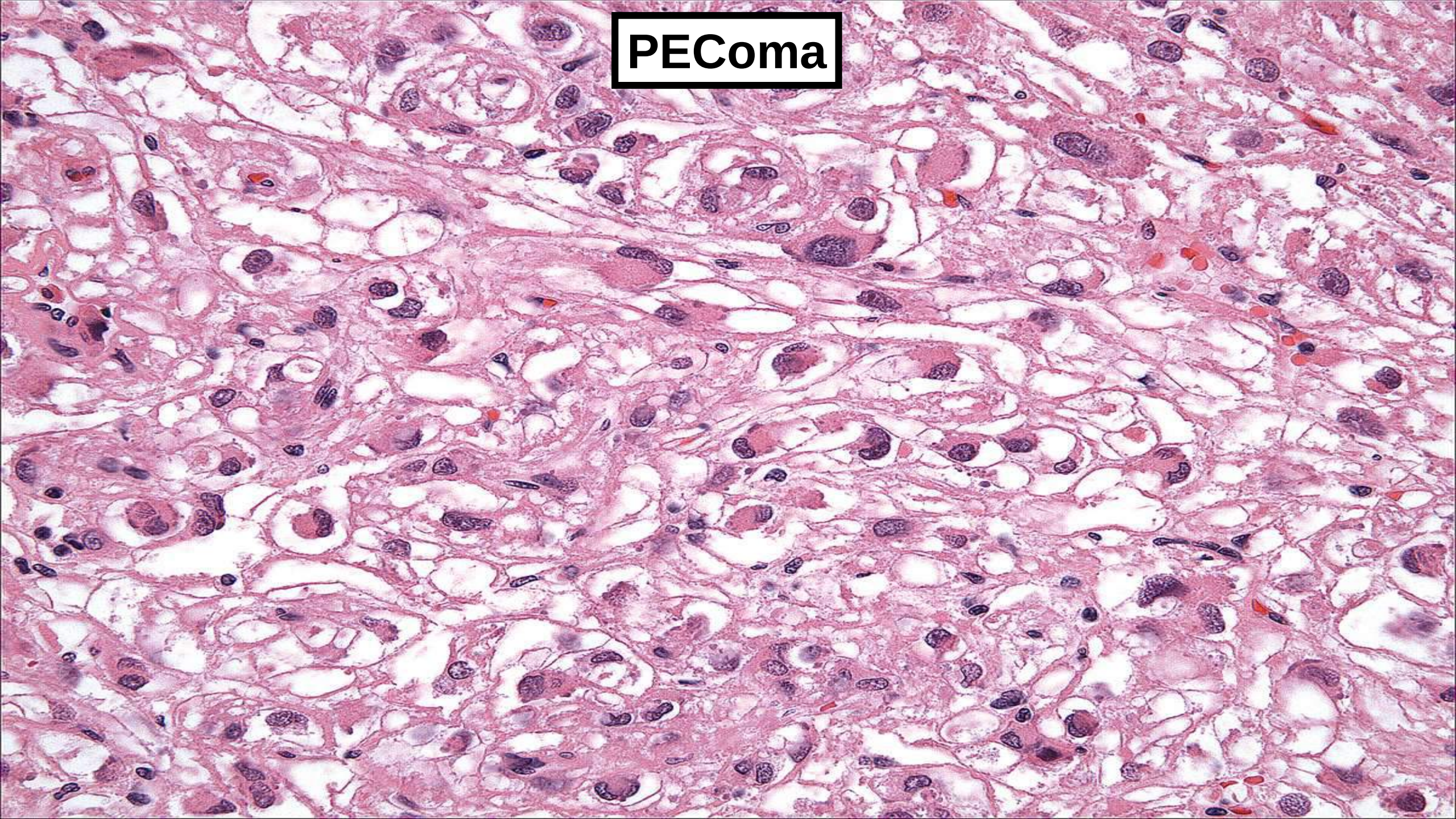
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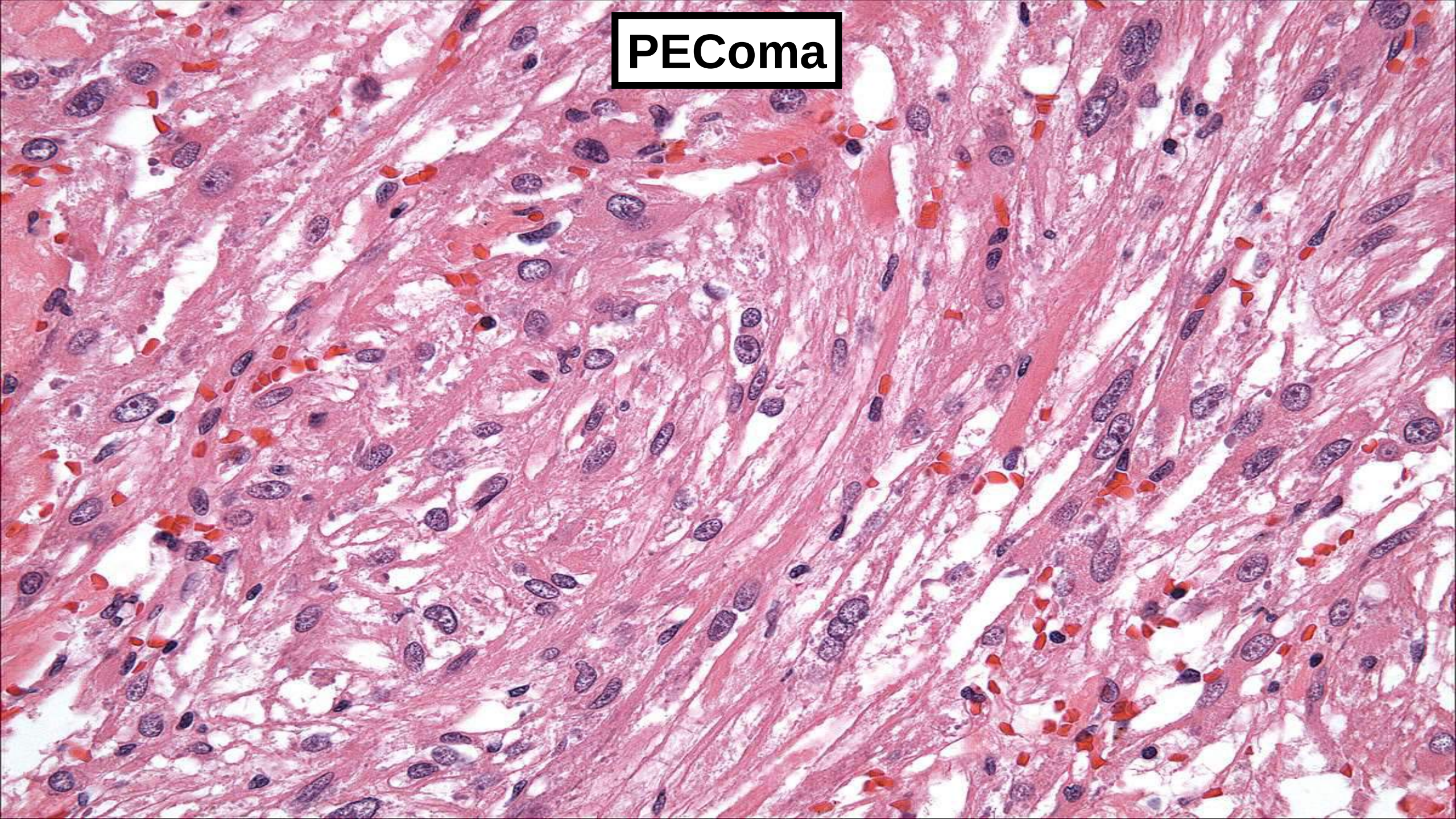
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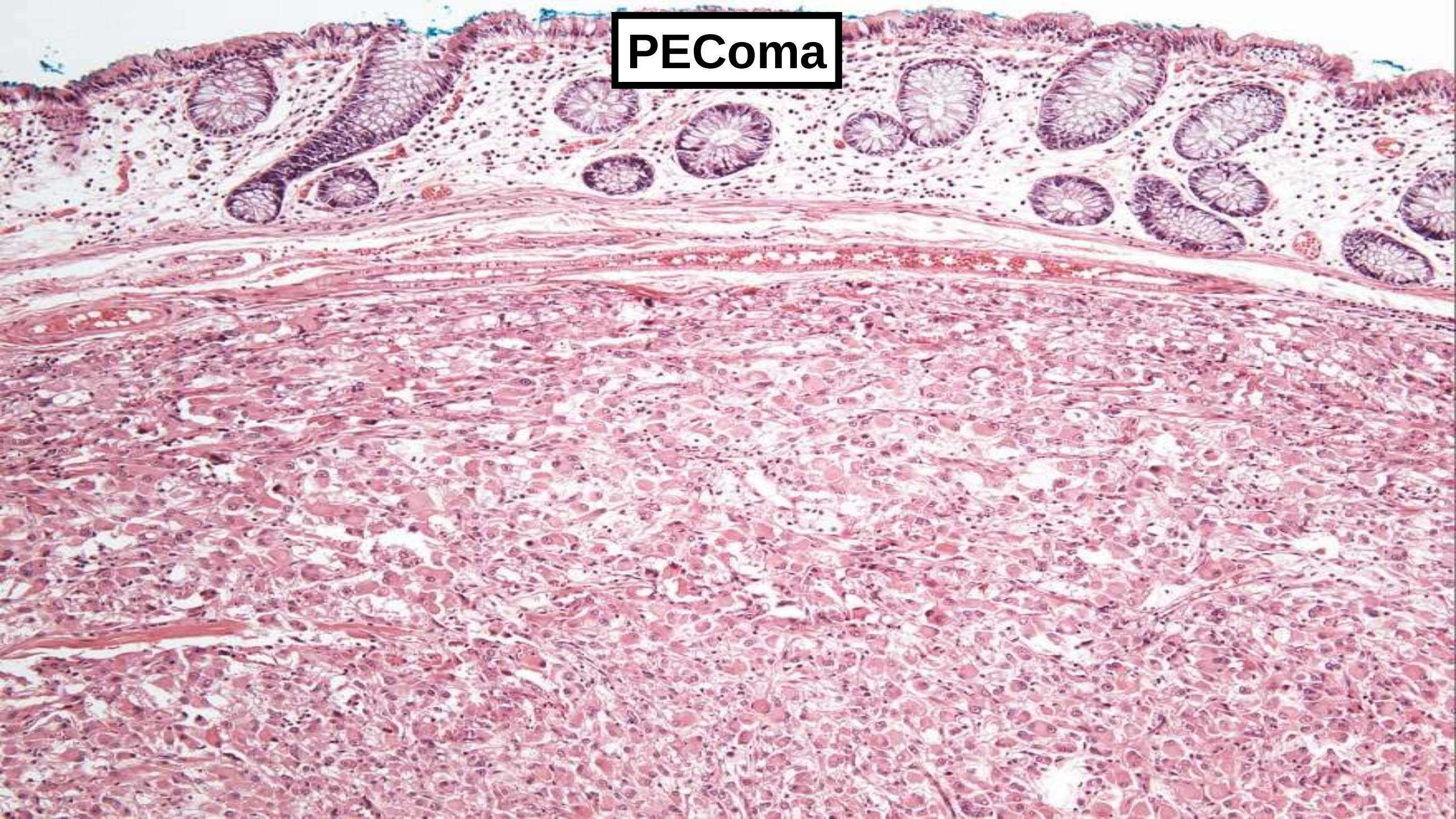
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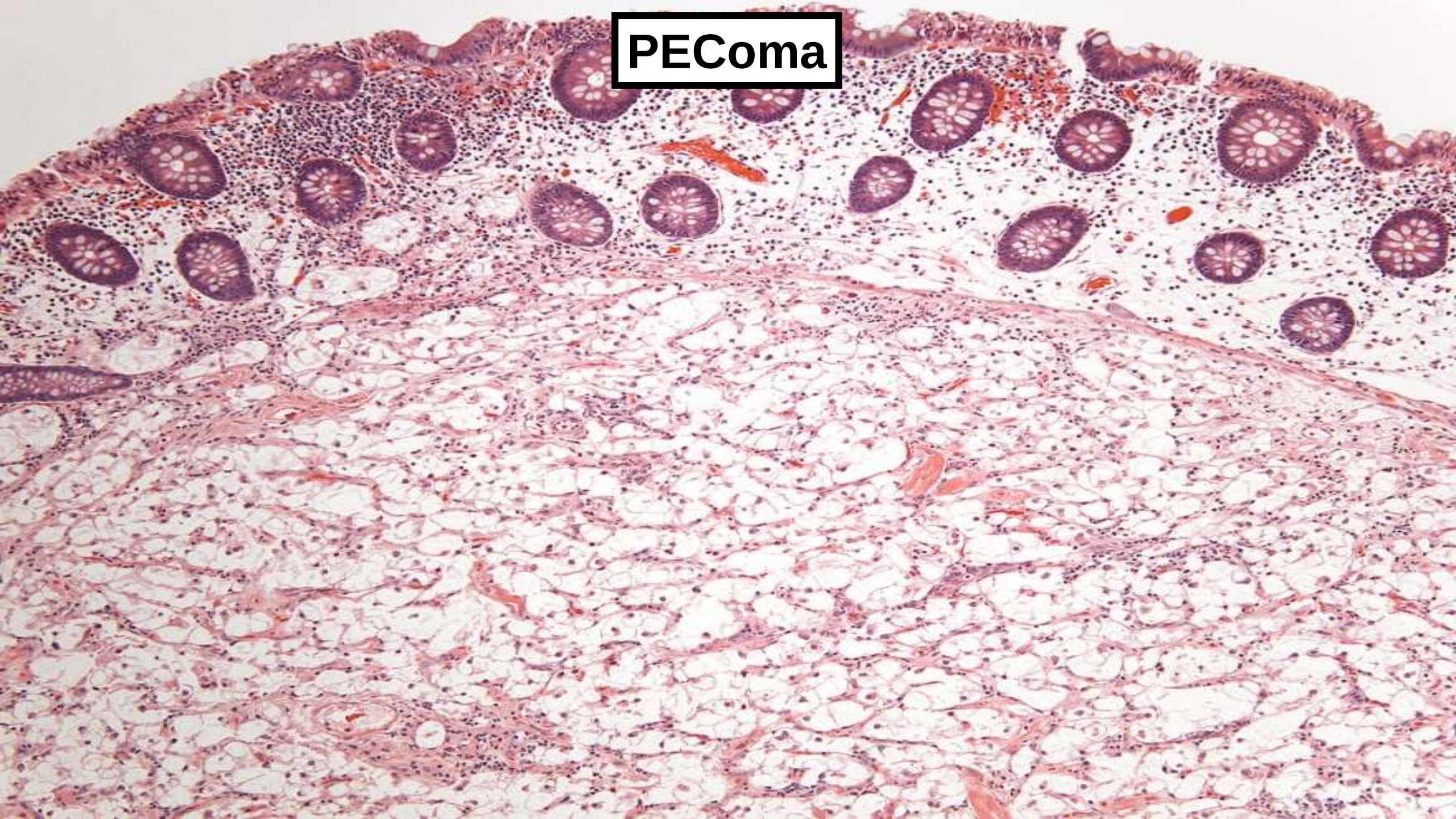
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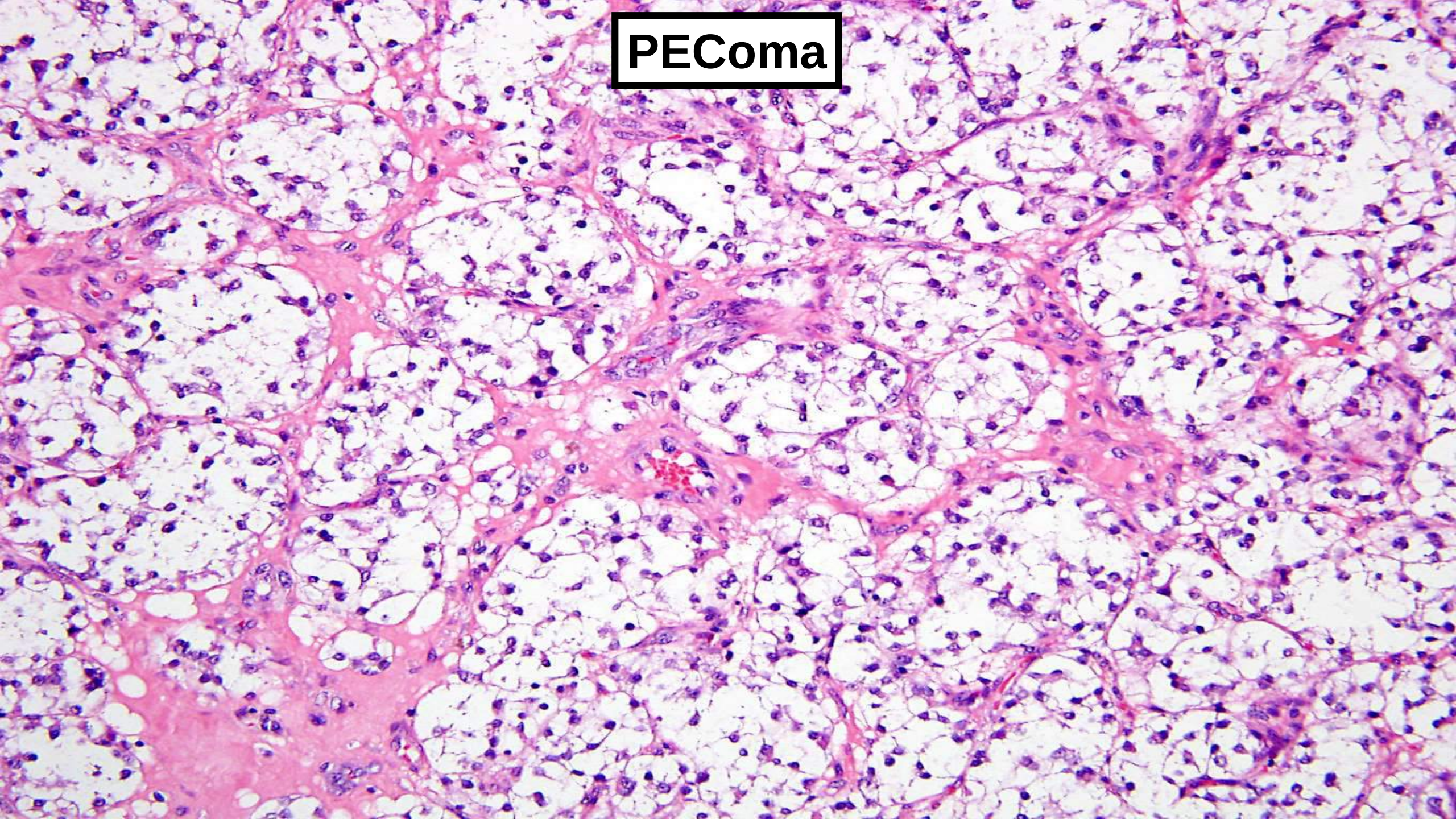
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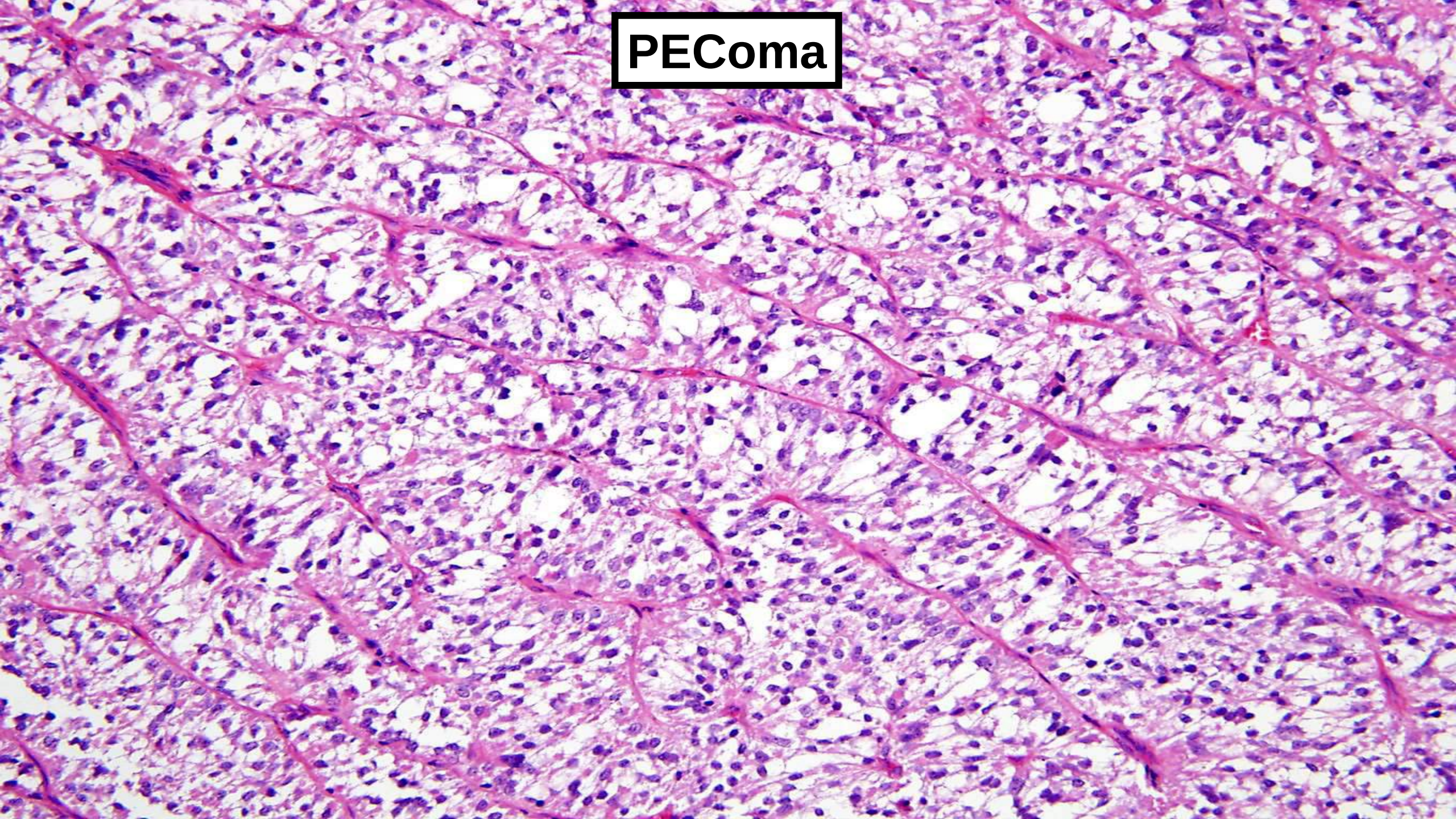
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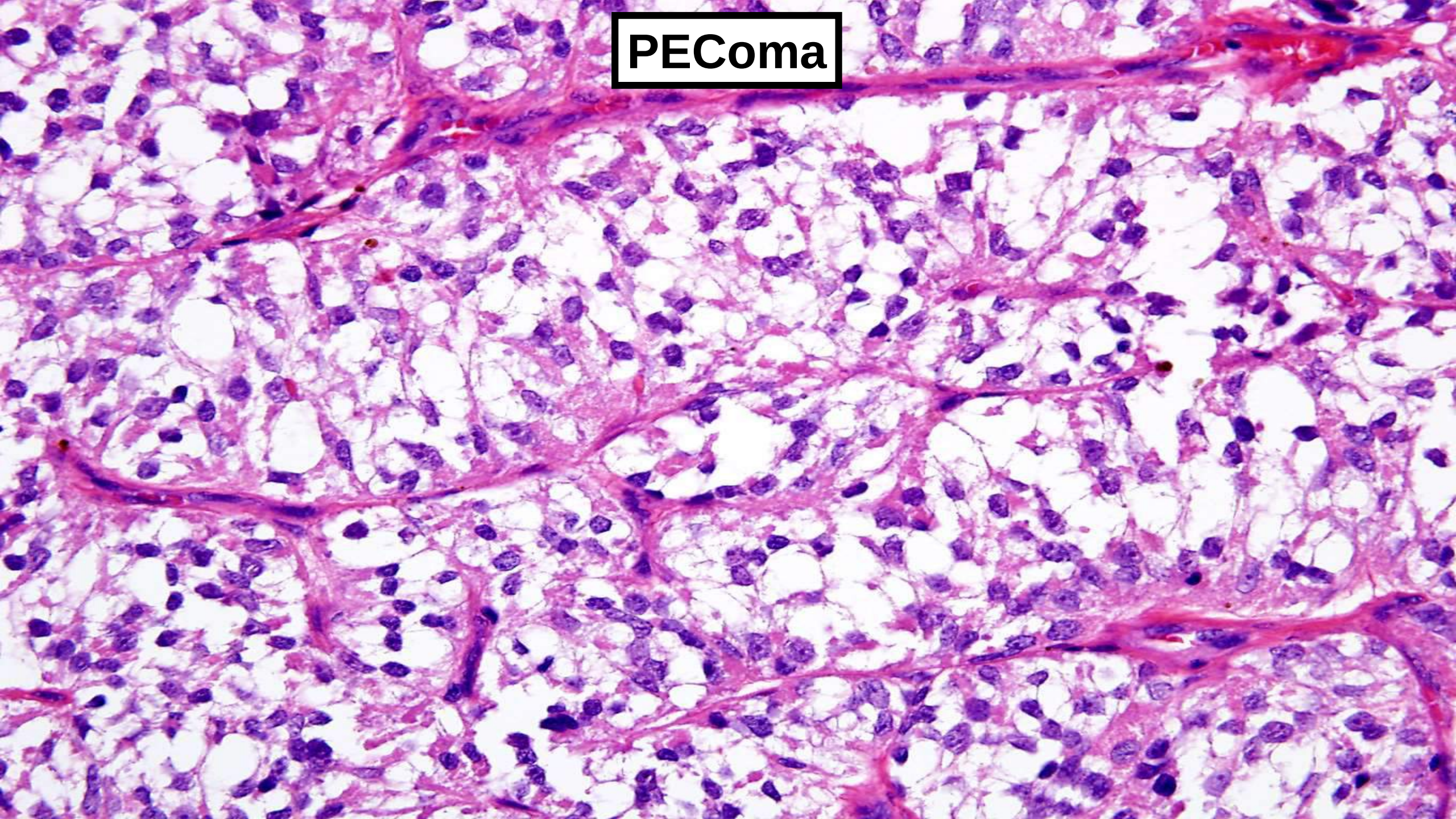
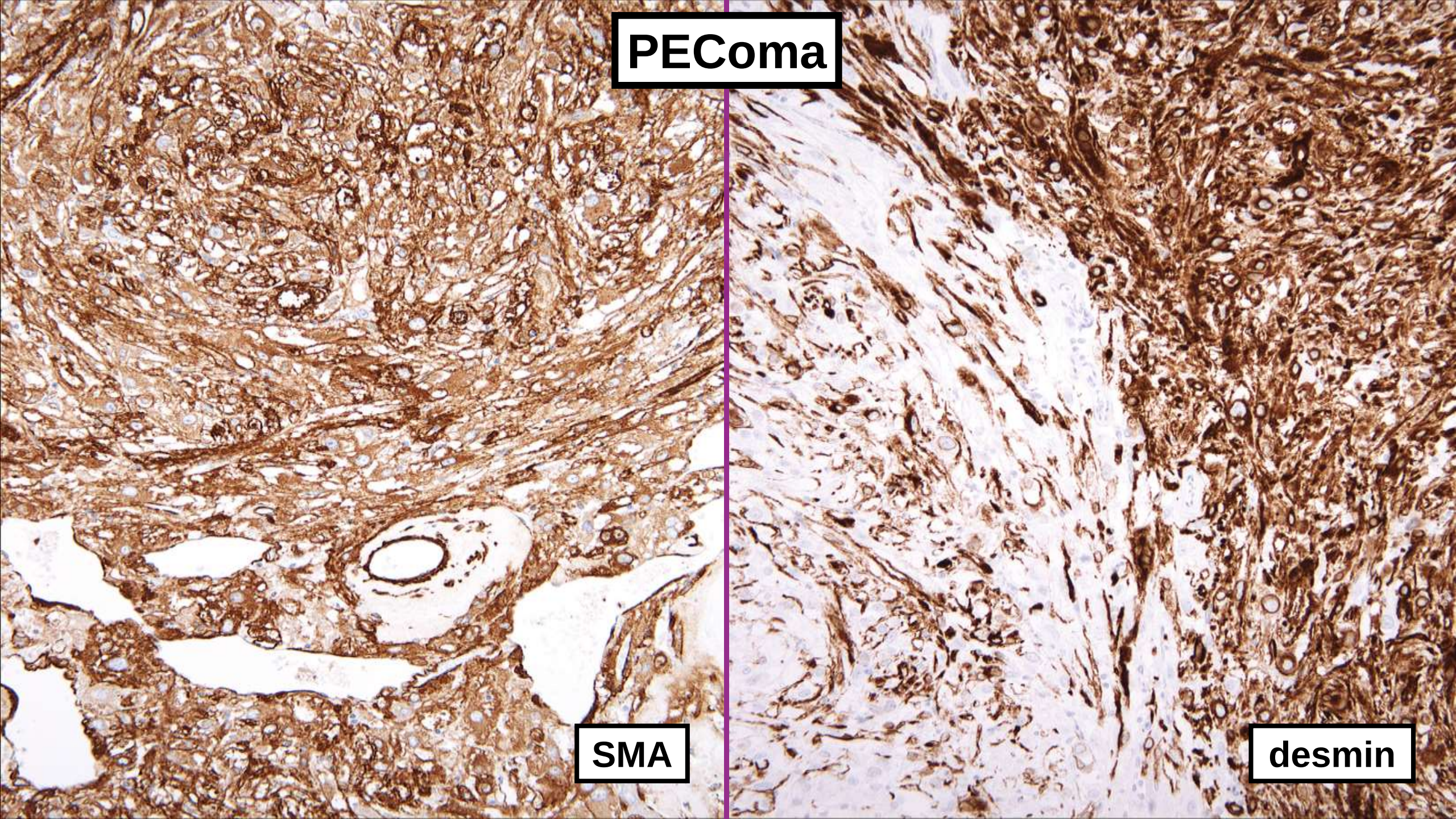
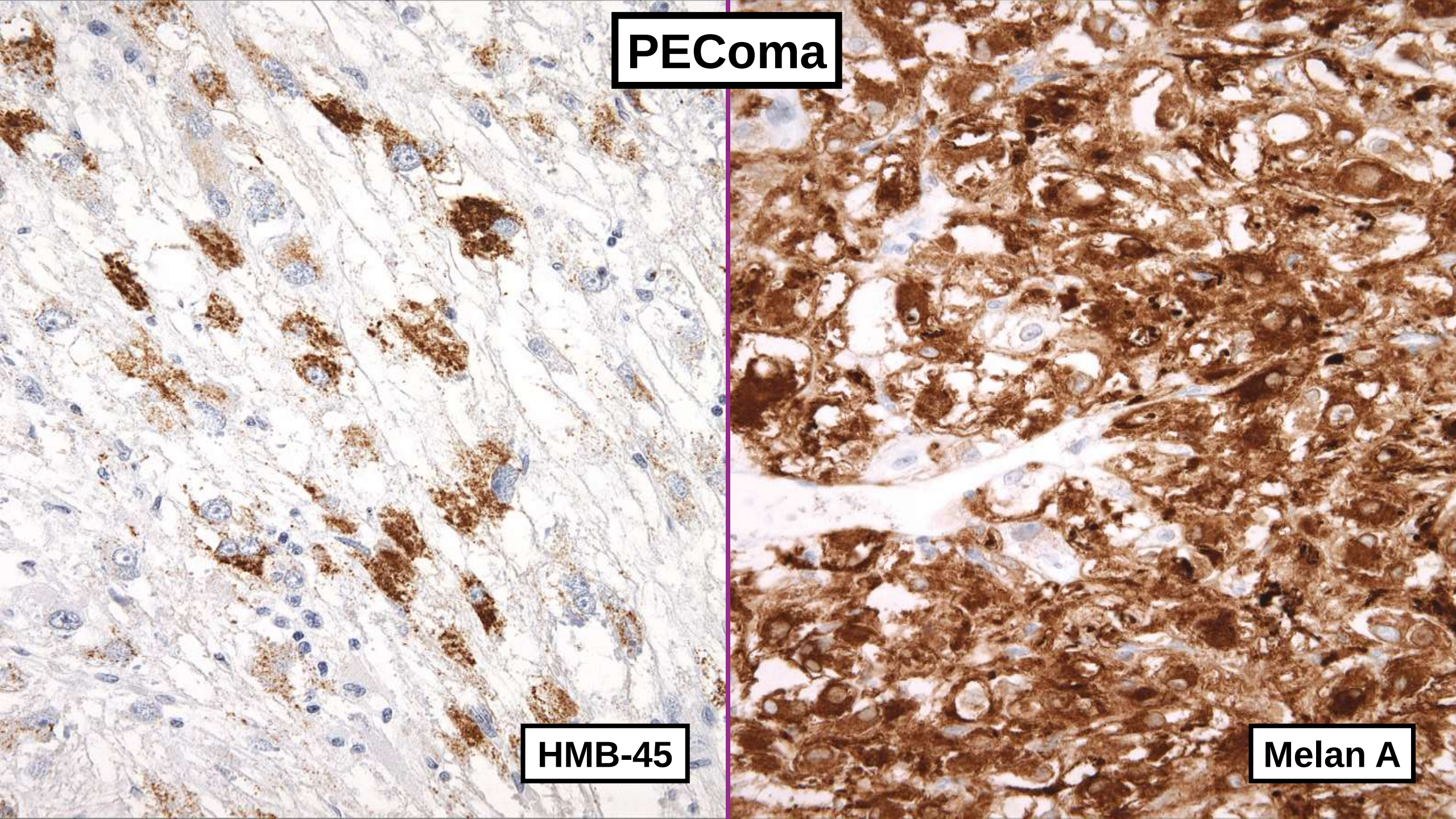

PEComa

PEComa: Immunophenotype

- Mixed melanocytic/myogenic phenotype
- Nearly all HMB-45 positive
- Most positive for MiTF
- SMA most sensitive myogenic marker
- Some lack smooth muscle markers (especially epithelioid/clear cell)
- Focal S100 protein in 10-20%
- TFE3 positive in 10-15%


PEComa
SMA
desmin

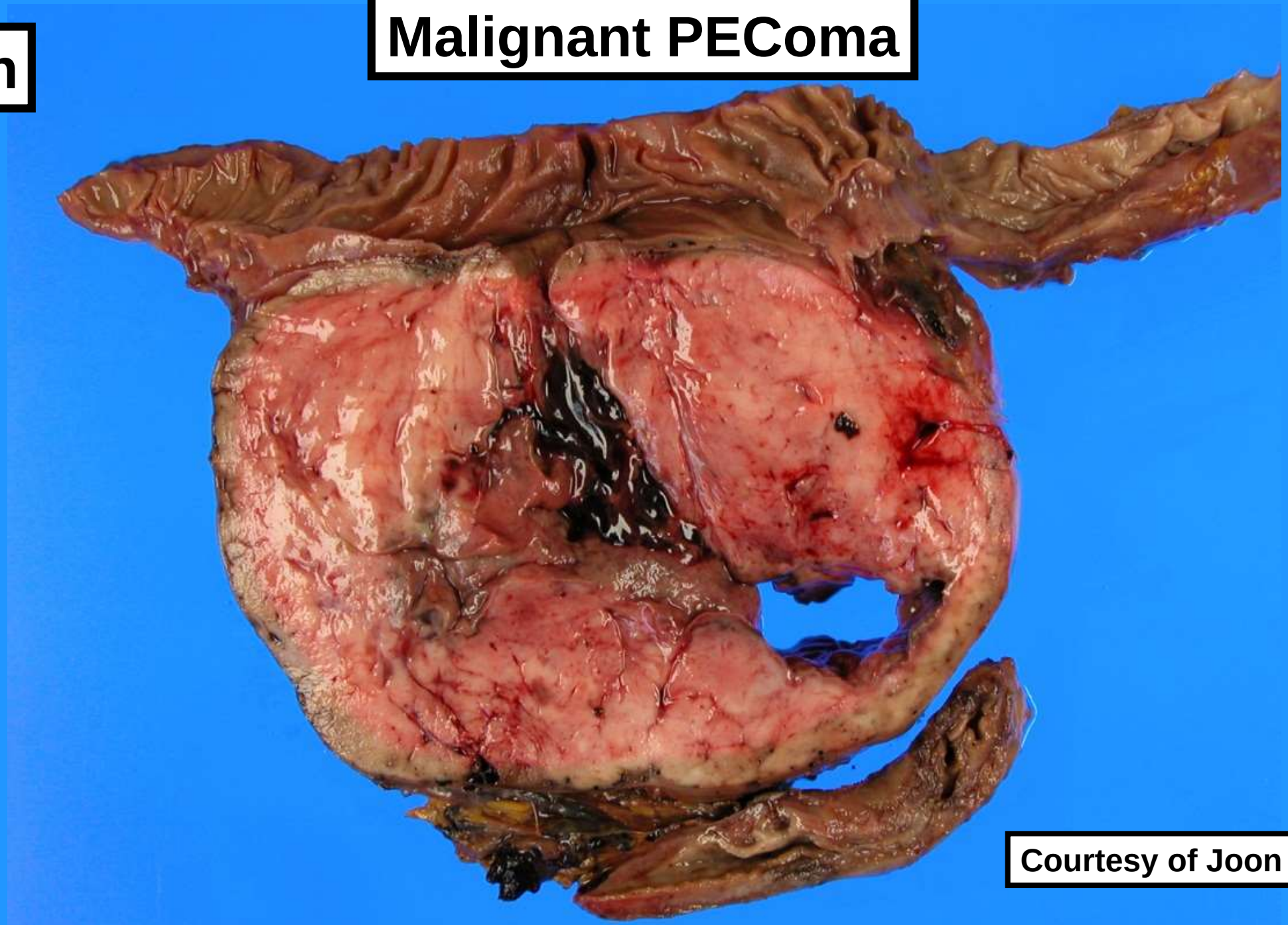

PEComa
HMB-45
Melan A

PEComa:
Criteria for Malignancy

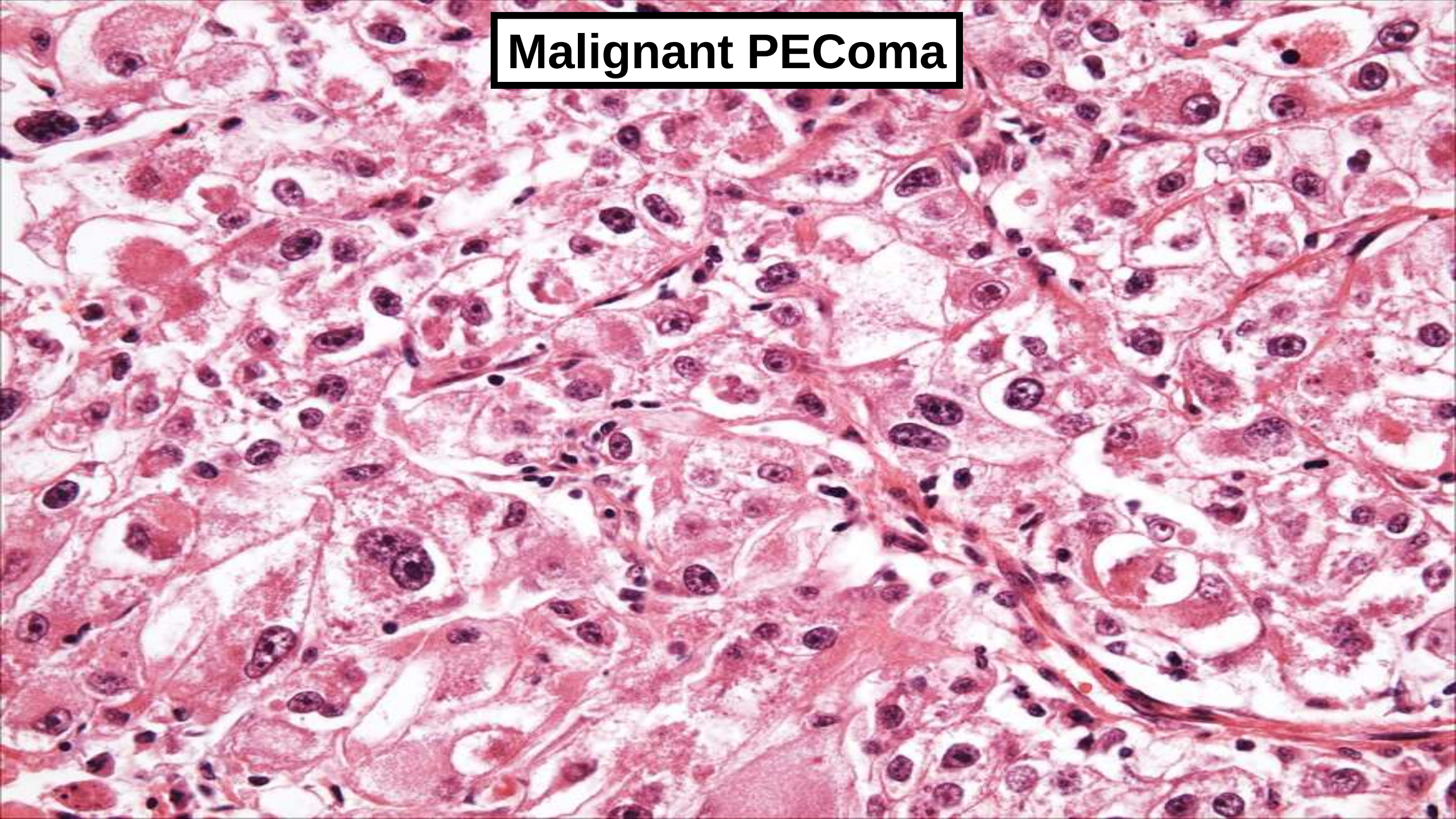
- **Features associated with malignant behavior in GI tract:**
  - **Mitotic activity (≥ 2 per 10 HPF)**
  - **Marked nuclear atypia**
  - **Diffuse pleomorphism**

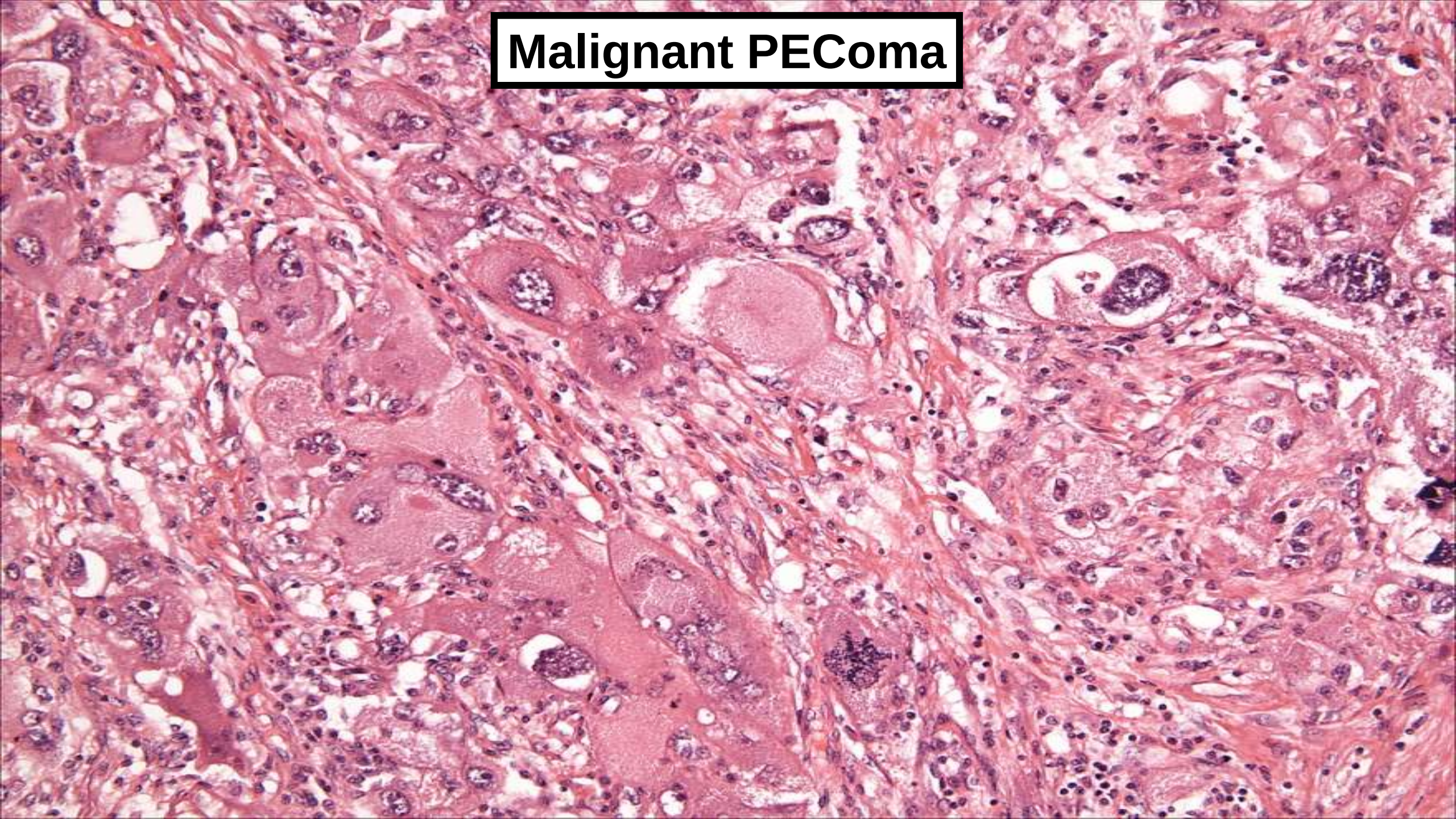
Colon

Malignant PEComa



Courtesy of Joon Choi, MD


Malignant PEComa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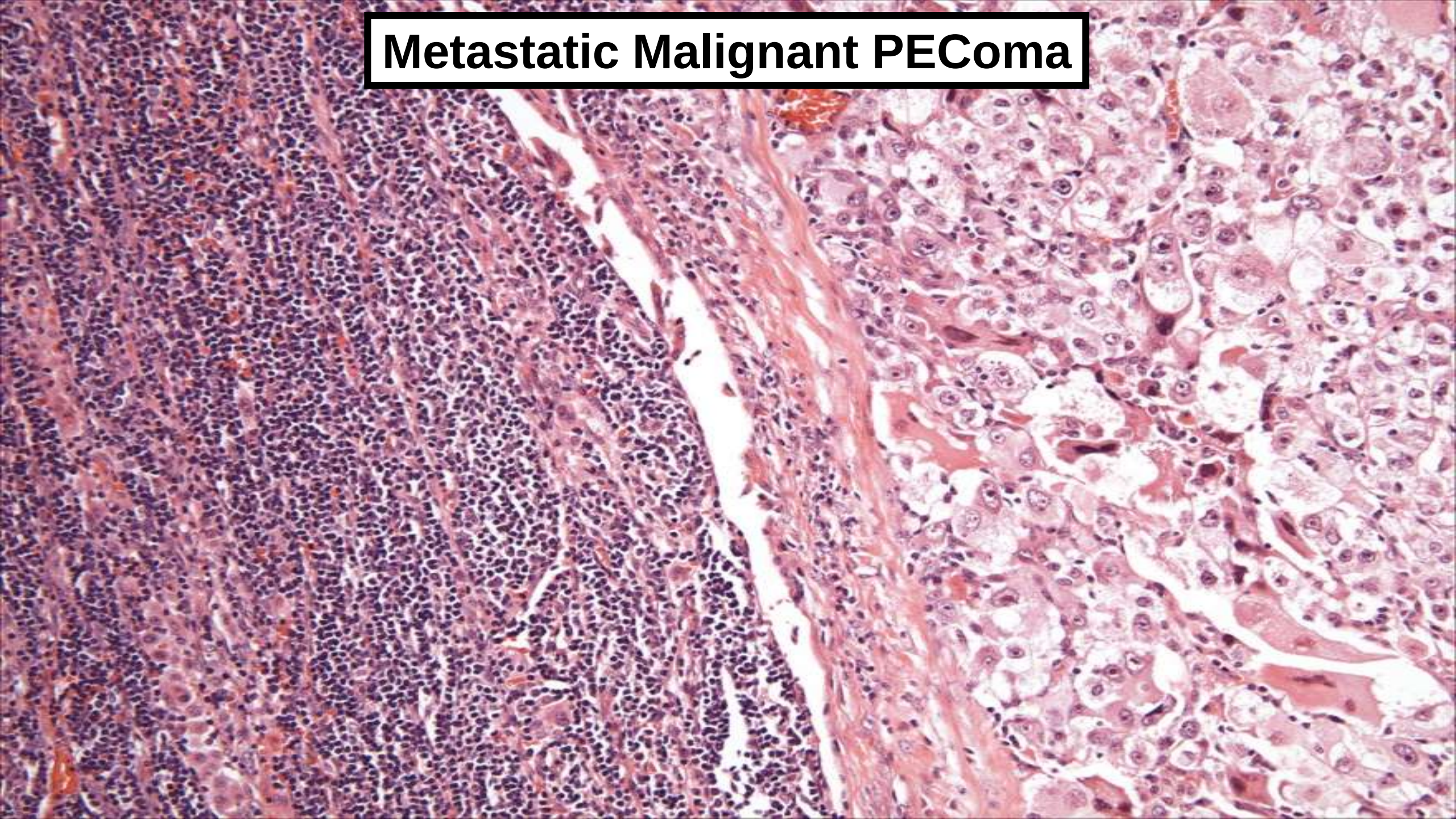
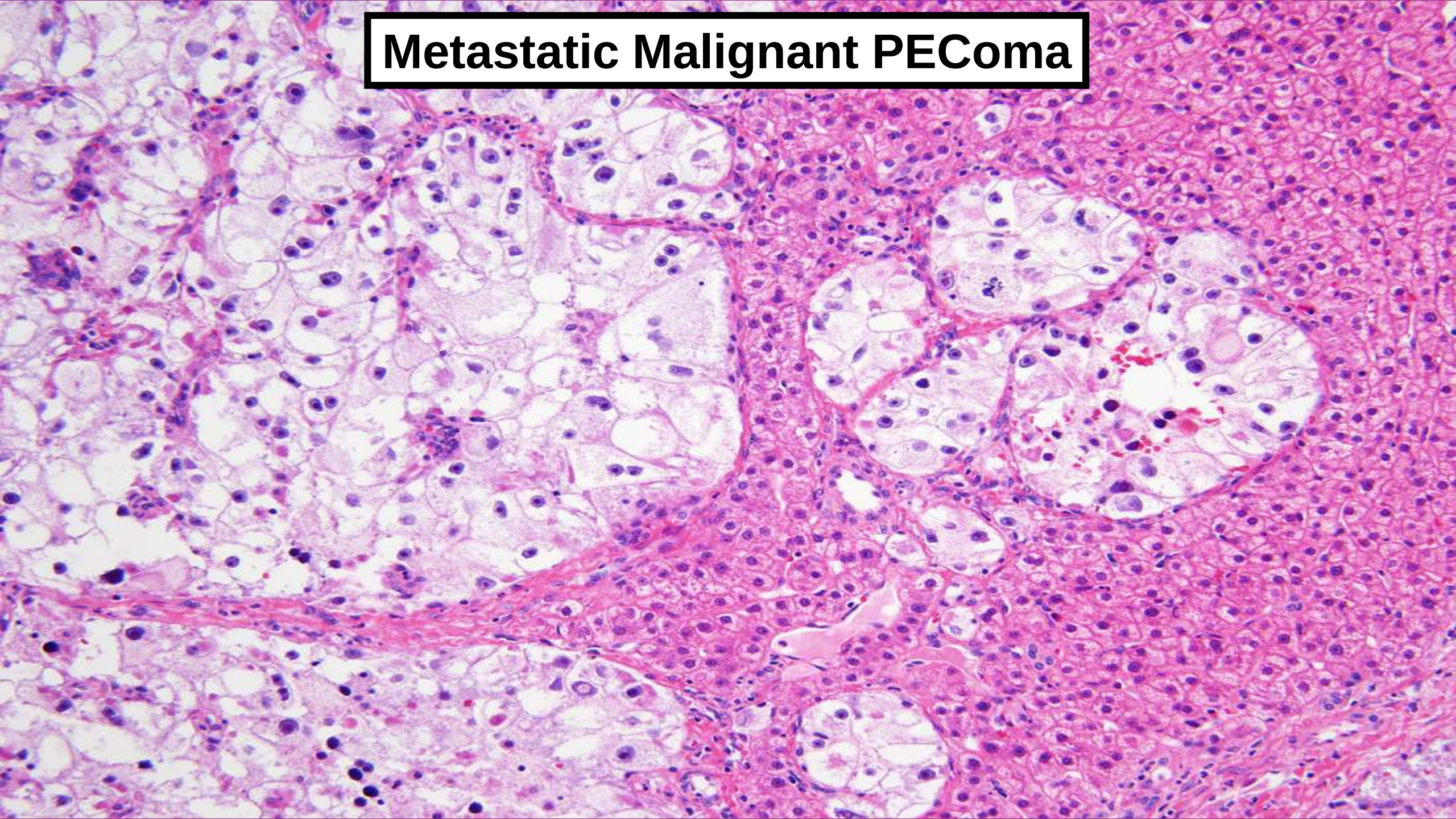
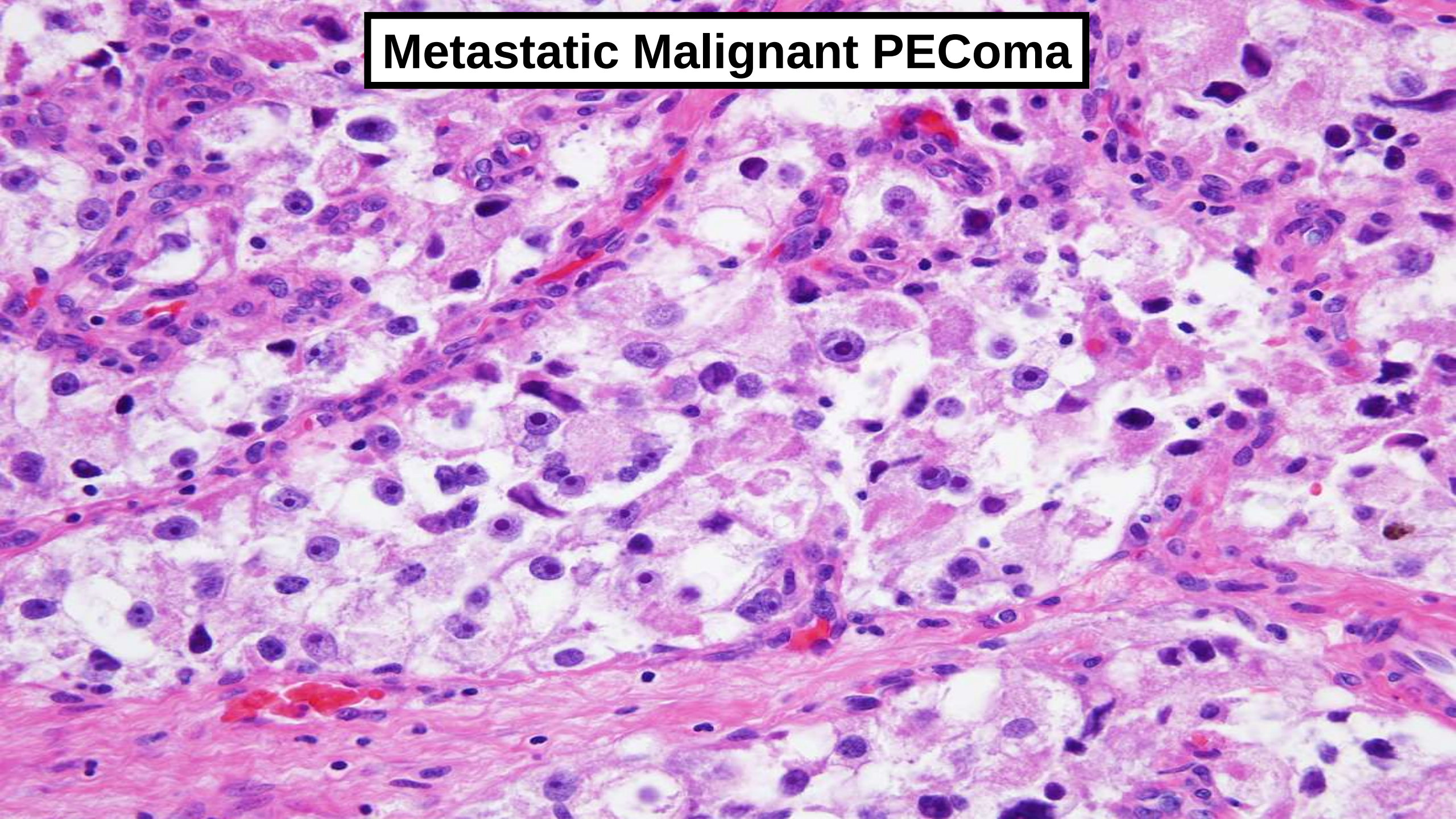

Metastatic Malignant PEComa


Metastatic Malignant PEComa


Metastatic Malignant PEComa

PEComa:
Molecular Findings

- Frequent deletions of *TSC2* at 16p13
- Activation of mTOR (mammalian target of rapamycin) signaling pathway
- Therapeutic implications for patients with clinically aggressive PEComas
- mTOR inhibitors
- Small subset with *TFE3* rearrangement

Dichotomy of Genetic Abnormalities in PEComas With Therapeutic Implications

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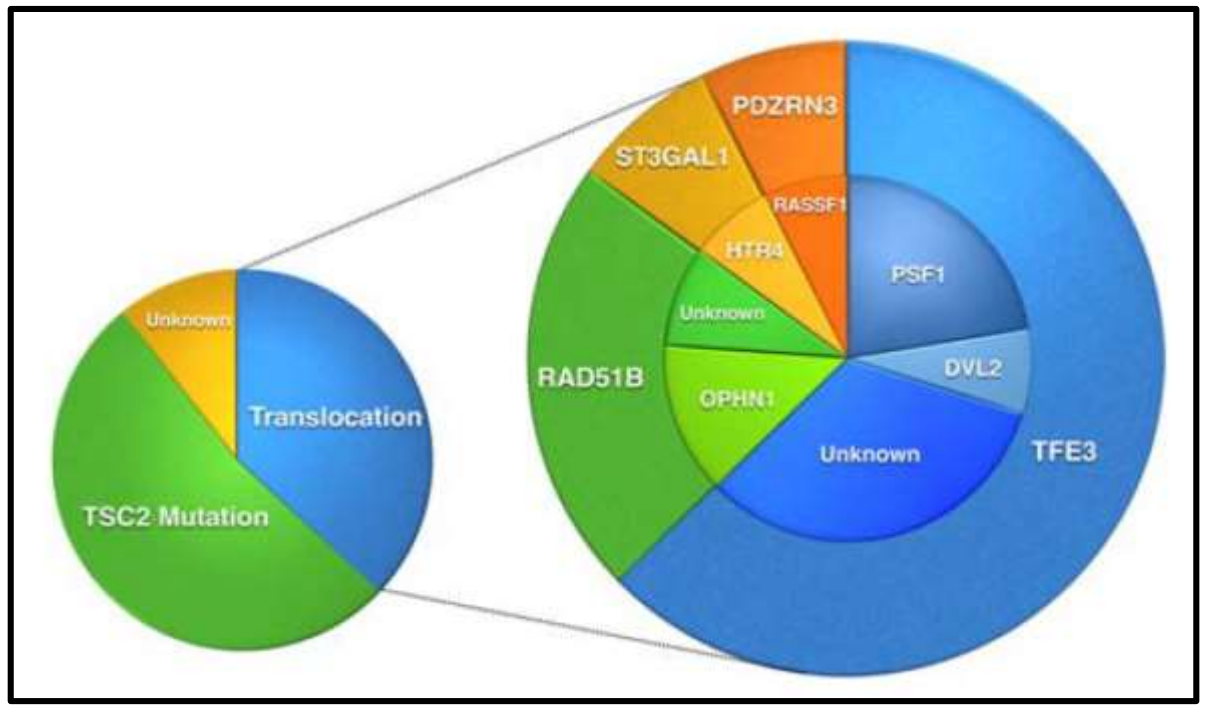
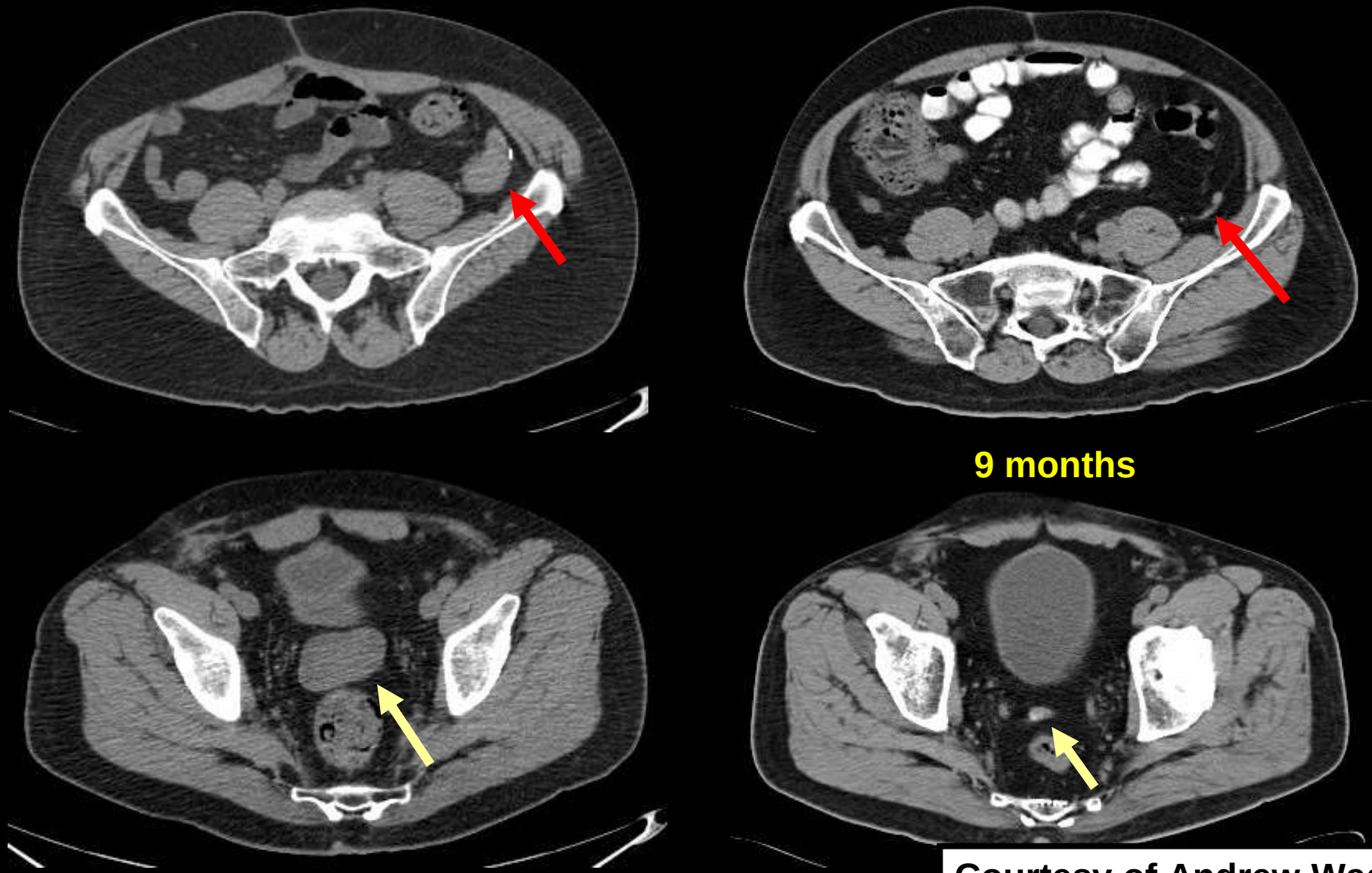


Malignant PEComa treated with sirolimus



9 months

Courtesy of Andrew Wagner, MD, PhD

Practice points

- Not all GI mesenchymal tumors are GIST
- Critical distinctions owing to marked differences in behavior and treatment
- After first considering GIST, ask yourself if there are any distinctive histologic features that might suggest an alternative diagnosis
- Order IHC based on differential diagnosis

THANK YOU