Rabdomiosarcoma en Pediatría

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UPMC LIFE CHANGING MEDICINE

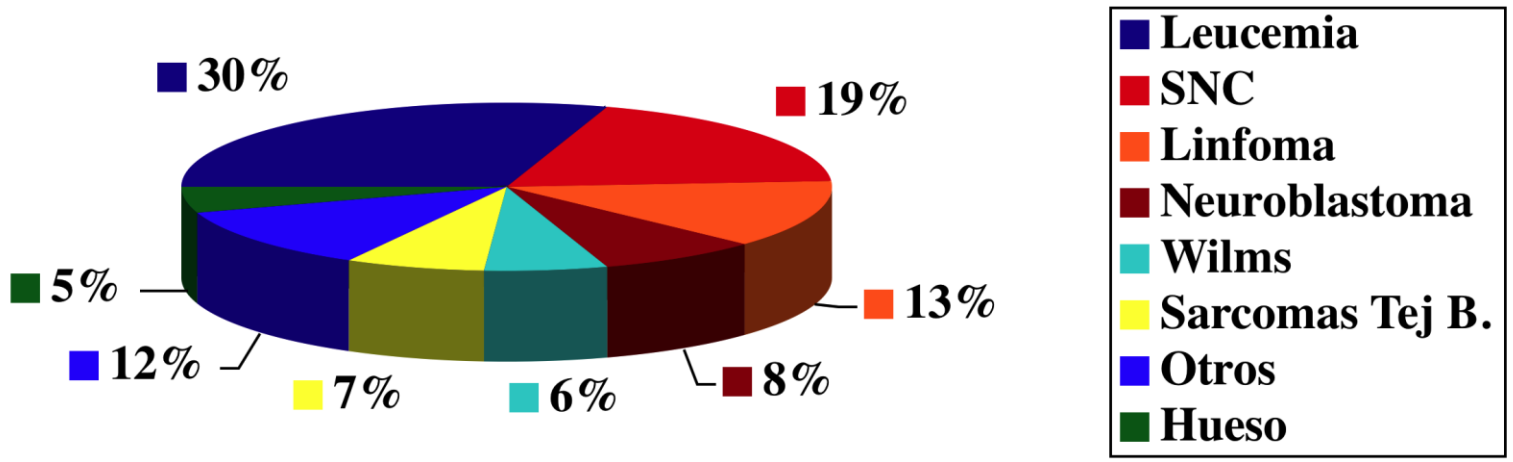
Objetivos

- Conceptos
- Clasificación
- Diagnósticos diferenciales
- Aspectos moleculares

RMS - Conceptos

- Tumor mesenquimático maligno con diferenciación musculoesquelética.
- Es el sarcoma de partes blandas más común en pacientes pediátricos (4.5 por 1 millón en menores de 20 años).
- Segundo tumor sólido maligno extracranial en frecuencia en pacientes pediátricos, luego del neuroblastoma.

Cáncer en Pacientes Pediátricos



RMS - Clasificación

- Se clasifica actualmente en cuatro subtipos:
  - Embrionario
  - Alveolar
  - Esclerosante/Fusocelular
  - Pleomórfico

Table 1. International classification of rhabdomyosarcoma[a]

Diagnosis	Histology	Incidence (%)[b]	Five-year survival (%)	Prognosis
Embryonal, botryoid	Favorable	6	95	Superior
Embryonal, spindle cell	Favorable	3	88	Superior
Embryonal, not otherwise specified (NOS)	Favorable	49	66	Intermediate
Alveolar, NOS or solid variant	Unfavorable	31	53	Poor
Anaplasia, diffuse	Unfavorable	2	45	Poor
Undifferentiated sarcoma	Unfavorable	3	44	Poor

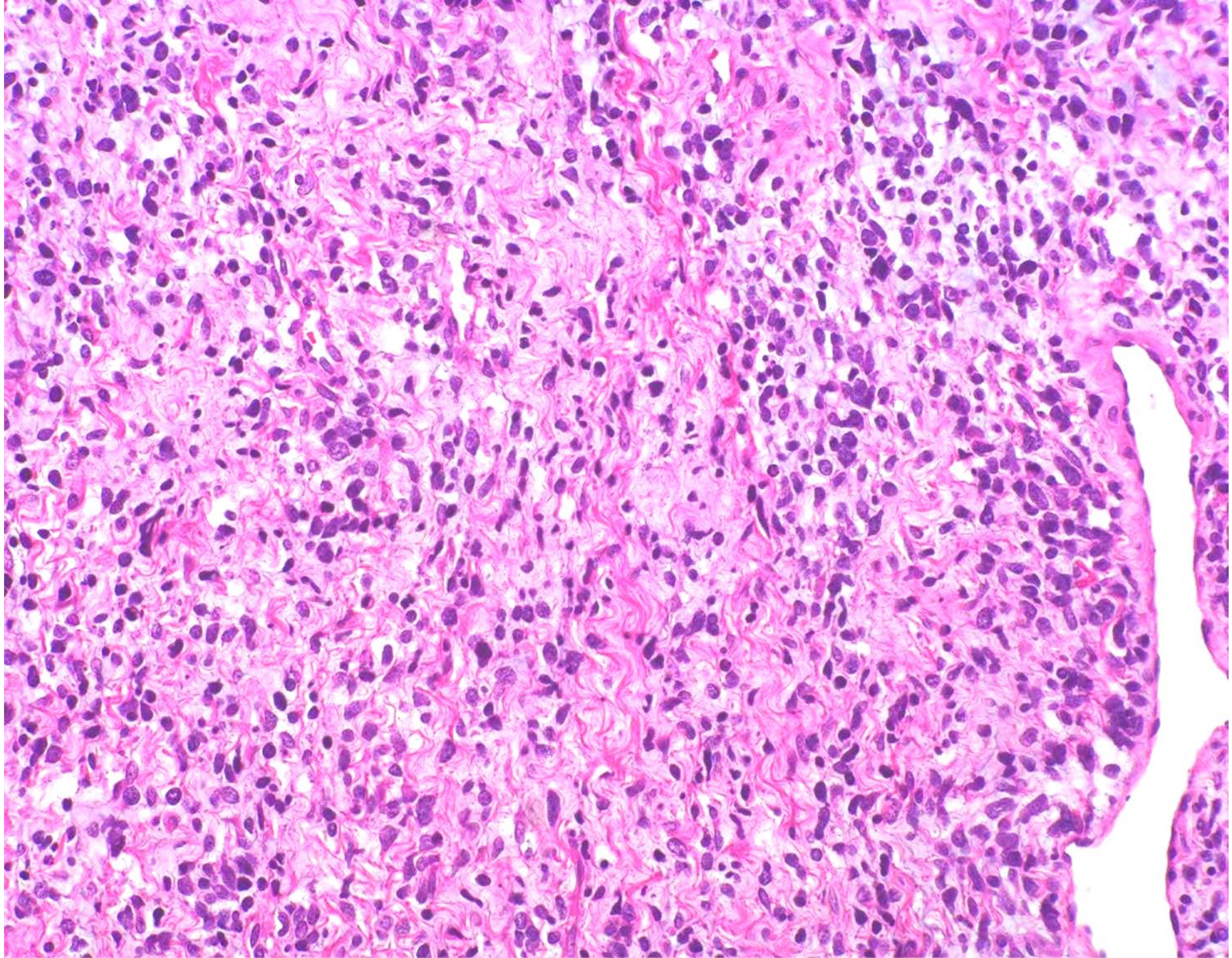
[a]With the addition of IRSG-defined anaplastic variant.

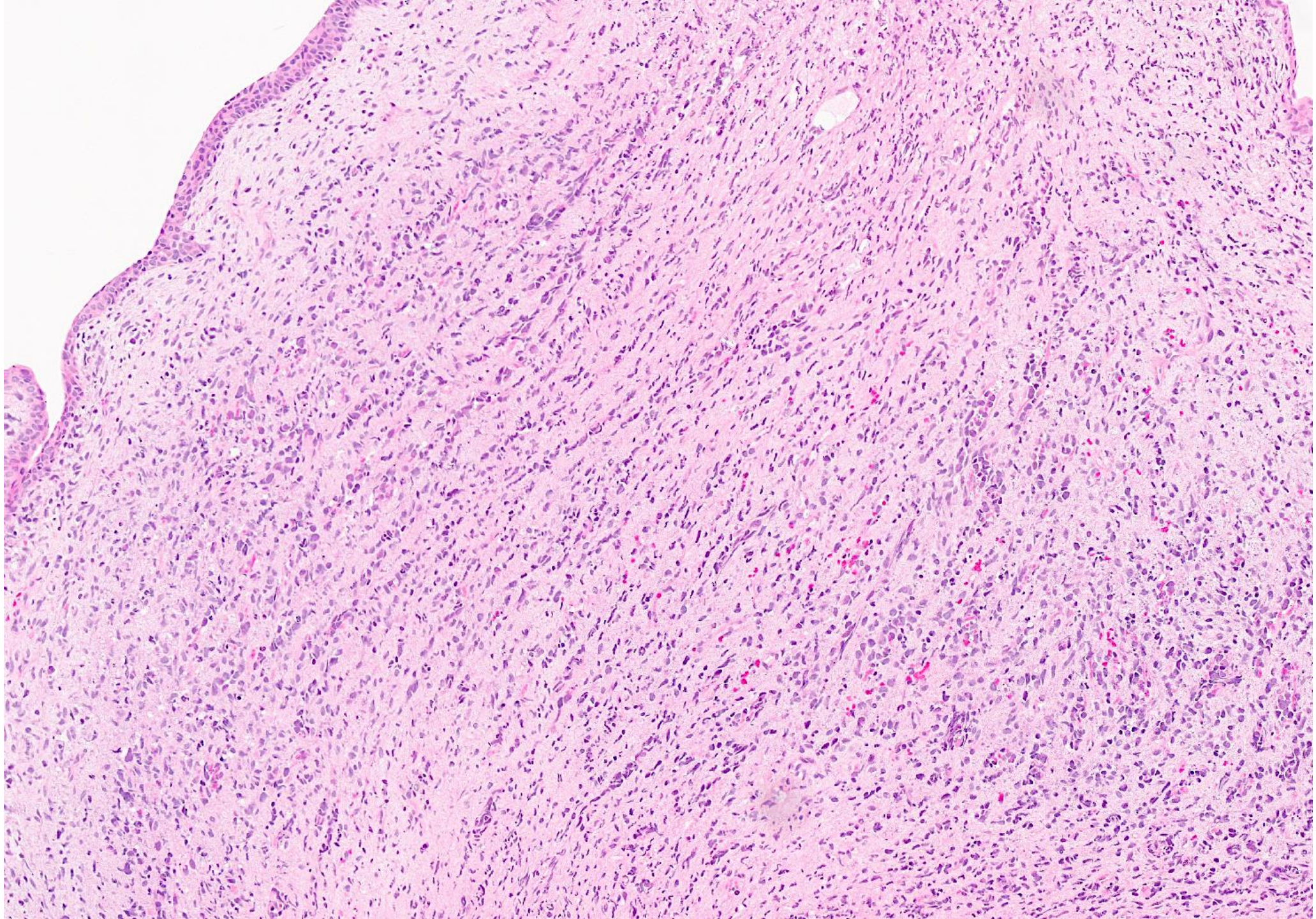
[b]Total incidence is only 94%; some 6% of accepted cases fall into the sarcoma NOS category because of insufficient or inadequate tissue to make a more specific diagnosis.

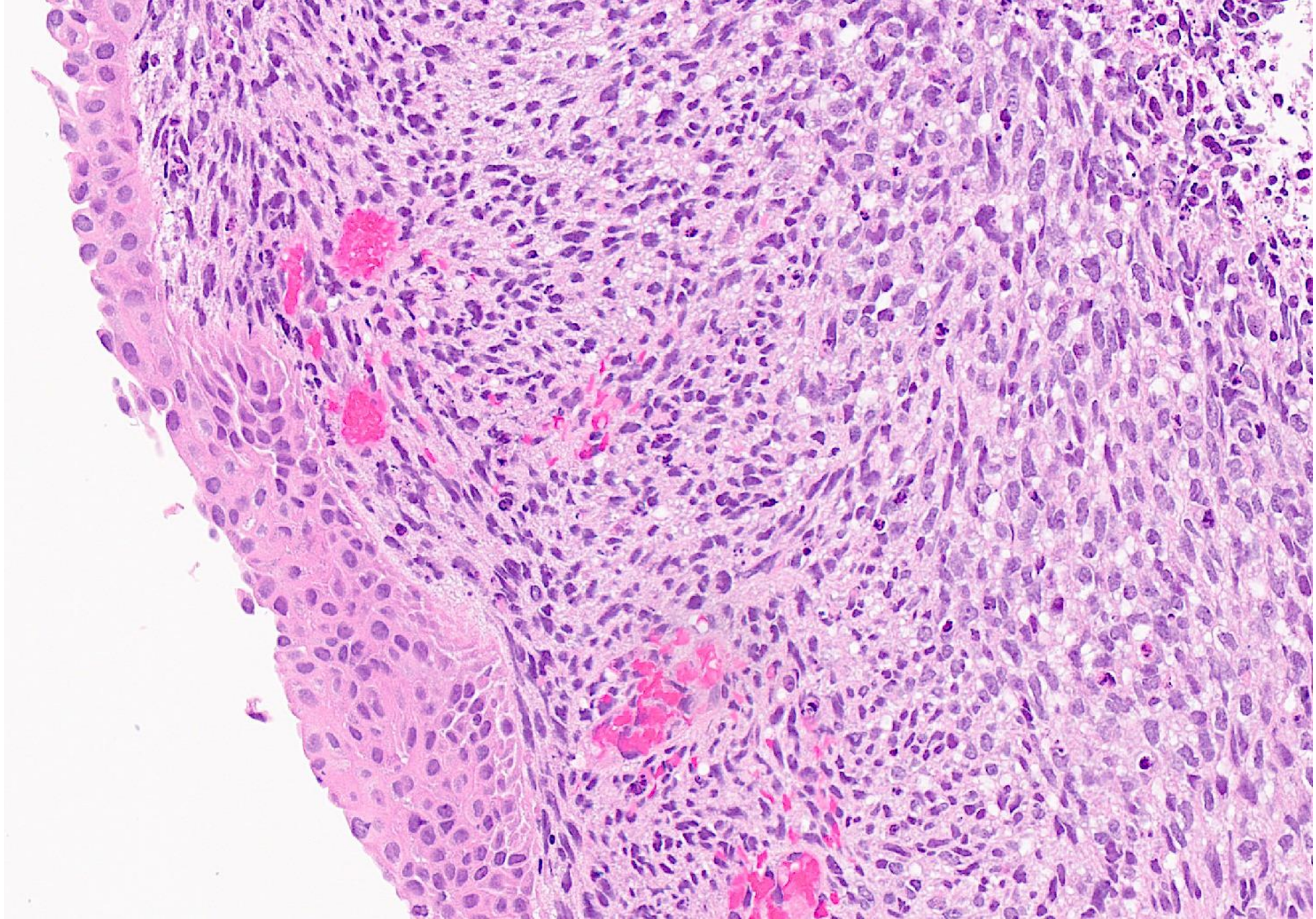
Qualman et al., 1998

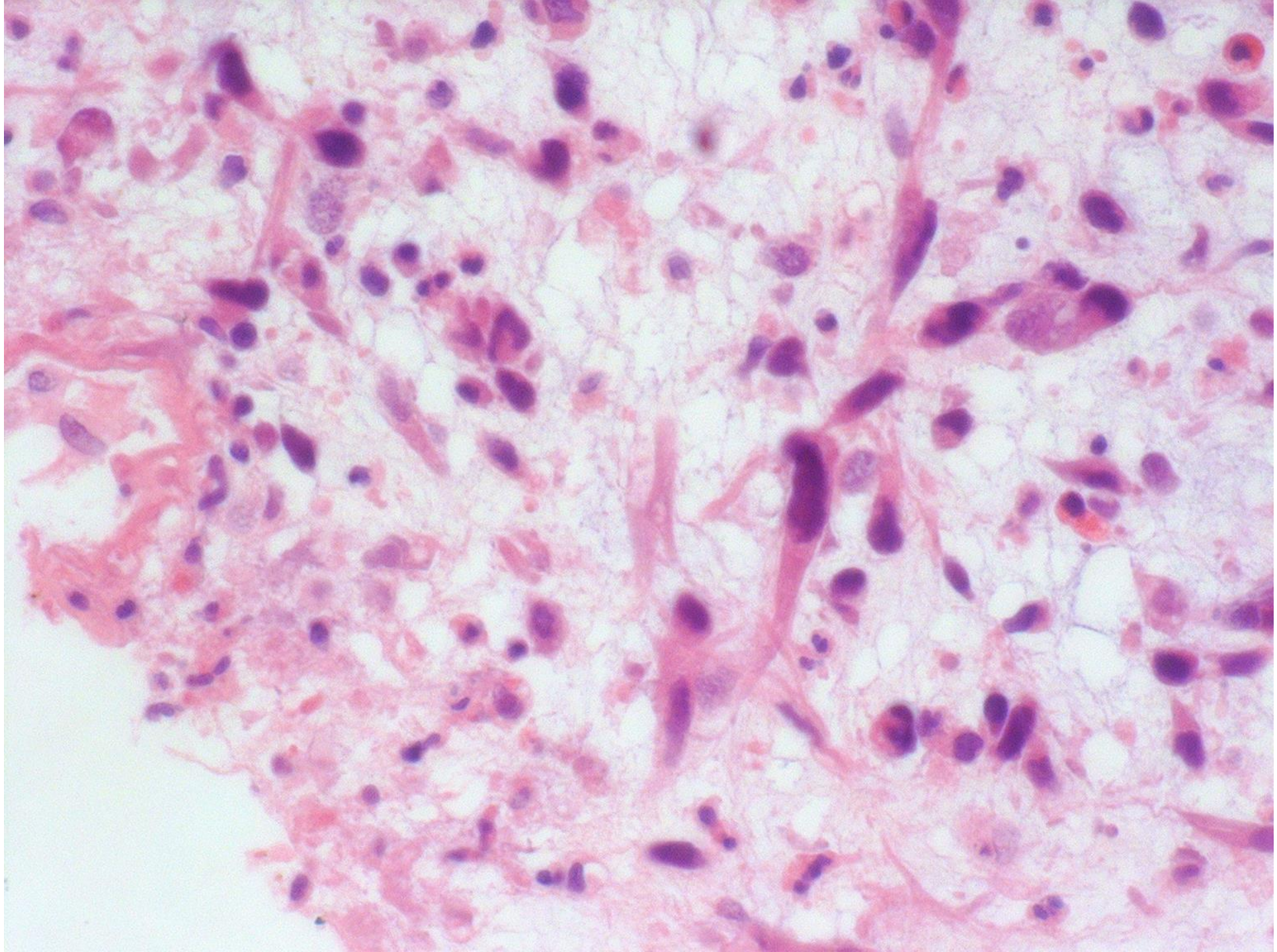
RMS Embrionario (ERMS)

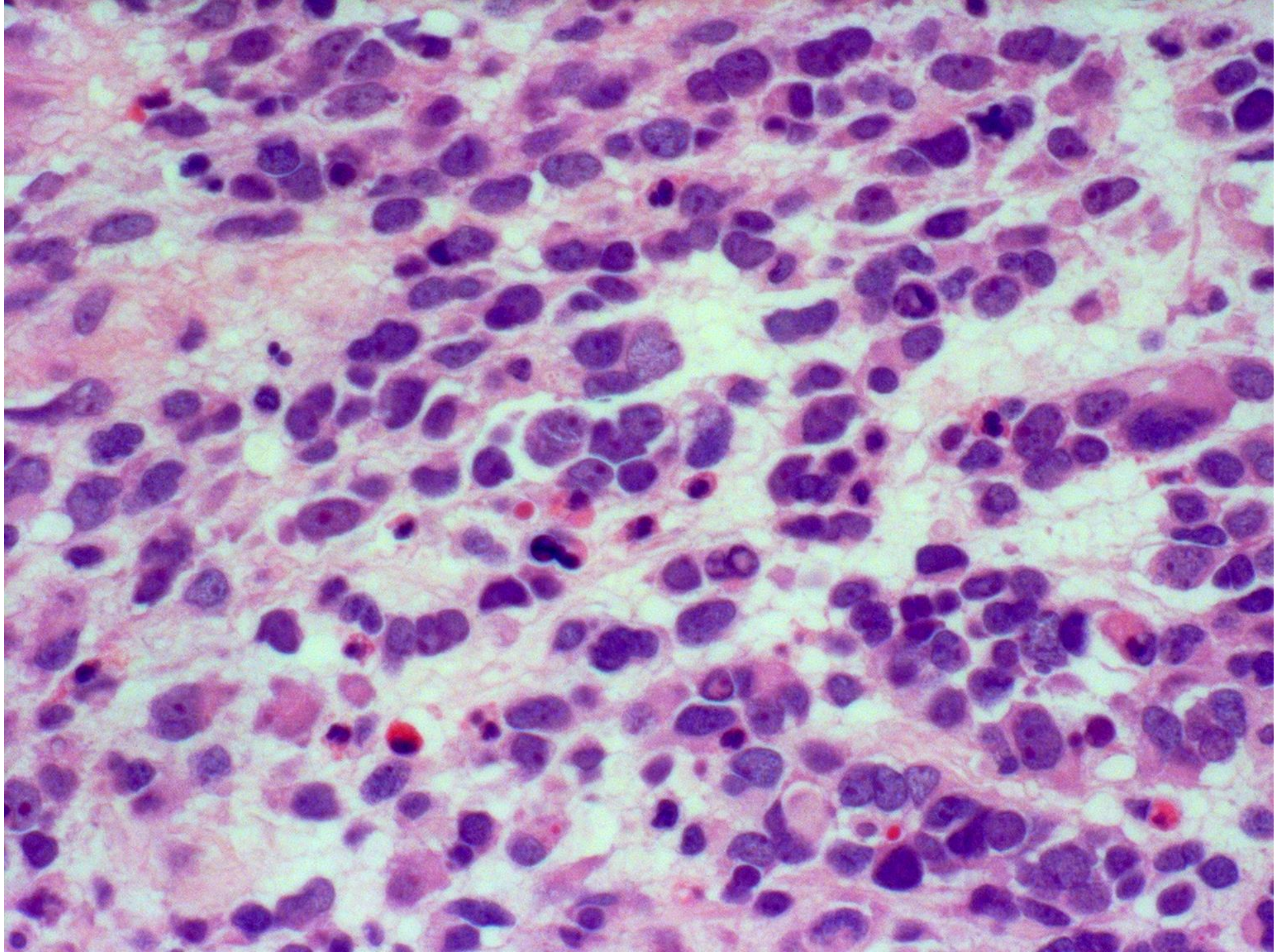
- 49% de RMS; más frecuente en <10 años
  - Cabeza y cuello, en particular órbita y para-meninges (~50%)
  - Tracto genitourinario (~50%)
  - Tejidos blandos profundos de extremidades, tracto biliar, pelvis y retroperitoneo (poco frecuentes)
- Variantes:
  - Sarcoma botrioides
  - Patrón denso
  - Anaplásico

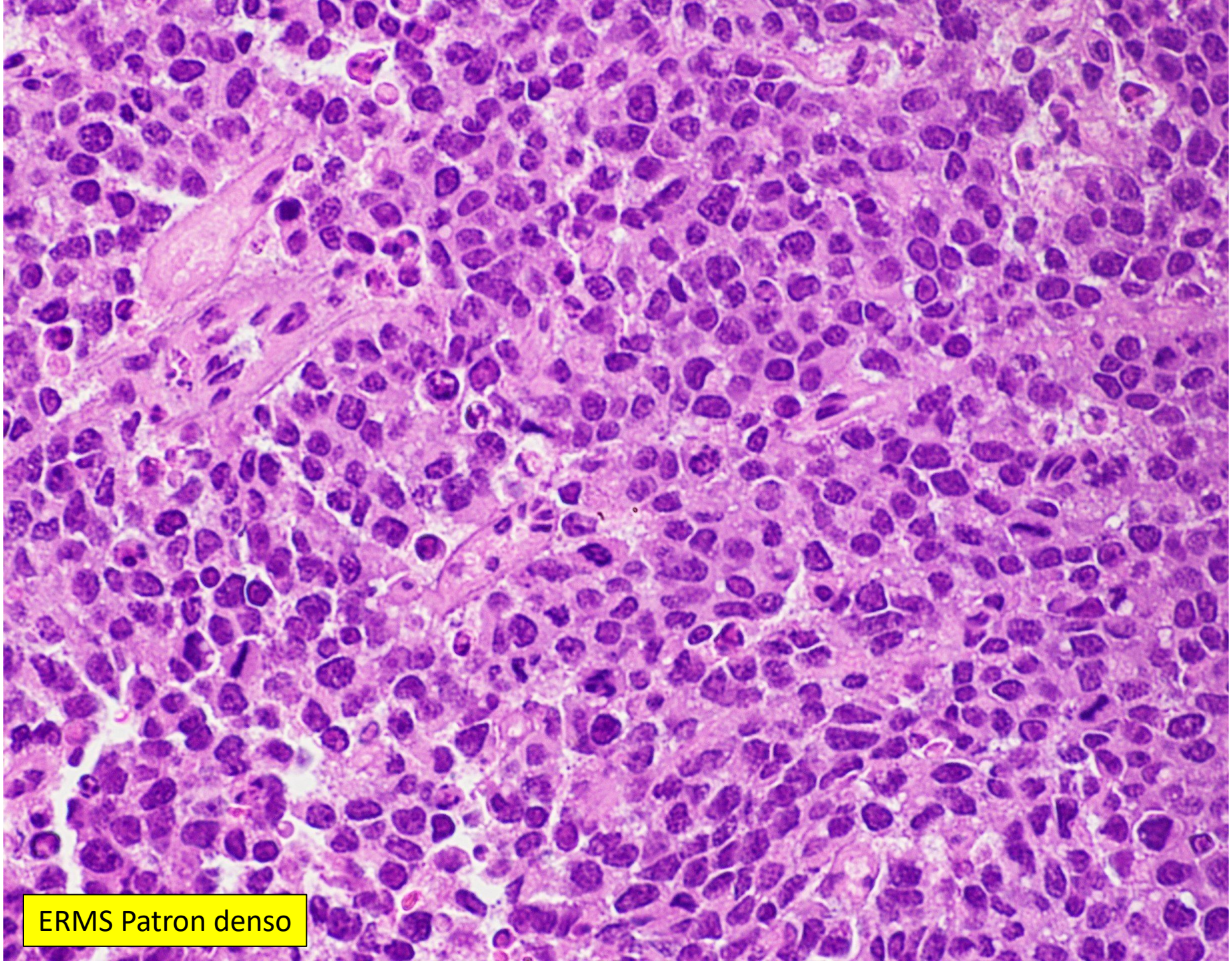


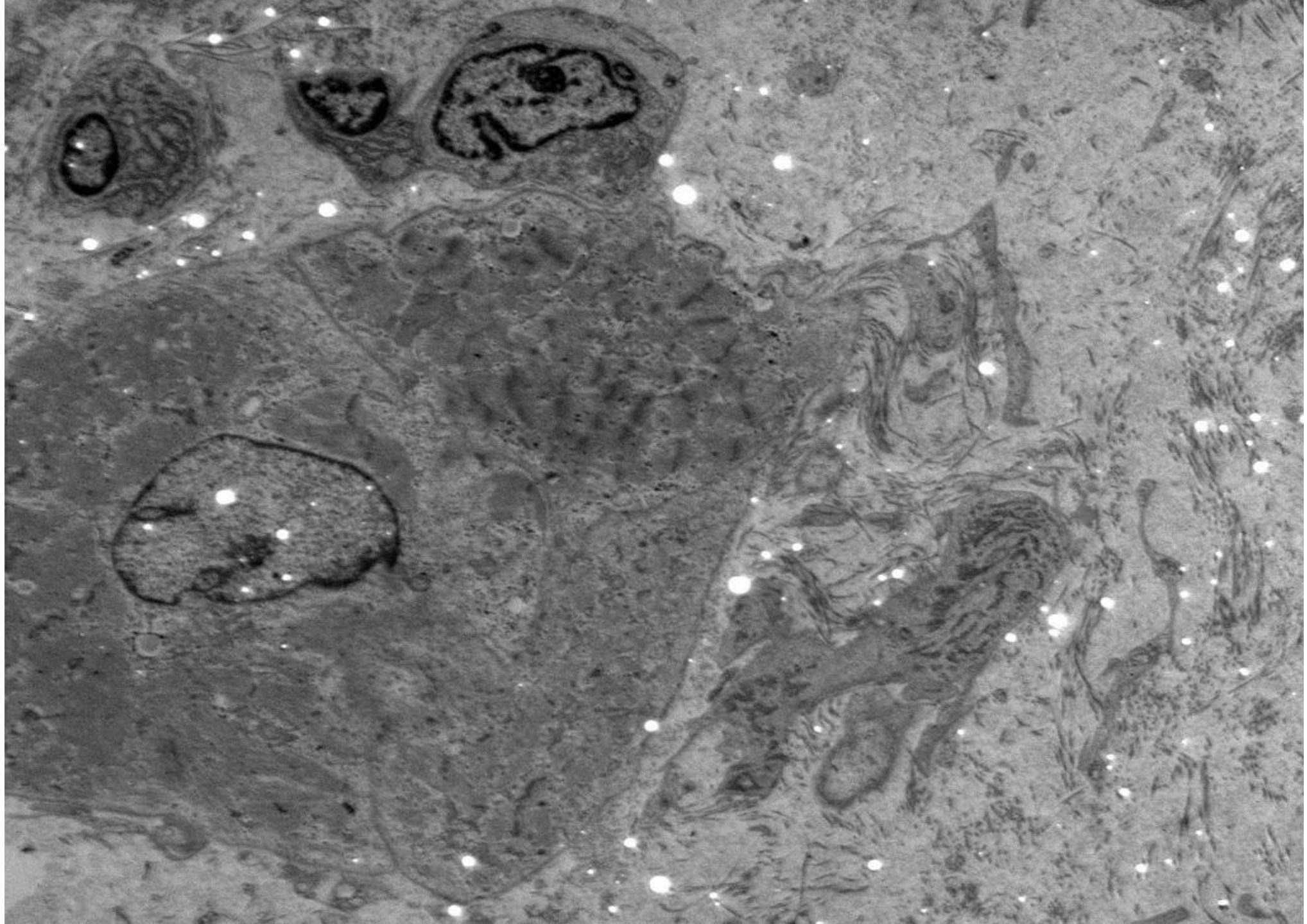


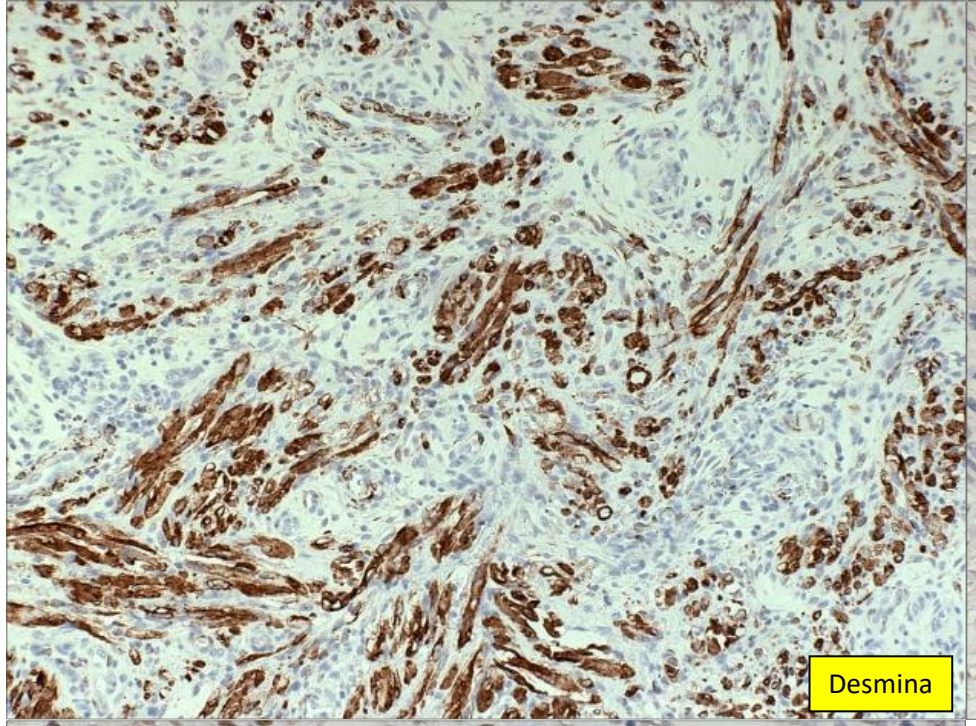


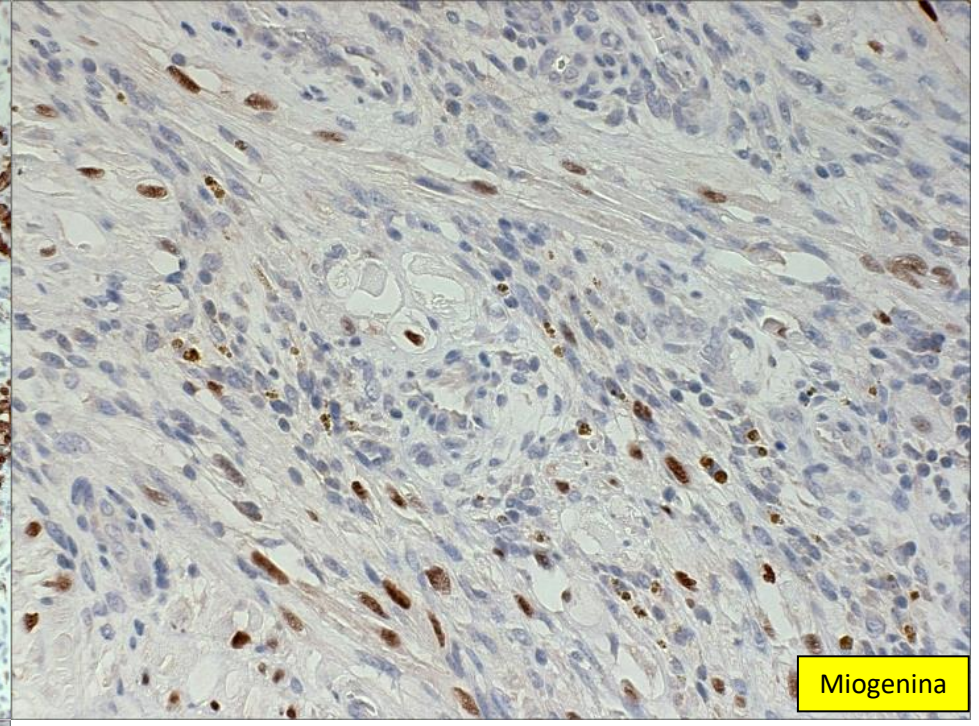


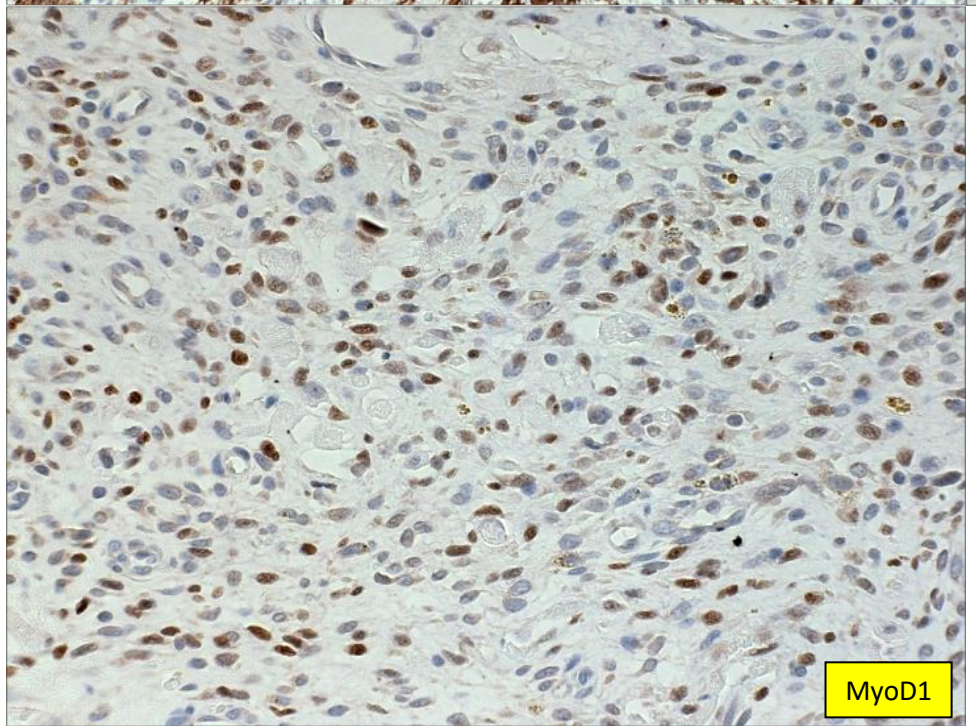



ERMS Patron denso

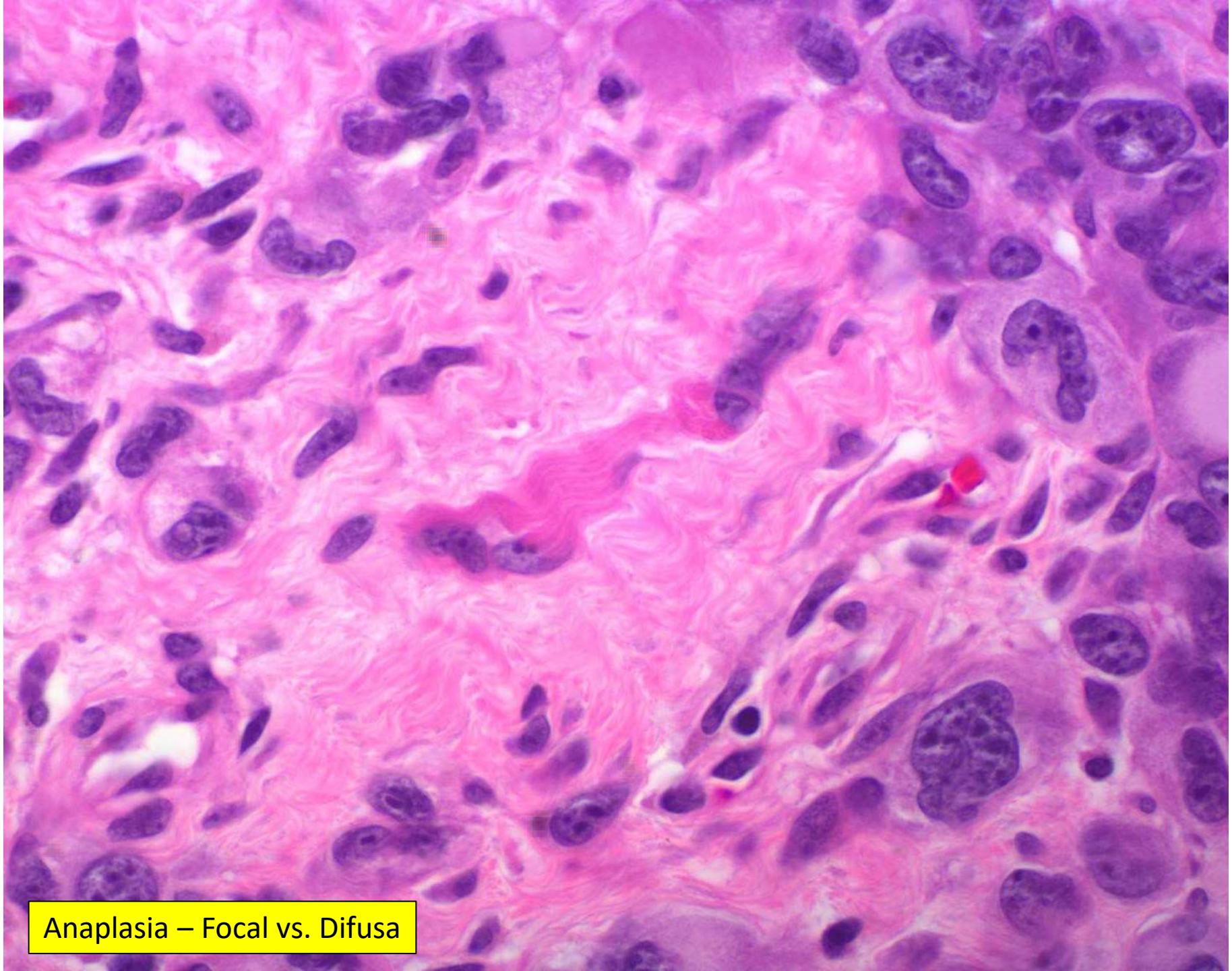








Marcadores IHQ más sensitivos y específicos para RMS


Anaplasia – Focal vs. Difusa

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Original Research

The prognostic significance of anaplasia in childhood rhabdomyosarcoma: A report from the Children's Oncology Group

Archana Shenoy [a,*], Elysia Alvarez [b], Yueh-Yun Chi [c], Minjie Li [d], Jack F. Shern [e], Javed Khan [e], Susan M. Hiniker [f], Candace F. Granberg [g], Douglas S. Hawkins [h], David M. Parham [i], Lisa A. Teot [j], Erin R. Rudzinski [h]

- 1648 pacientes diagnosticados con RMS:
  - Mayoria de anaplasia en ERMS 27% (11% ARMS, 11% SRMS)
  - Anaplasia focal: 133
  - Anaplasia diffusa: 176
- Anaplasia no es un factor pronóstico independiente en RMS con sobrevidas similares a RMS sin anaplasia.
- Cambios anaplásicos están frecuentemente asociadas con mutaciones en *TP53* (69%).

ERMS- Aspectos Genéticos/Moleculares

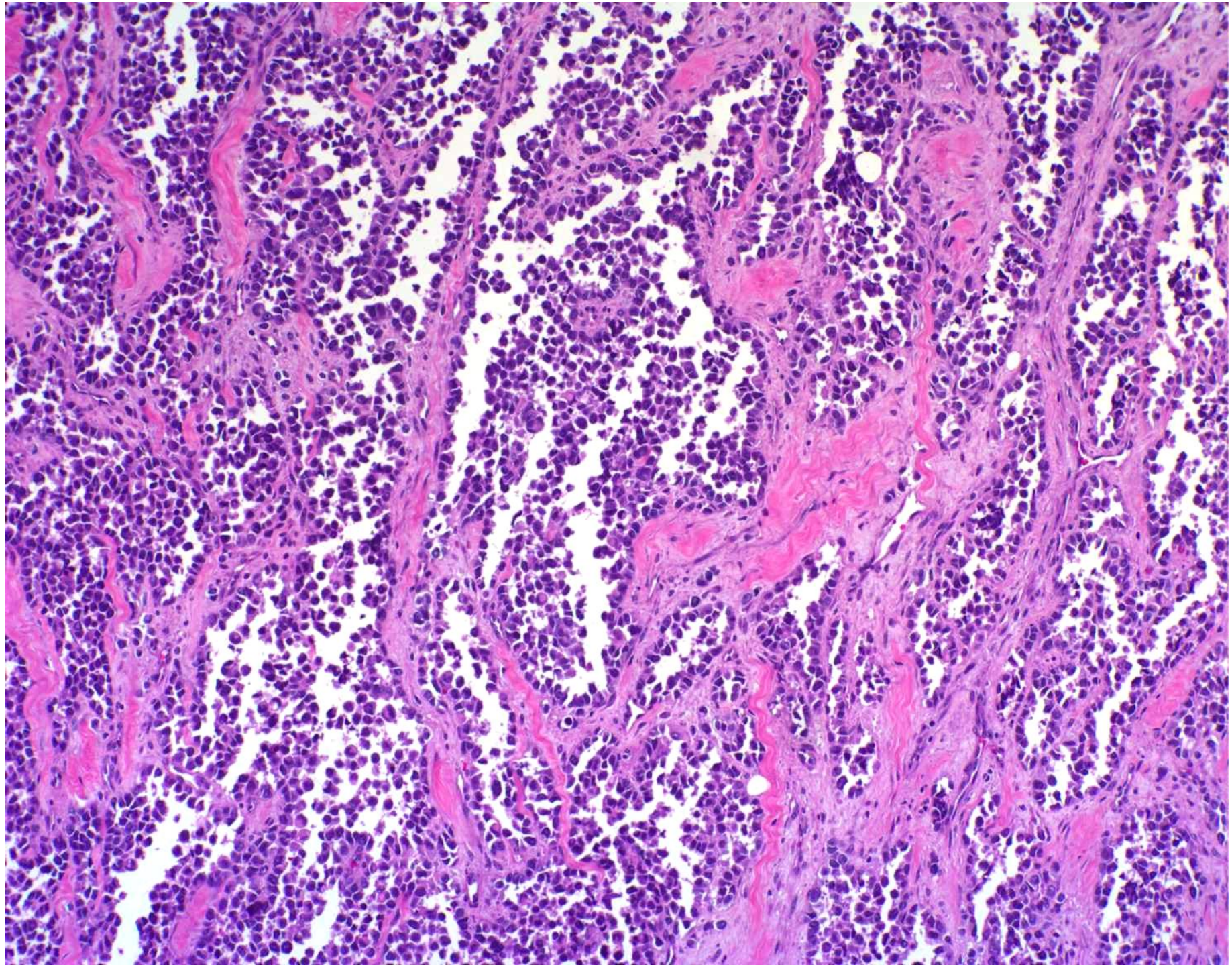
- Tumores aneuploides
  - Polisomía 8, 2, 11, 12, 13, y/o 20
  - Monosomía 10 y 15.
- Pérdida de heterocigosidad en varios loci en 11p15.5, que contienen genes "imprinted" que codifican para factores de crecimiento (*IGF2*) y supresores de crecimiento (*H19* y *CDKN1C*).
- Mutaciones genéticas más frecuentes:
  - Vía RAS (~50%) (*HRAS*, *KRAS* en infantes; *NRAS* en adolescentes*; NF1; FGFR4*)
  - Efectores de PI3K (*PTEN*, *PIK3CA*)
  - Genes que controlan el ciclo celular (*FBXW7*, *CTNNB1*)
  - 30% presenta más de una mutación
  - 25% no mutaciones
  - Modificaciones epigenéticas (*BCOR*) en 15%

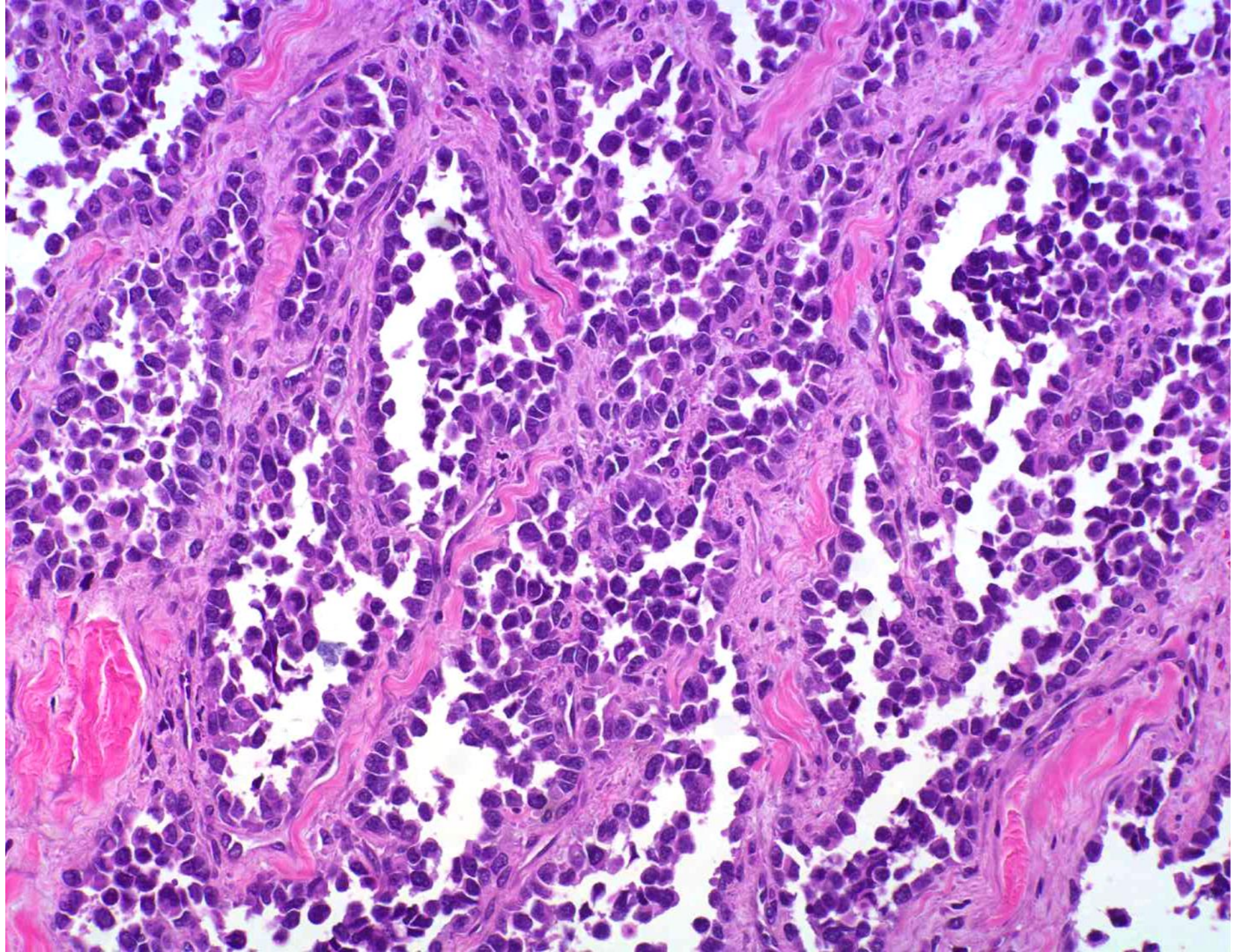
ERMS - Síndromes Genéticos

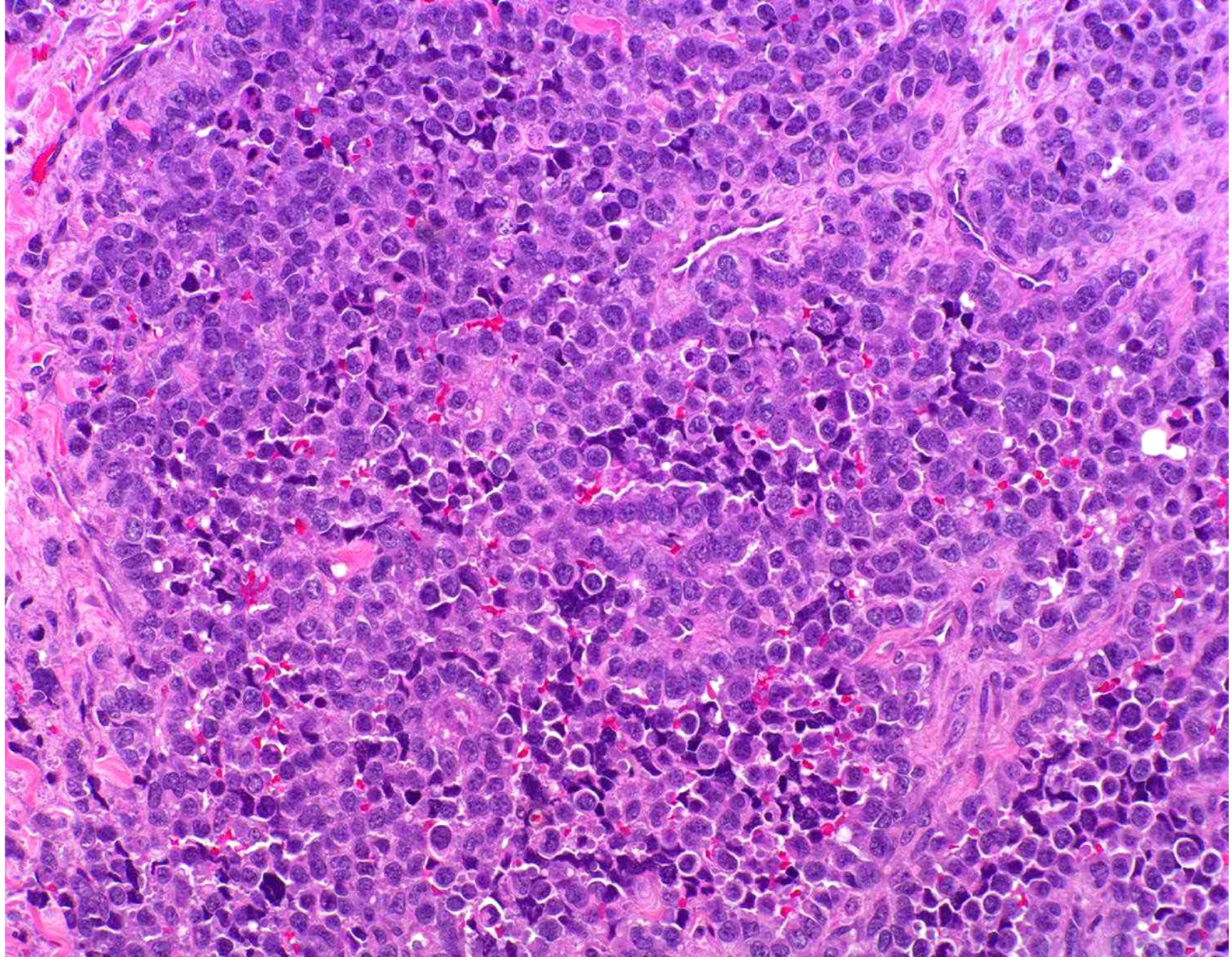
- Alteraciones de la vía RAS:
  - Síndrome de Costello (*HRAS*)
  - Neurofibromatosis tipo 1 (*NF1*)
  - Síndrome de Noonan (varios genes)
- Síndrome de Beckwith–Wiedemann (disregulación del “imprinting” en la región 11p15.5)
- Síndrome *DICER1:* ERMS uterino
- Síndrome de Li–Fraumeni (*TP53*)

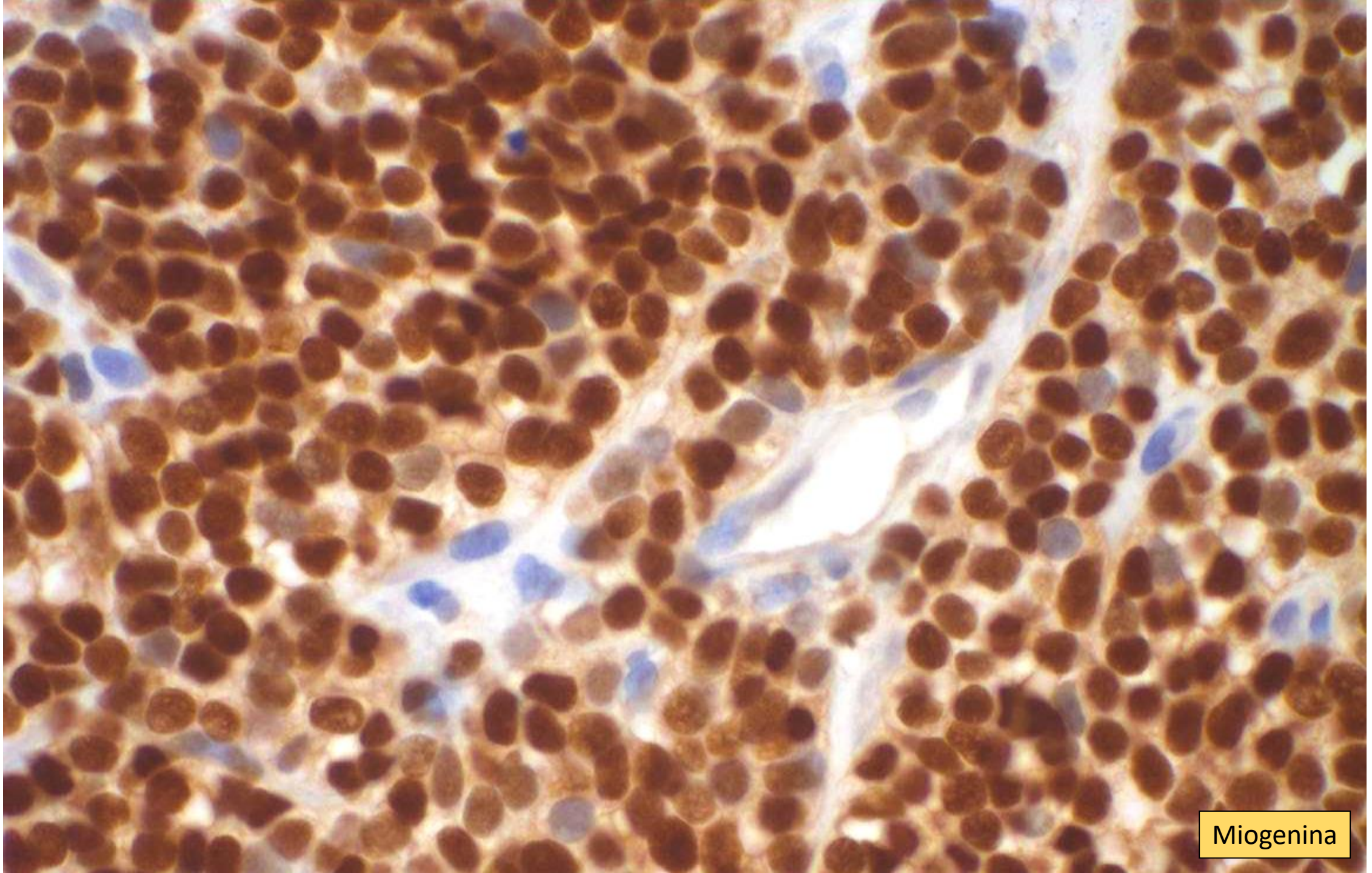
RMS Alveolar

- 31% de RMS
- Más frecuentemente entre 10 y 25 años
  - Tejidos blandos profundos de las extremidades
  - Menos frecuentemente en:
    - Cabeza y cuello
    - Perineo
    - Pelvis
    - Retroperitoneo
- Variante sólida
- Metástasis temprana a hueso o ganglios linfáticos

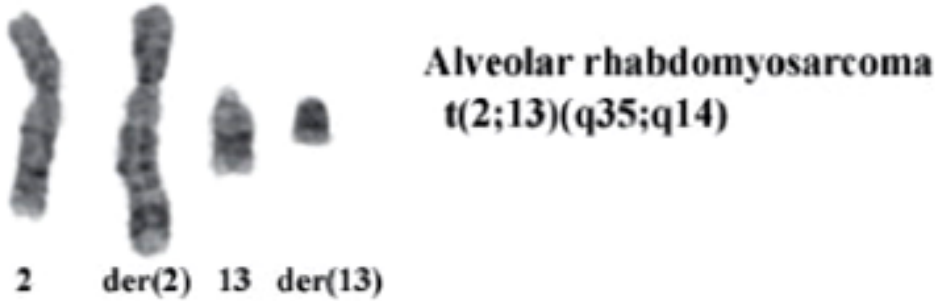







Miogenina

- Las translocaciones t(2;13)/*PAX3-FOXO1* o t(1;13)/*PAX7-FOXO1* se encuentran presente en la mayoría de casos de RMS alveolar (ca. 82%)
- La t(2;13)/*PAX3-FOXO1* es más común (80% de casos) y está asociada a un peor pronóstico que la t(1;13)/*PAX7-FOXO1*



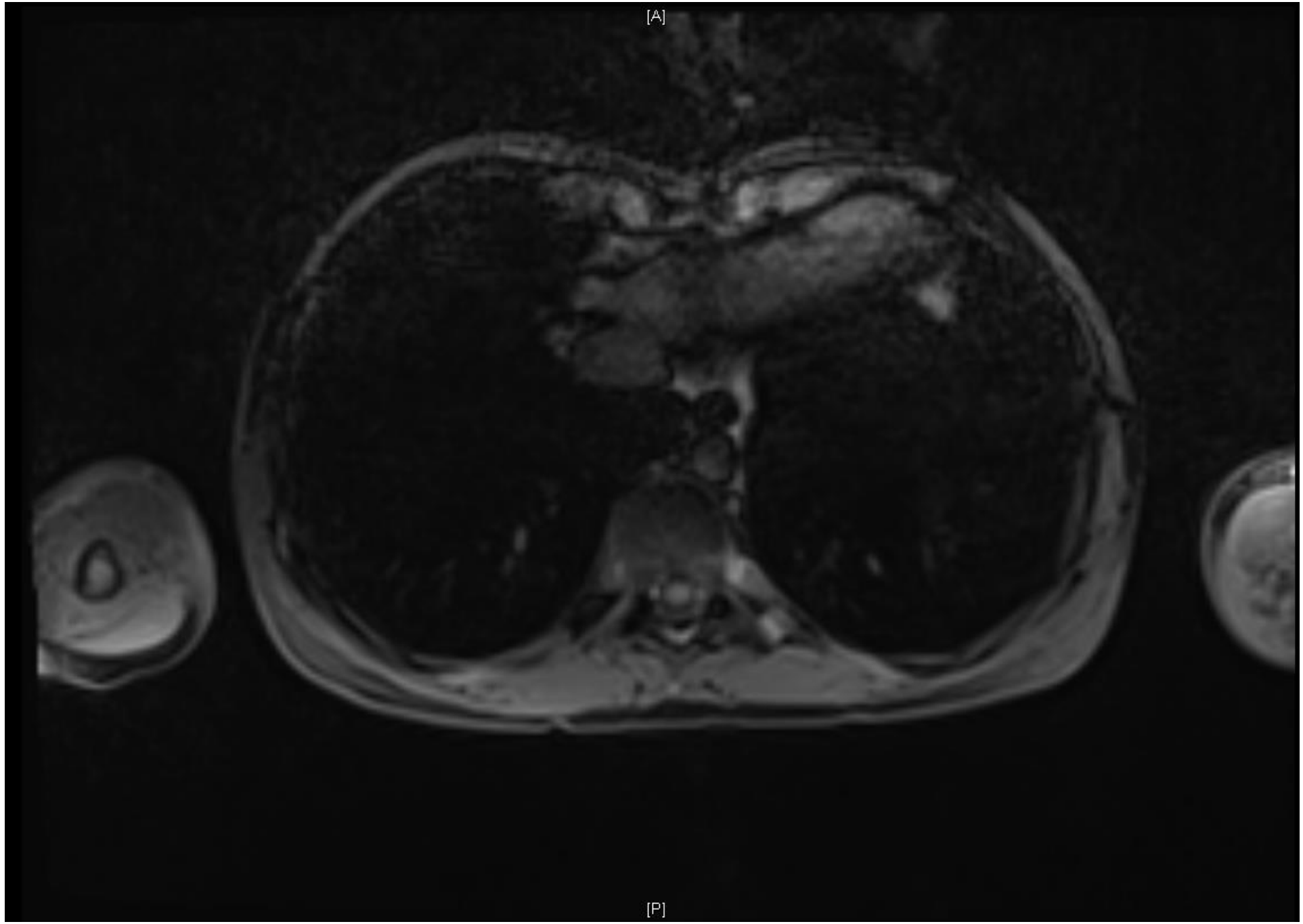
- Fusiones genéticas menos comunes incluyen:
  - *PAX3* con *FOXO4, NCOA1* o *INO80D*
  - *FOXO1-FGFR1*
- RMS con morfología alveolar sin rearreglos genéticos *PAX* o *FOX01* se comportan como ERMS

Caso Clínico

- Adolescente masculino de 17 años de edad s/p transplante de corazón >10 años por atresia pulmonar
- Masa esternal de varias semanas de evolución en aspecto anterior de incisión de esternotomía previa

Imágenes

- Estudios por imágenes iniciales revelan lesión de 1.9 x 1.3 cm en pared torácica anteroinferior, adyacente a proceso xifoide

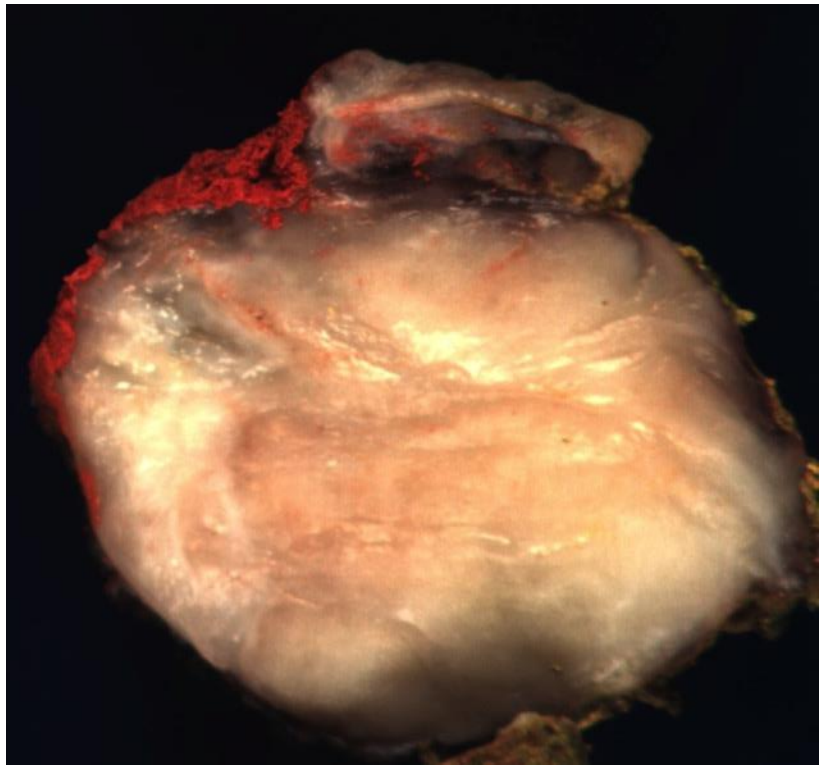

[A]
[P]

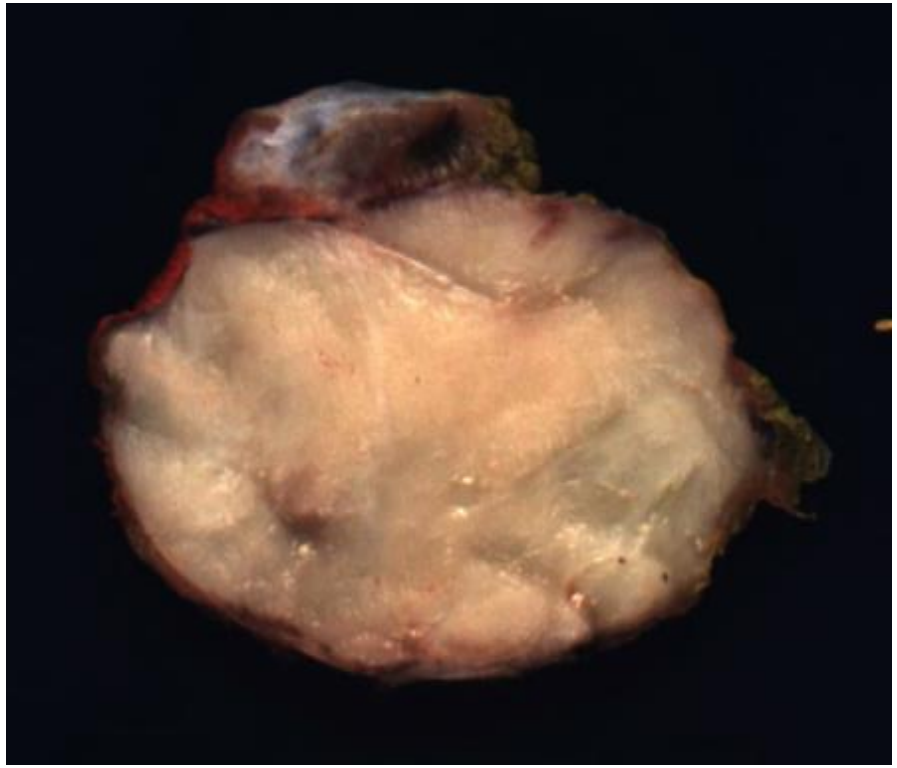
- Inicialmente considerada probable cicatriz hipertrófica
- La lesión aumenta de tamaño a *ca.* 4.5 cm en los tres meses siguientes
- Se decide realizar biopsia excisional
- Diagnóstico clínico provisional:

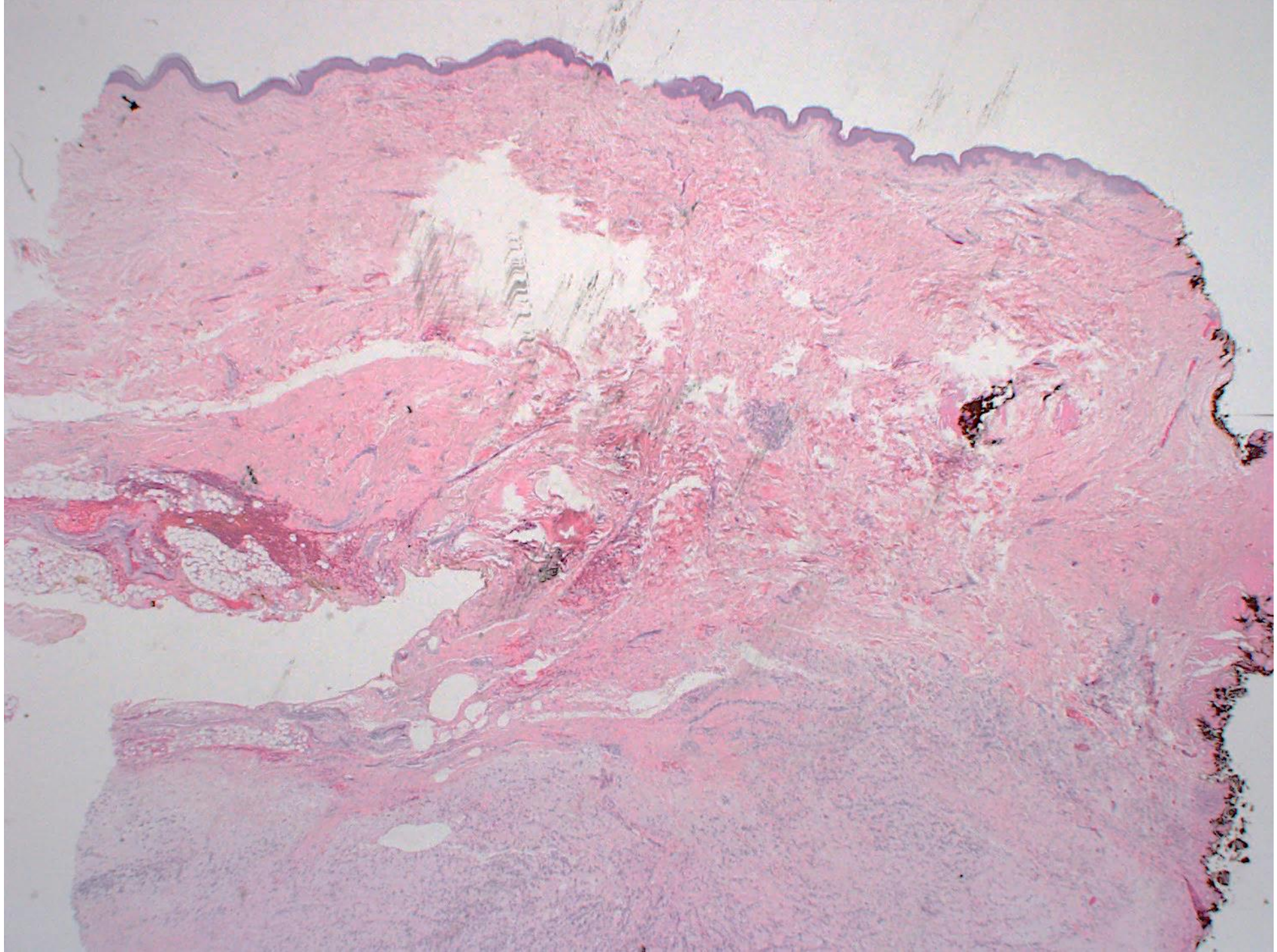
Trastorno Linfoproliferativo Post-Transplante

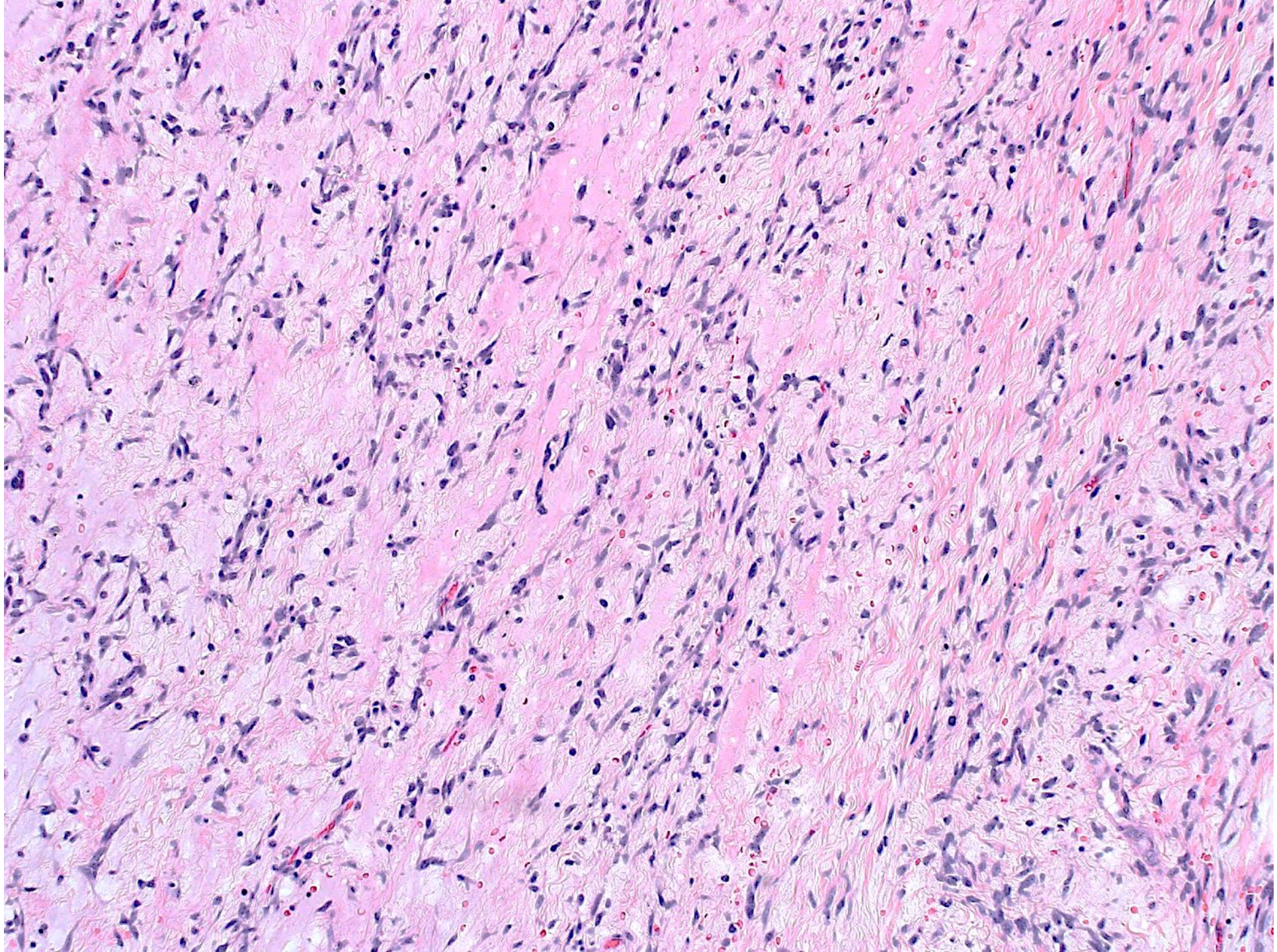
Patología

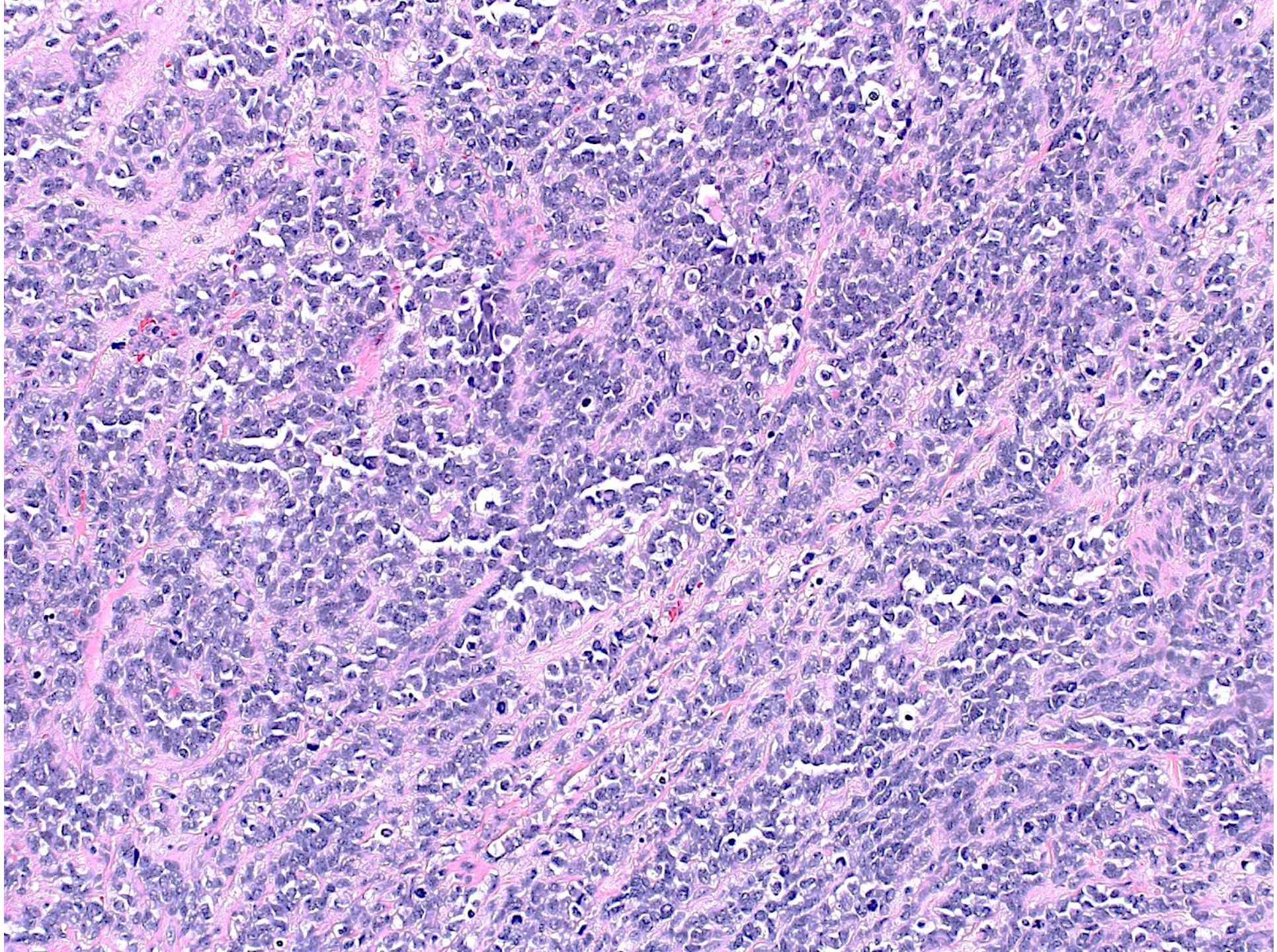
- Elipse cutánea de 3.5 x 1.5 cm con partes blandas subyacentes (7.5 x 4.5 x 4.3 cm)

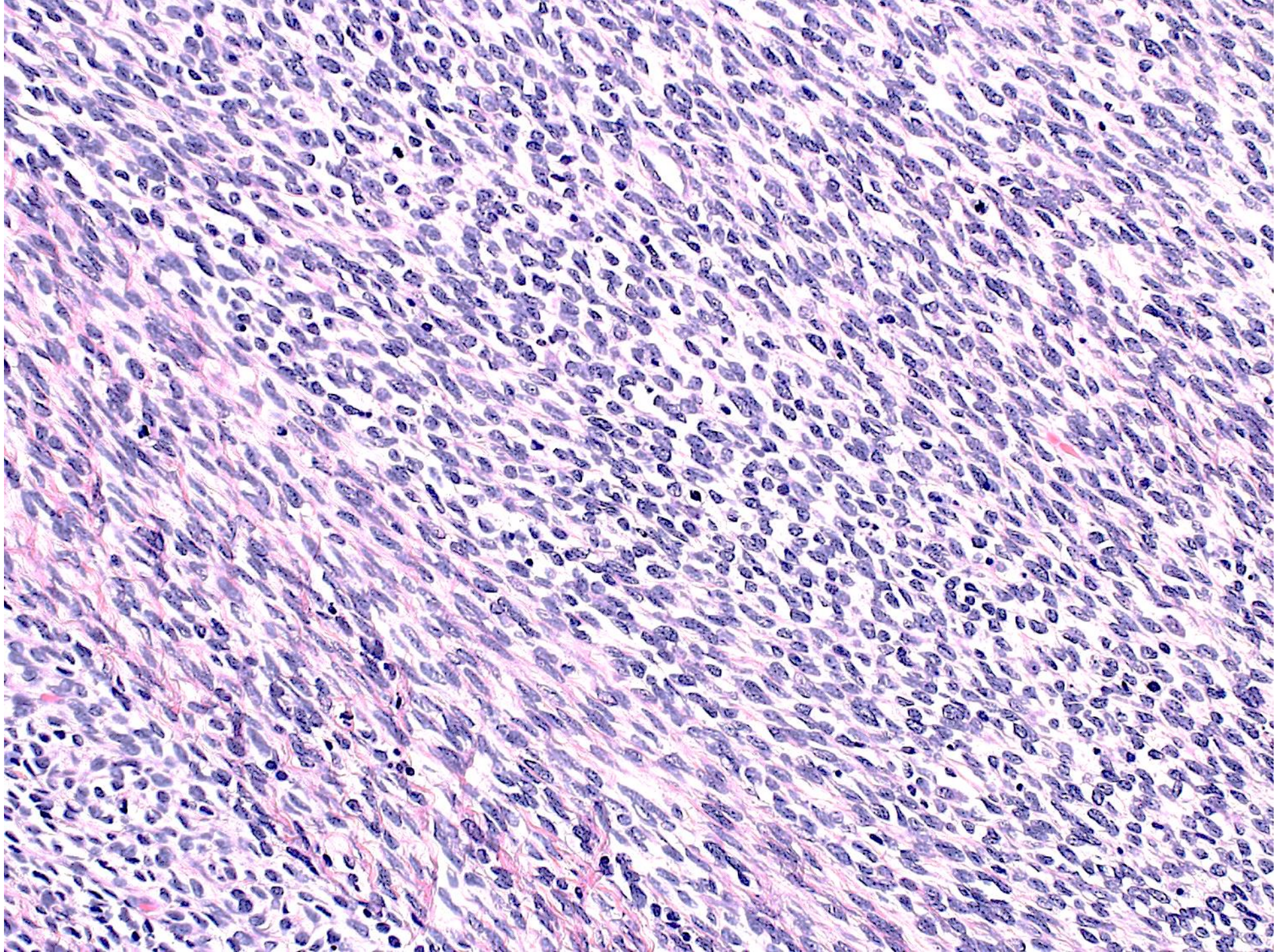


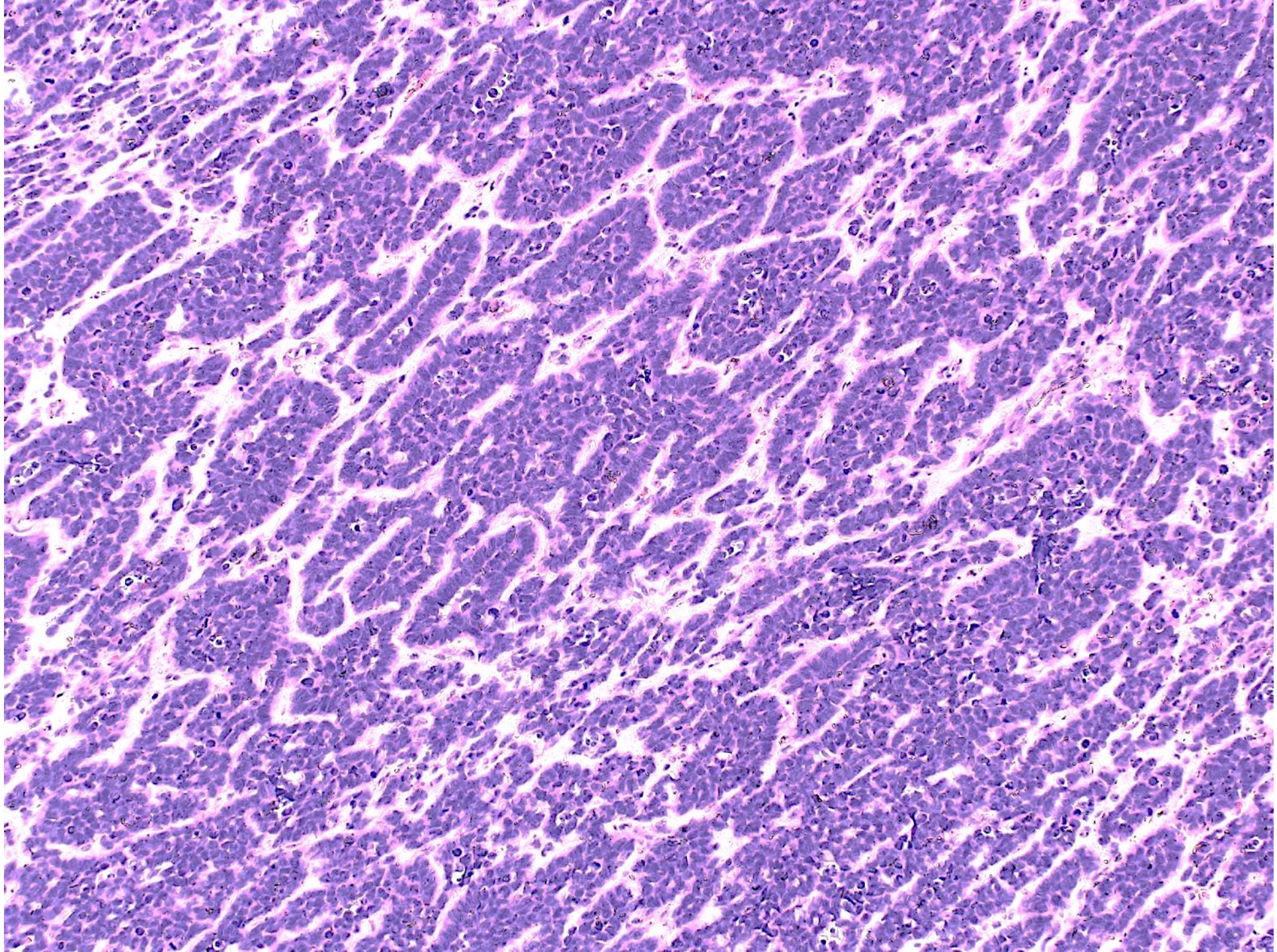


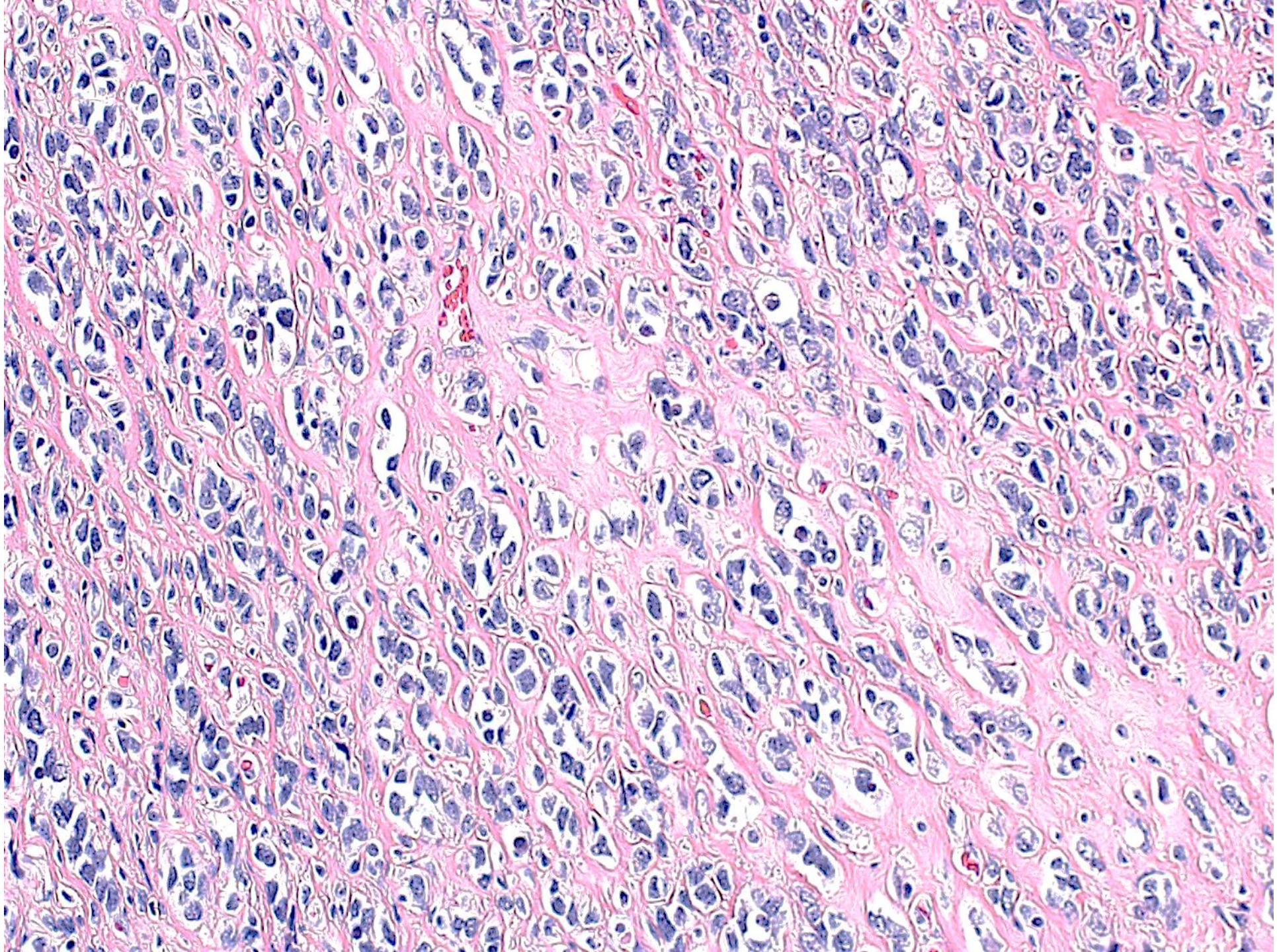


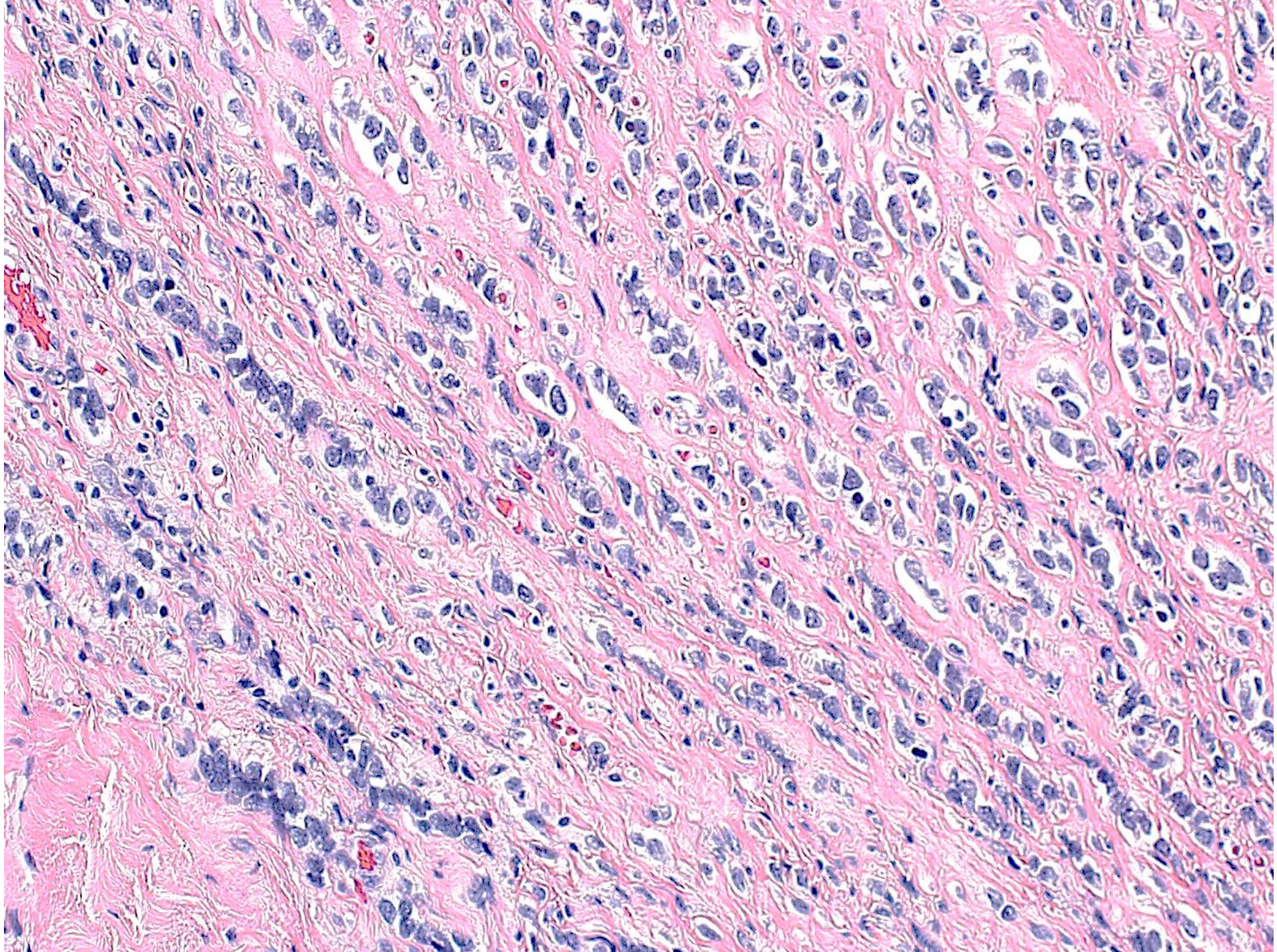


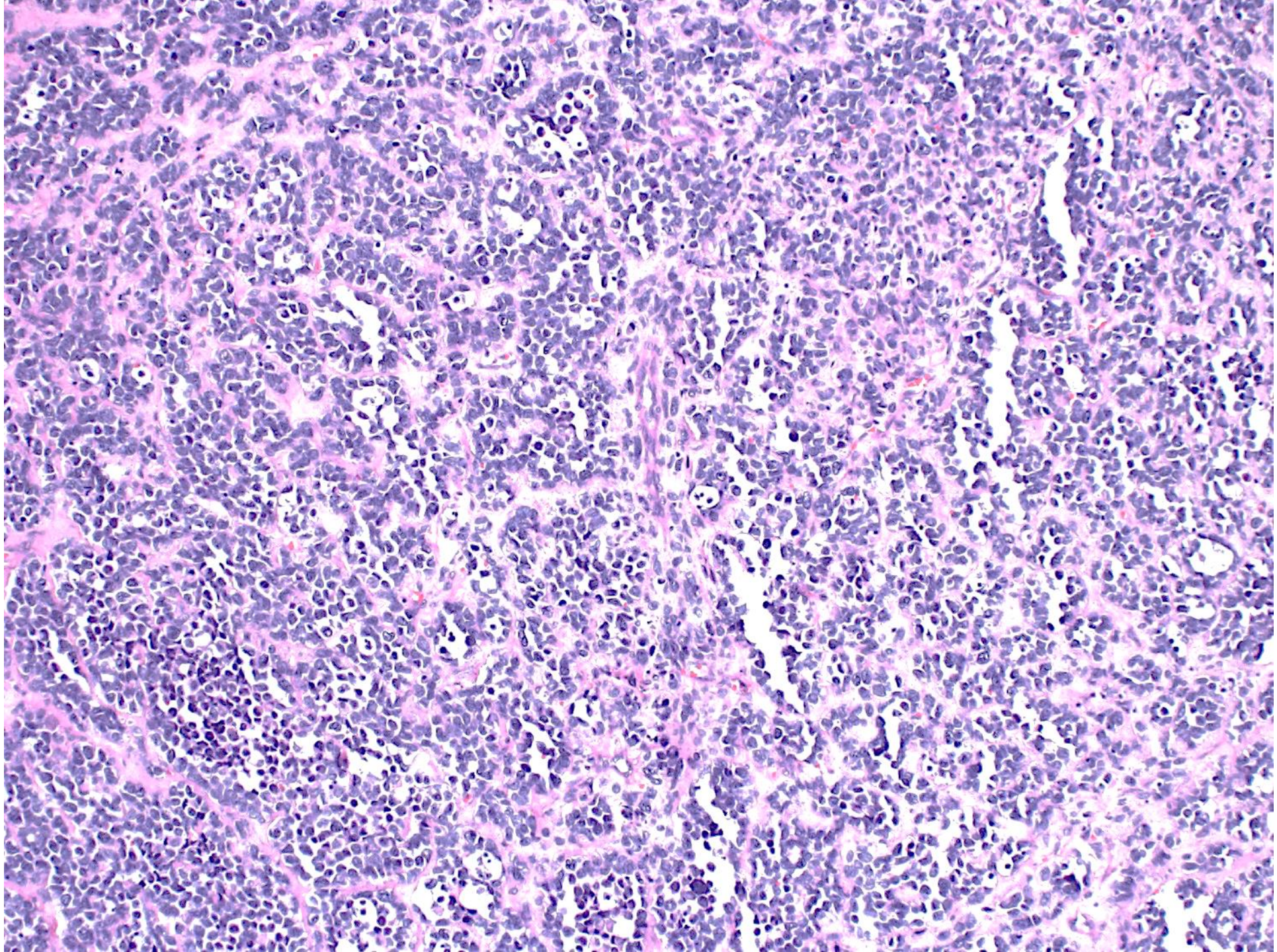


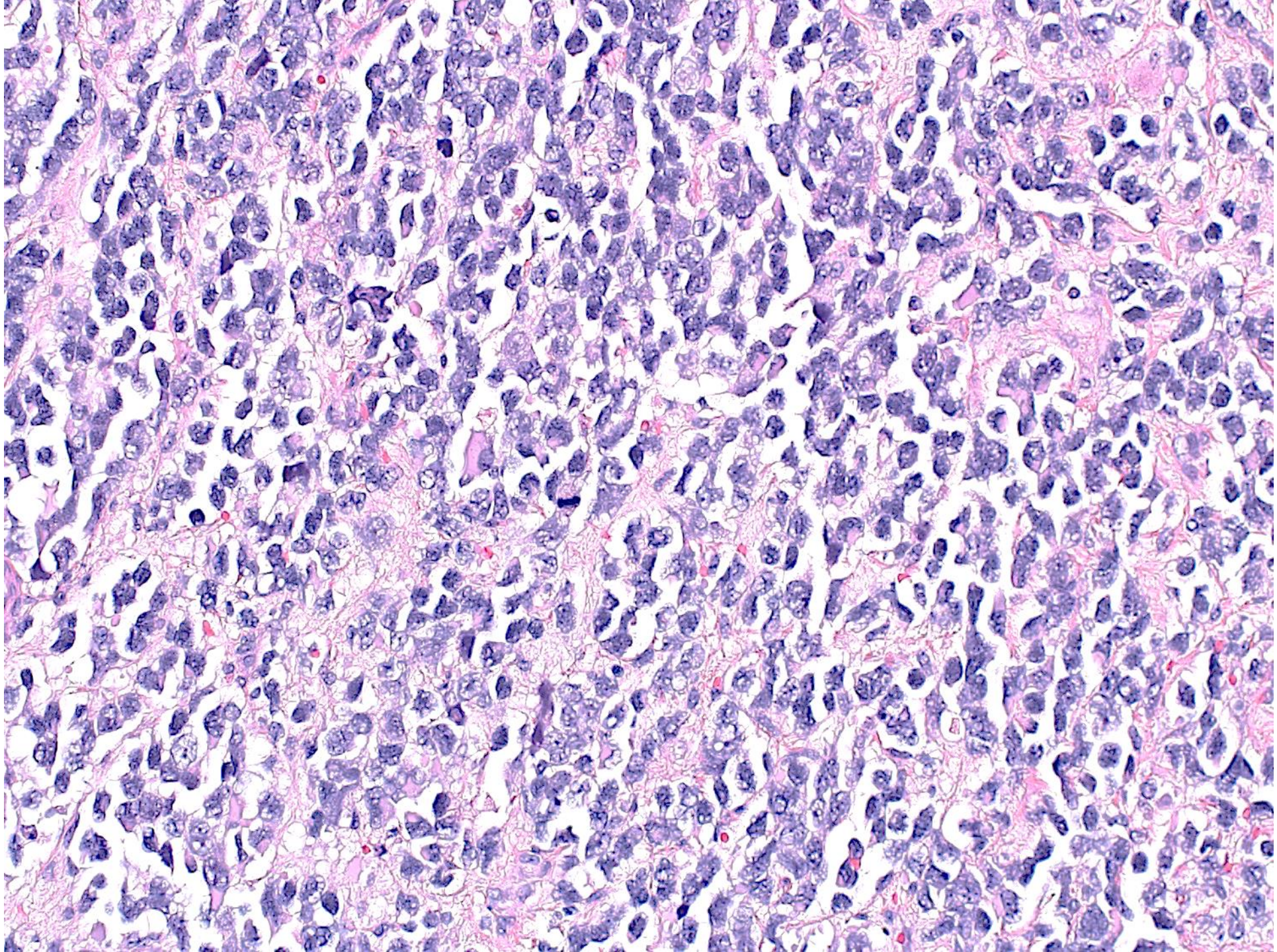


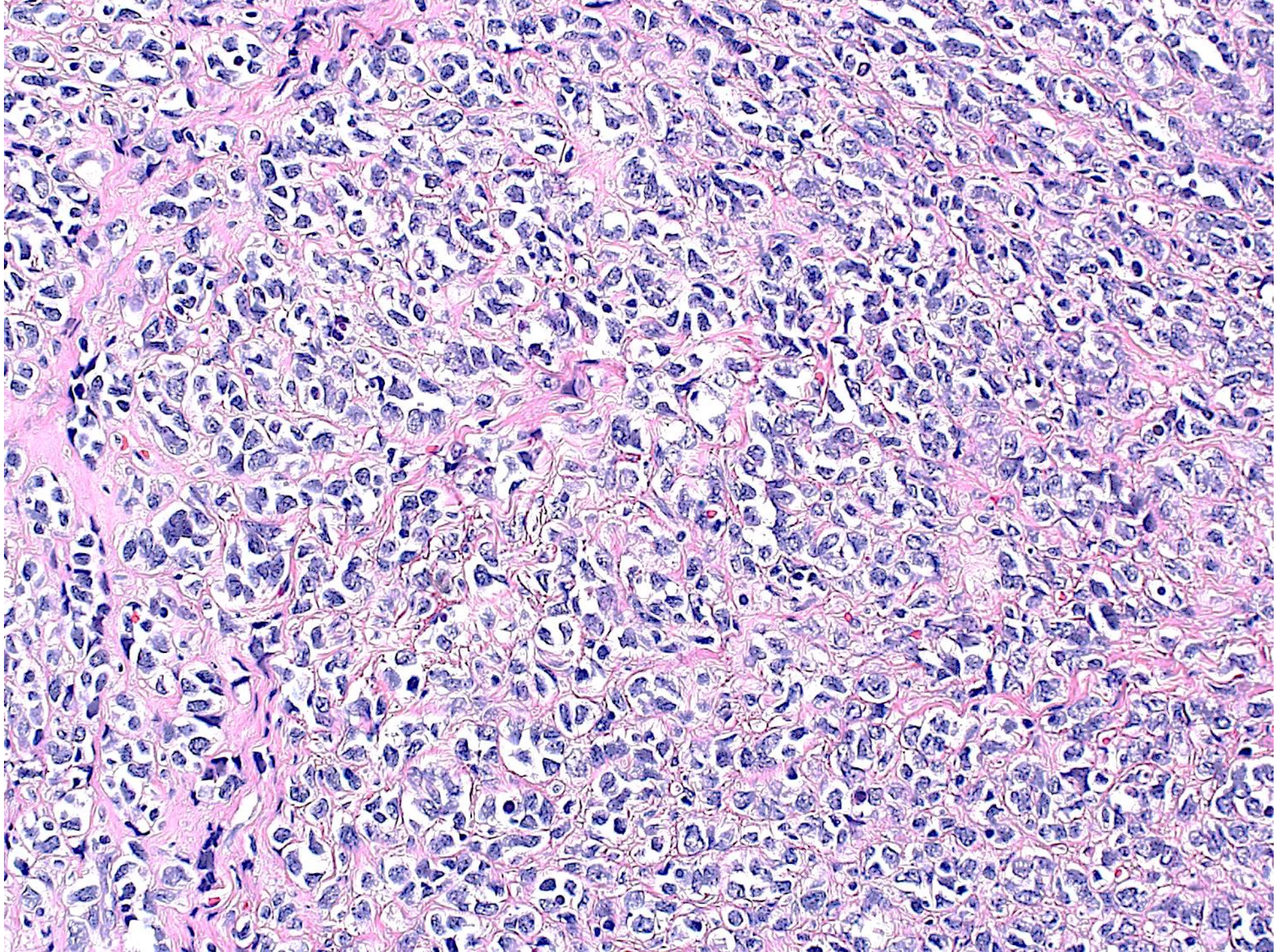


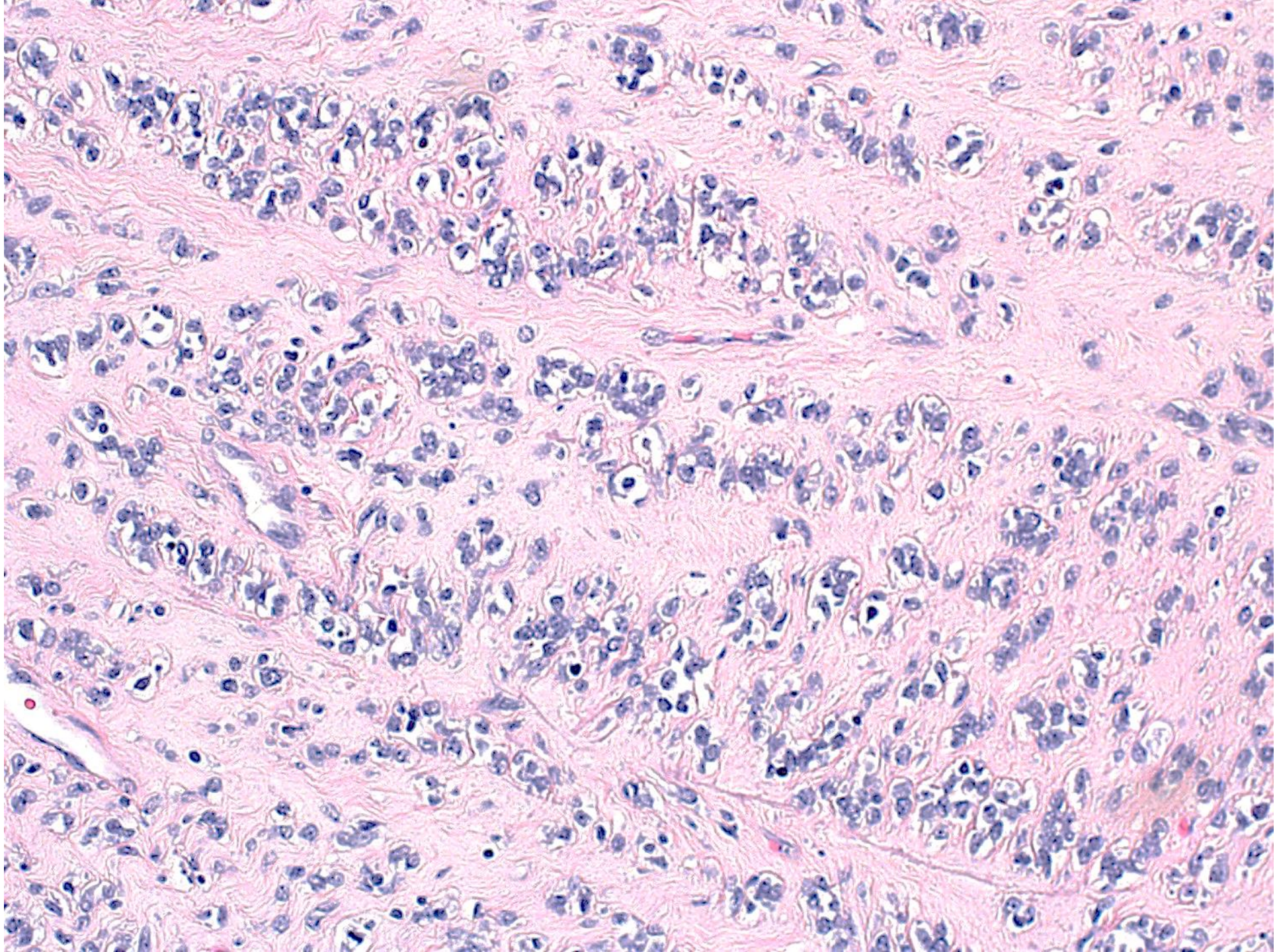


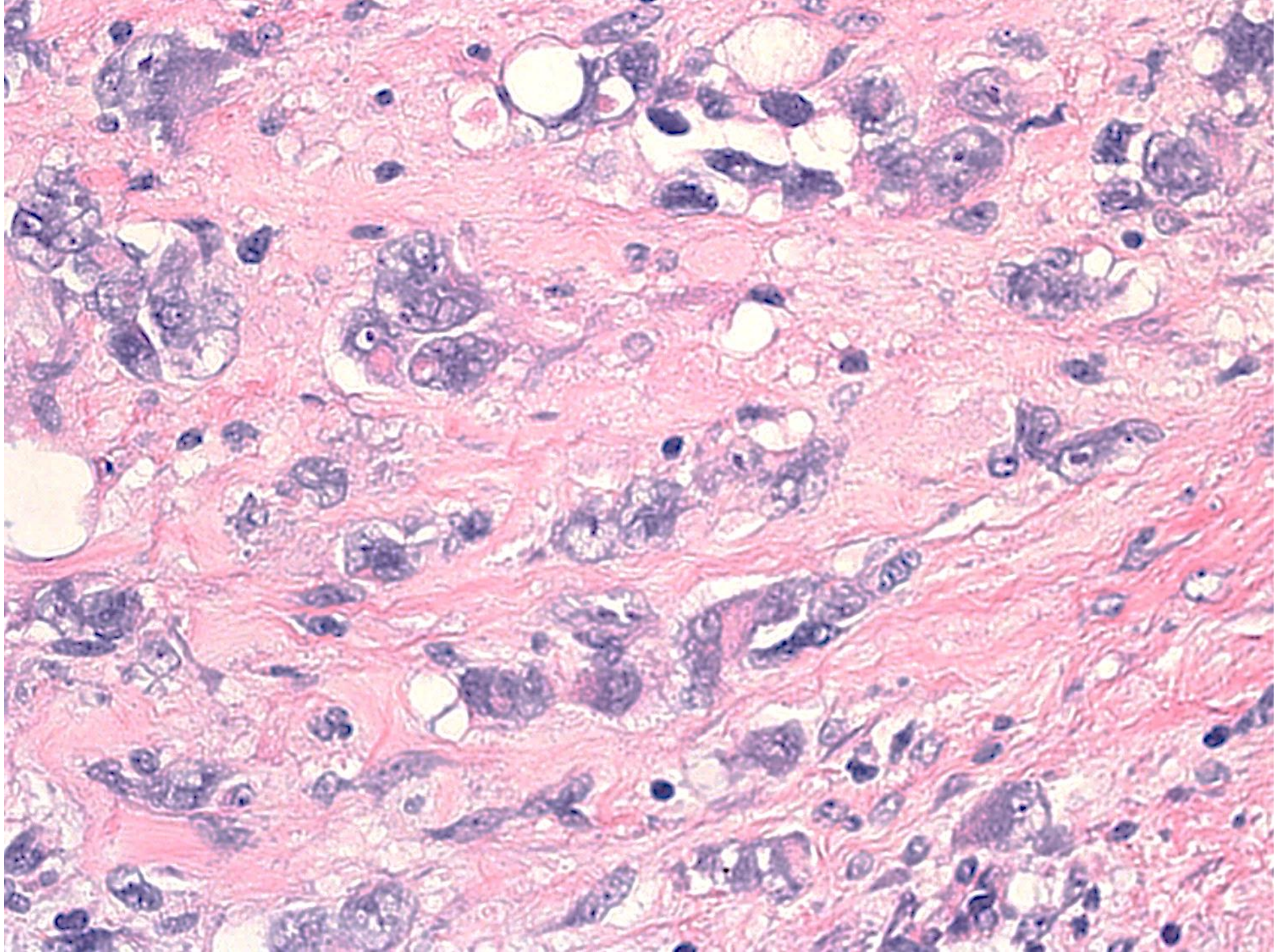


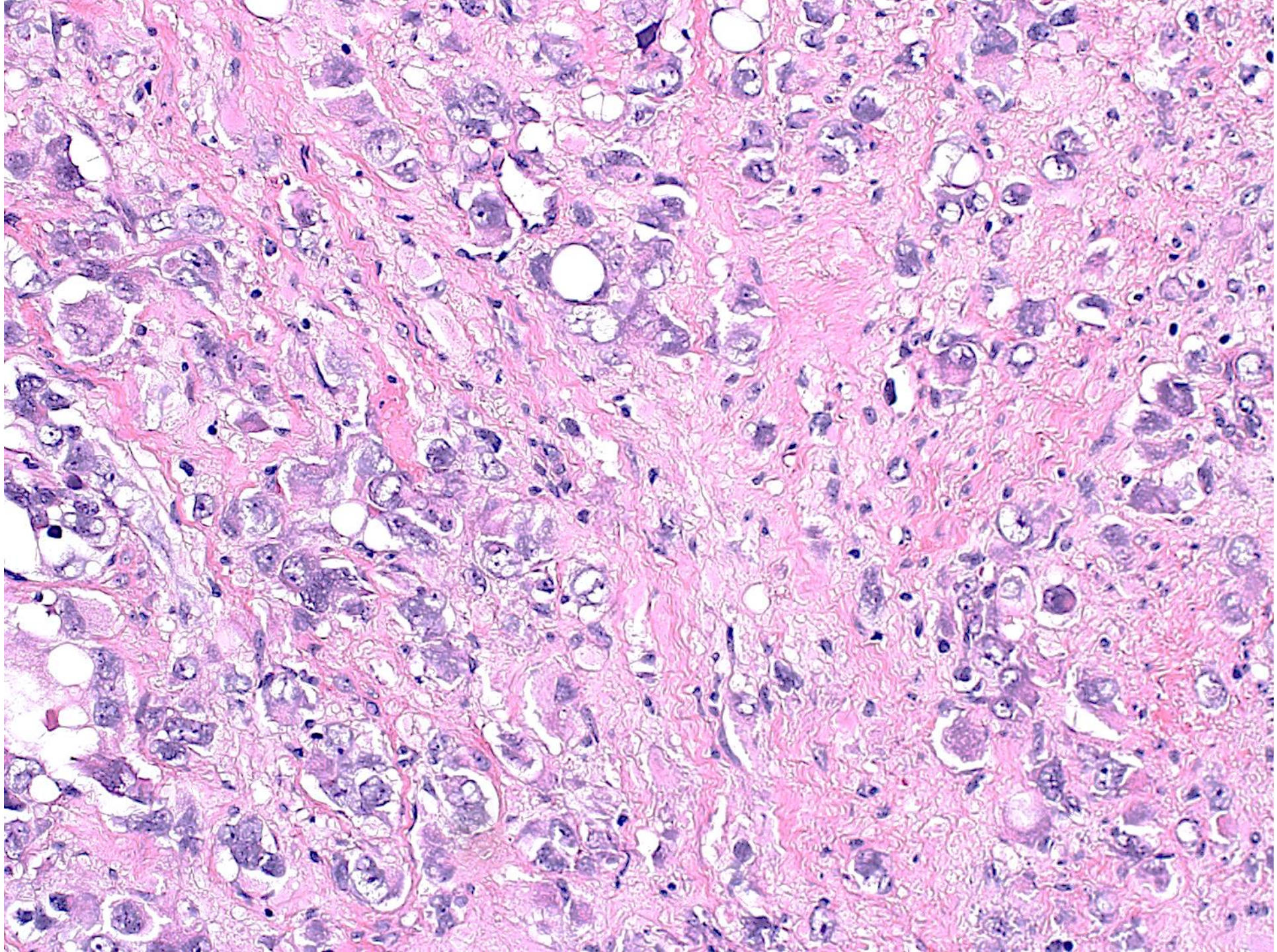


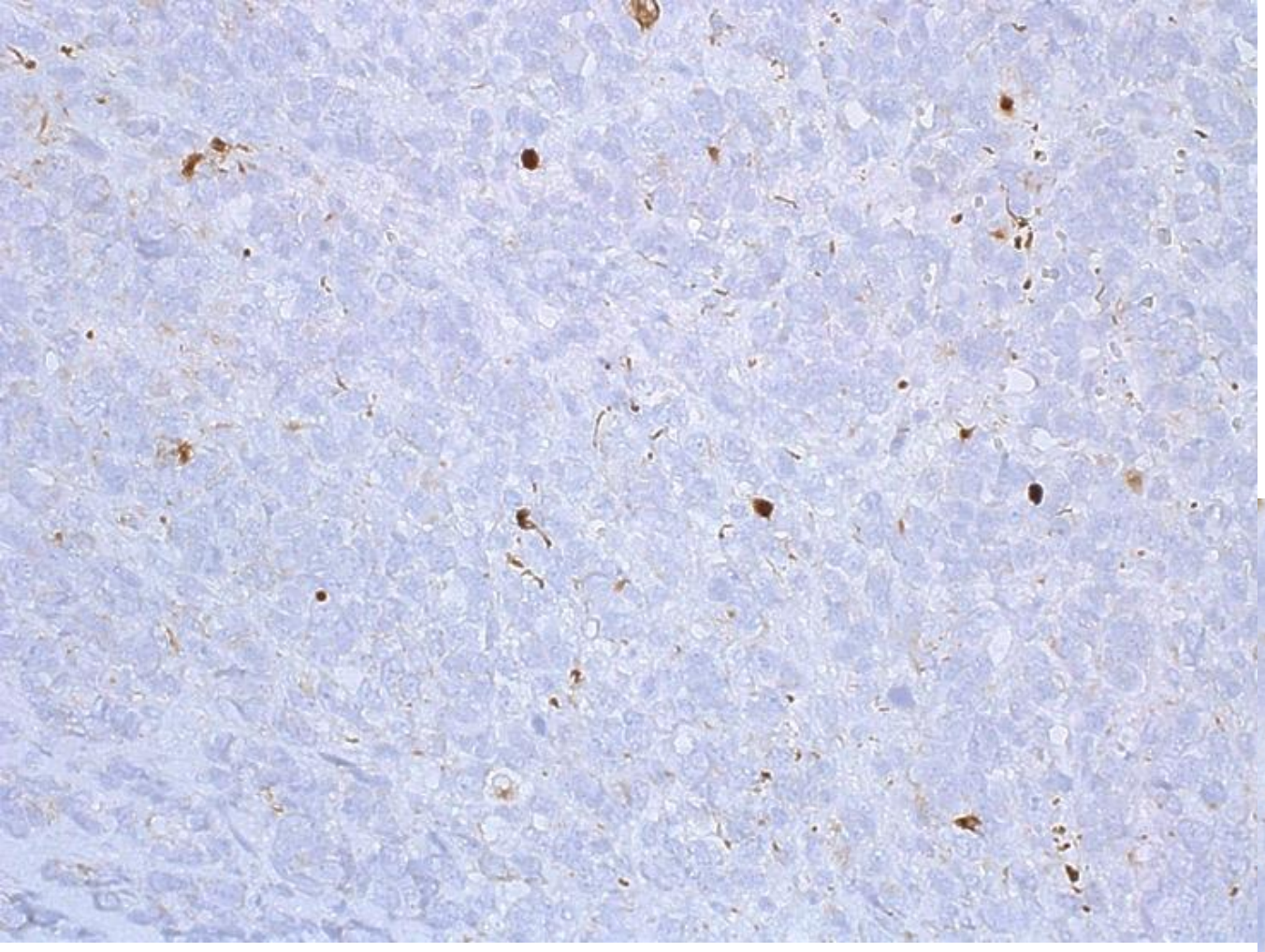












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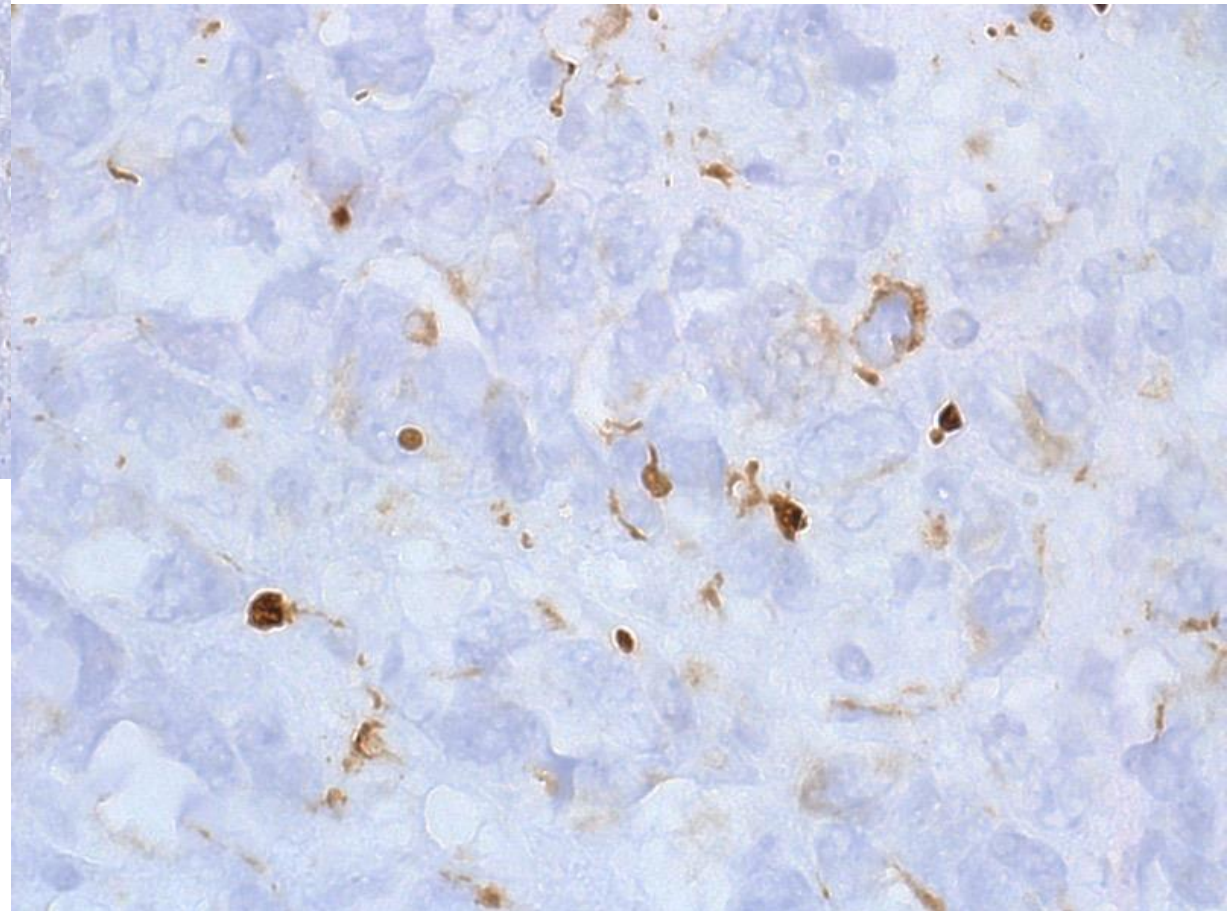
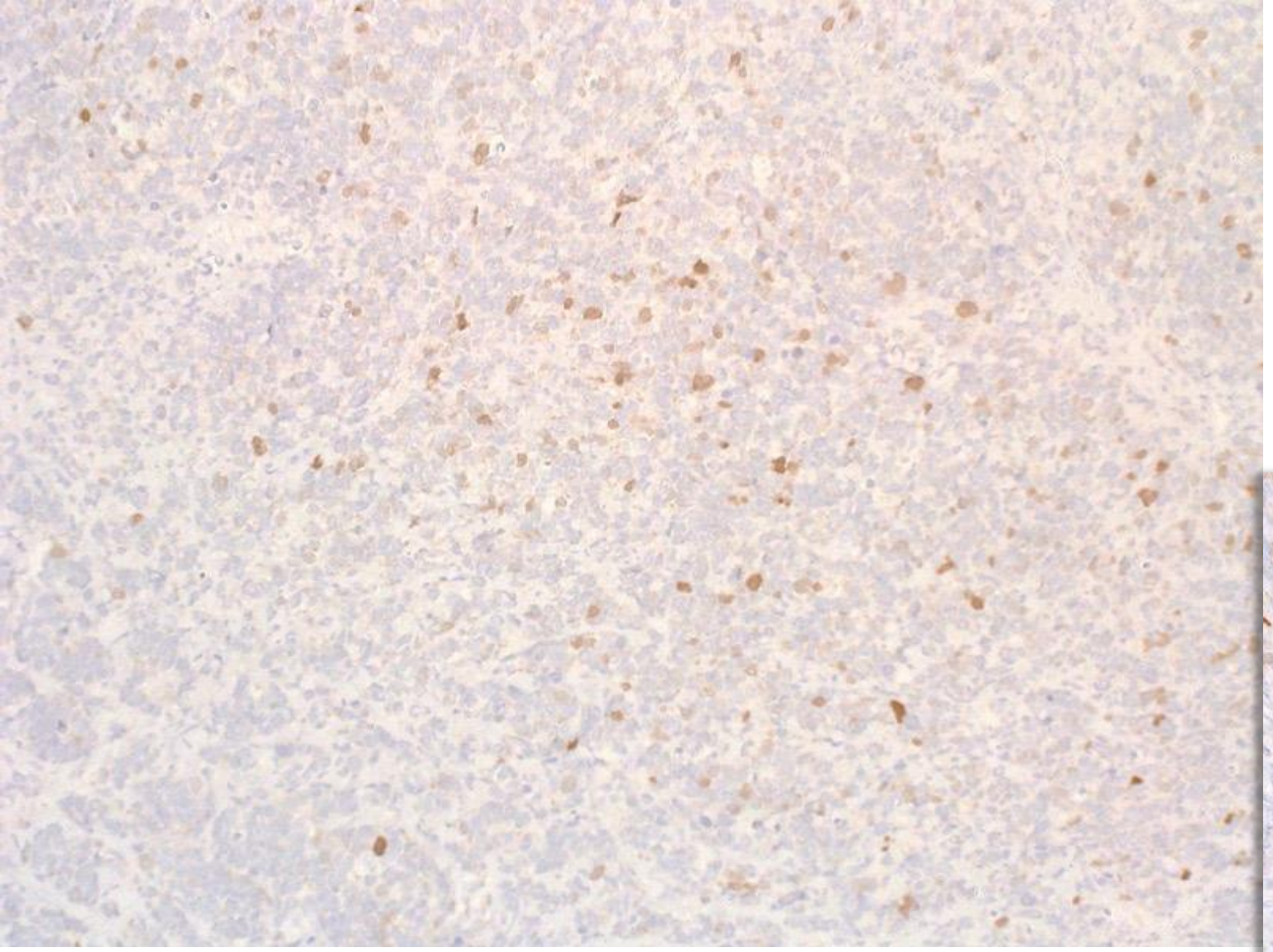
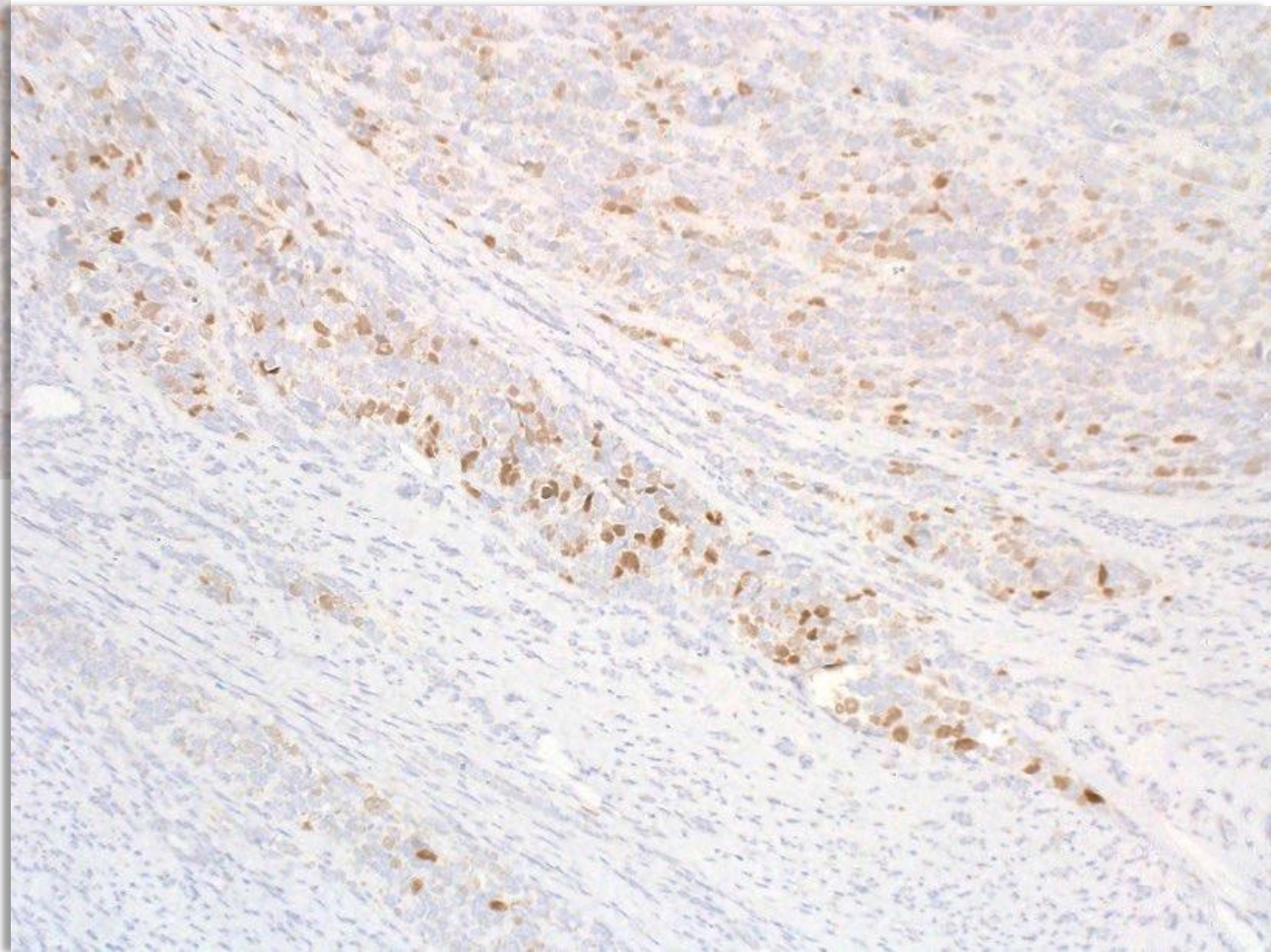
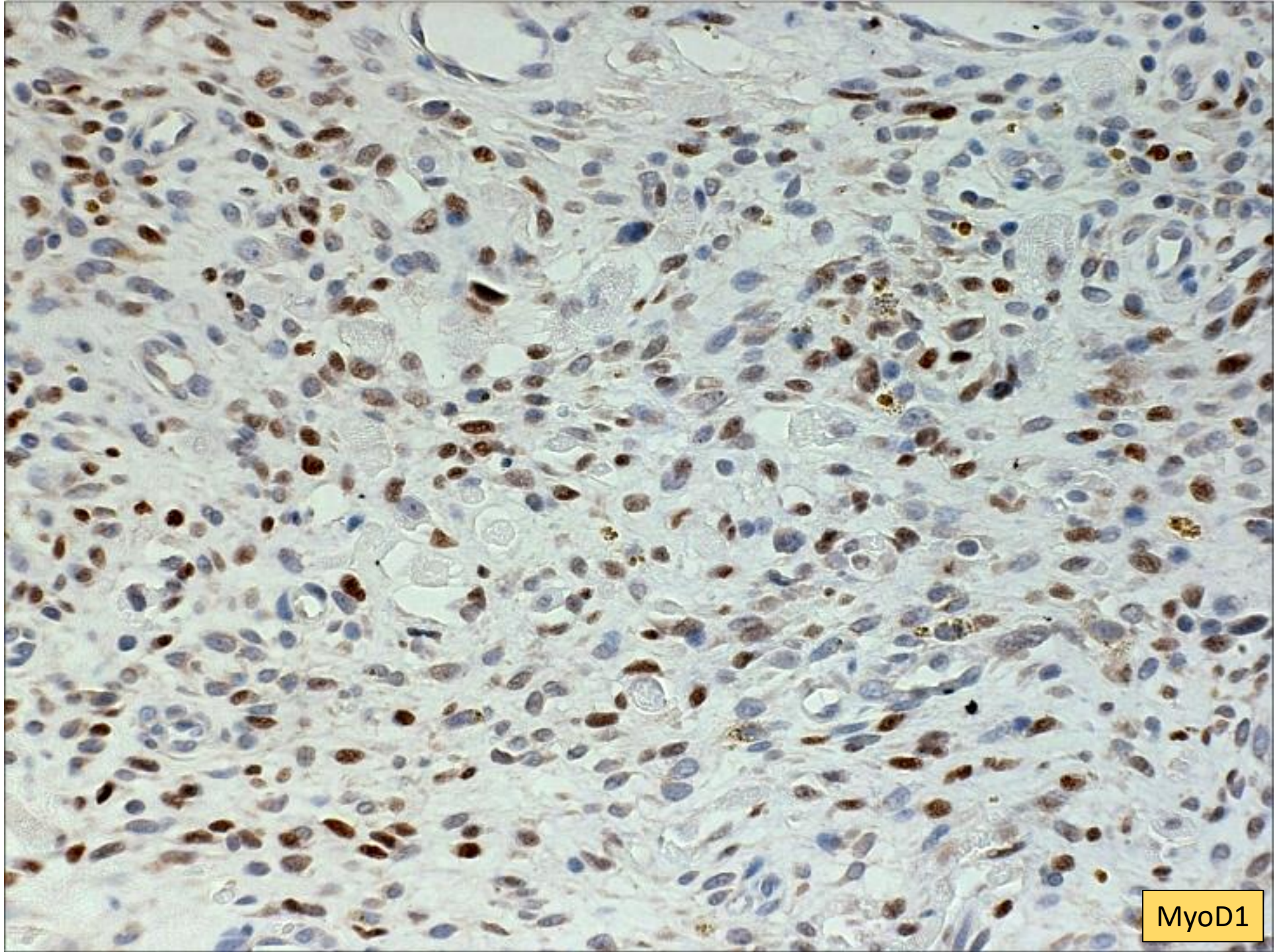




Miogenina



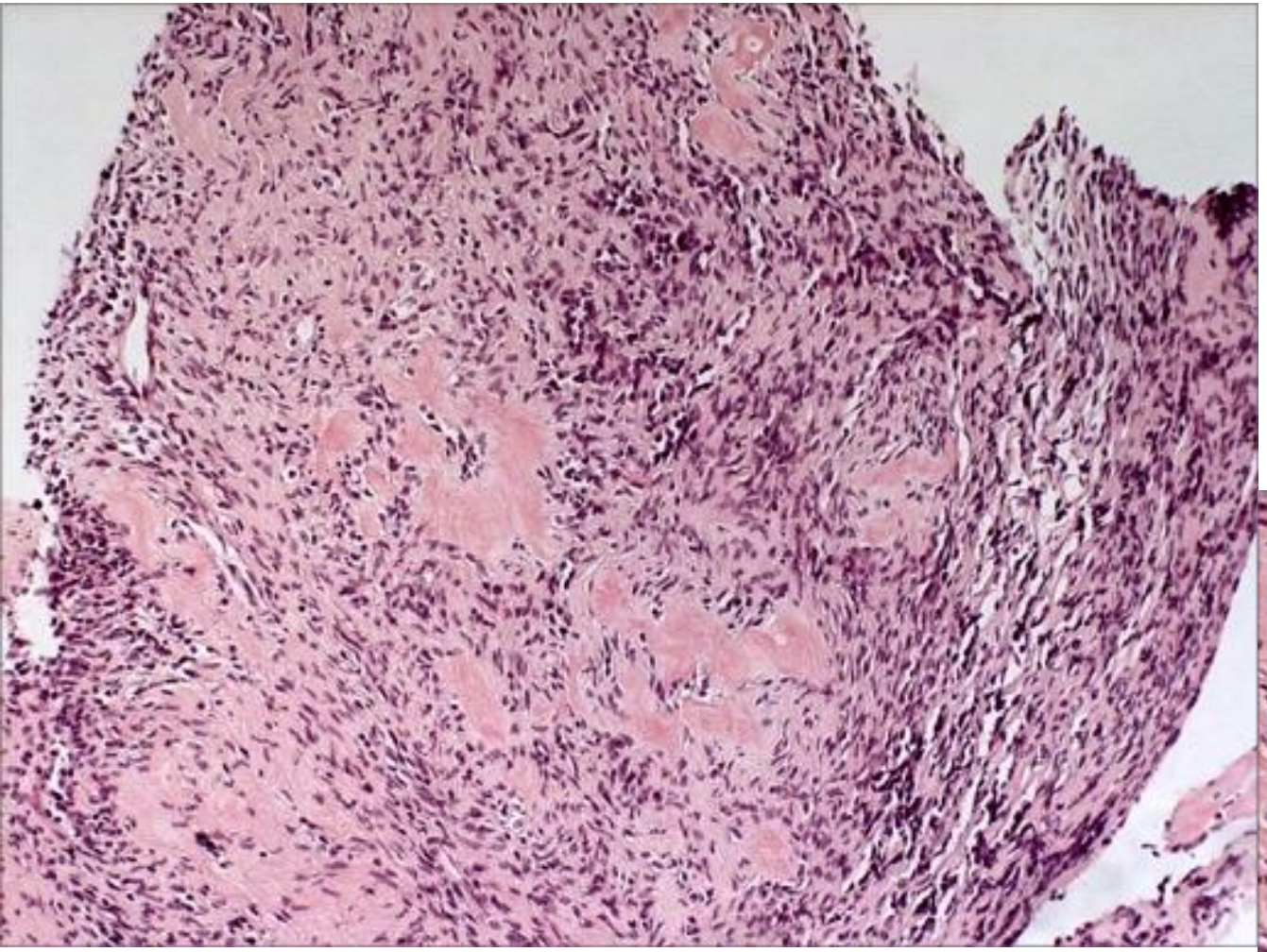

MyoD1

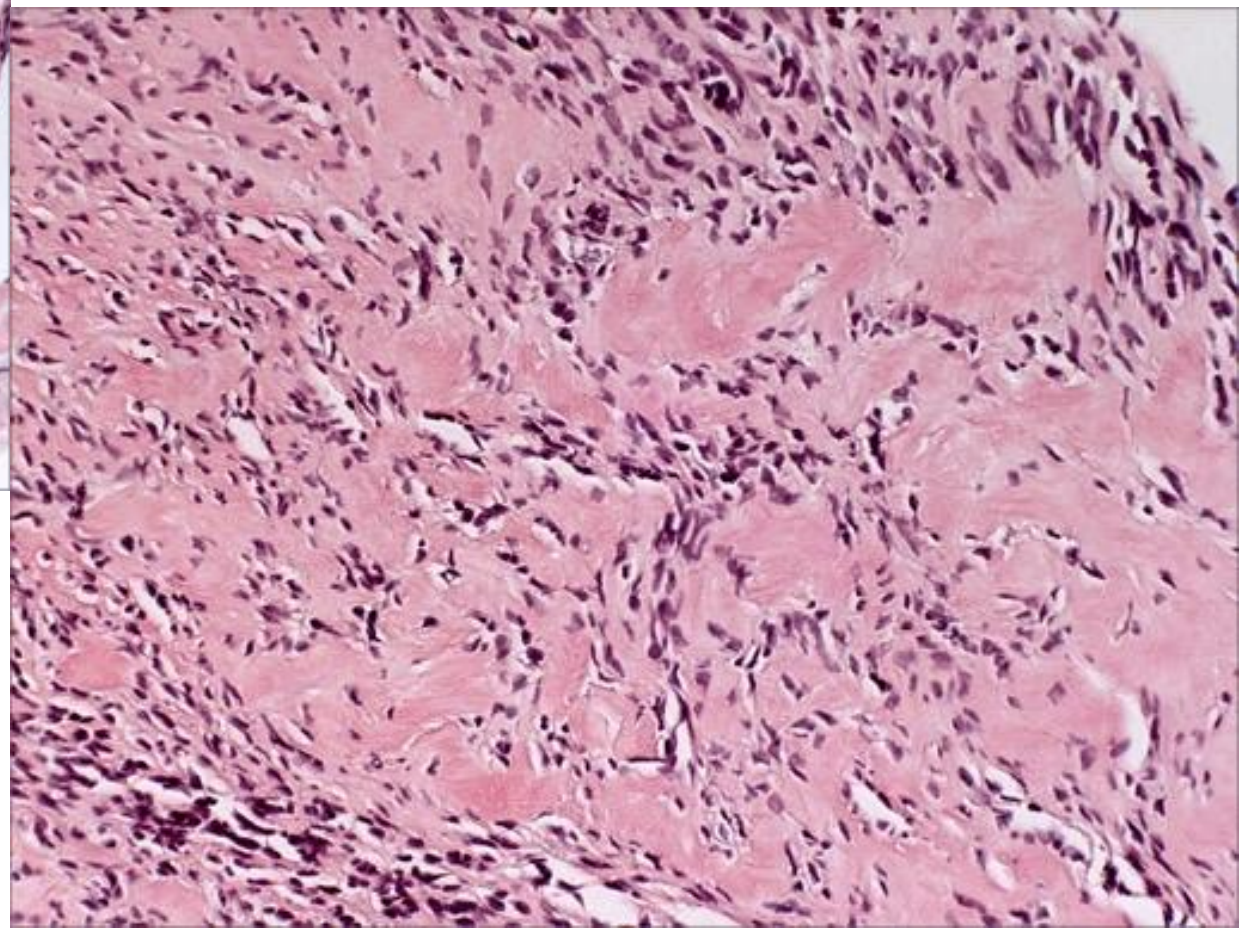
Diagnóstico:

Rabdomiosarcoma fusocelular/esclerosante

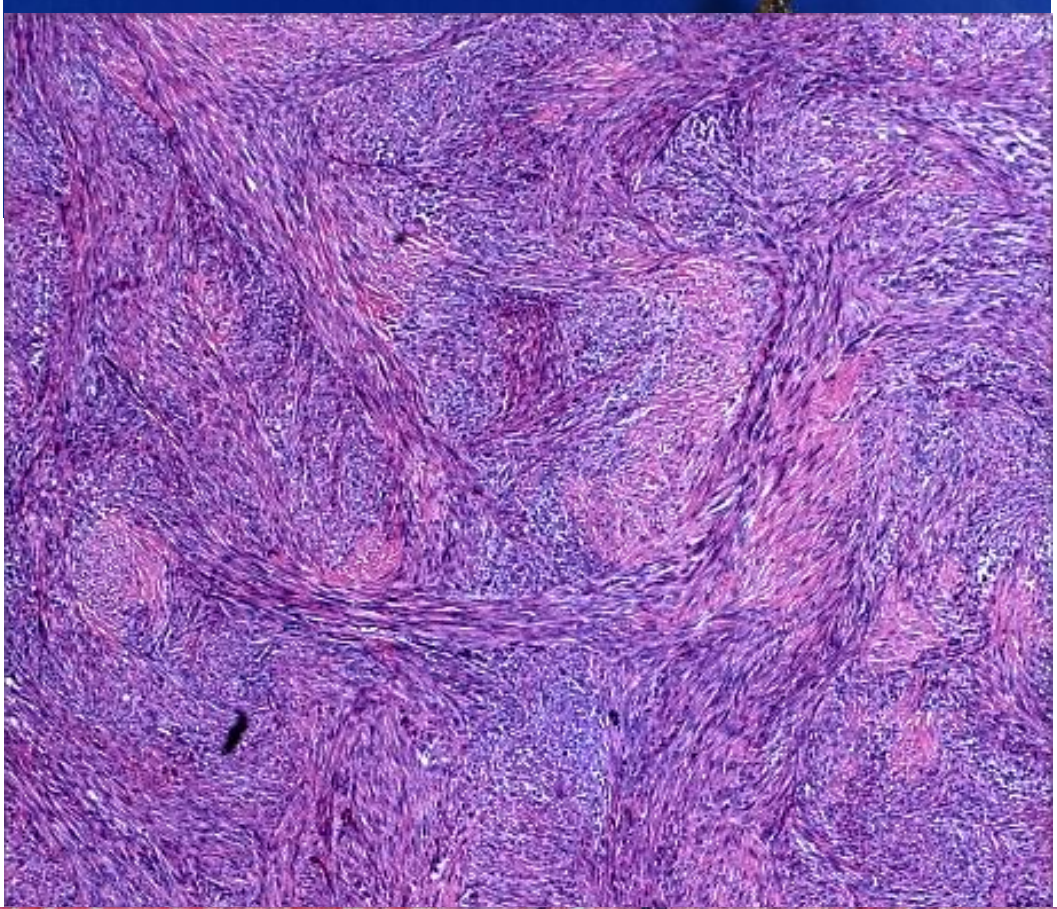
RMS Fusocelular/Esclerosante

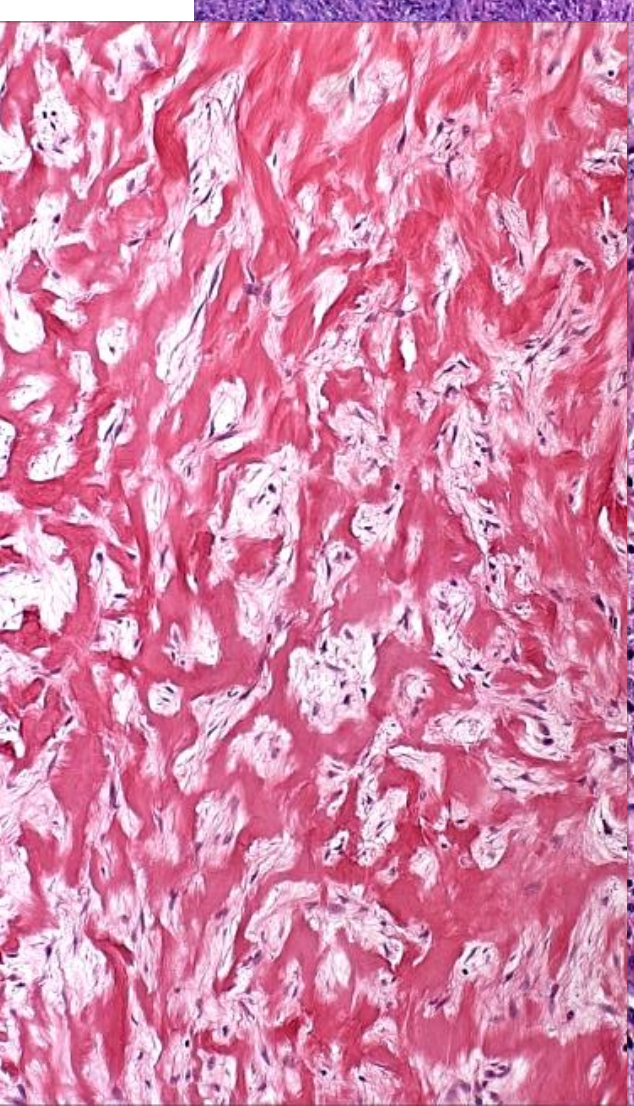
- Variante caracterizada por abundante estroma colagenoso
- Puede simular otros tumores mesenquimáticos malignos
  - Osteosarcoma
  - Condrosarcoma
  - Angiosarcoma
  - Fibrosarcoma epiteliode esclerosante

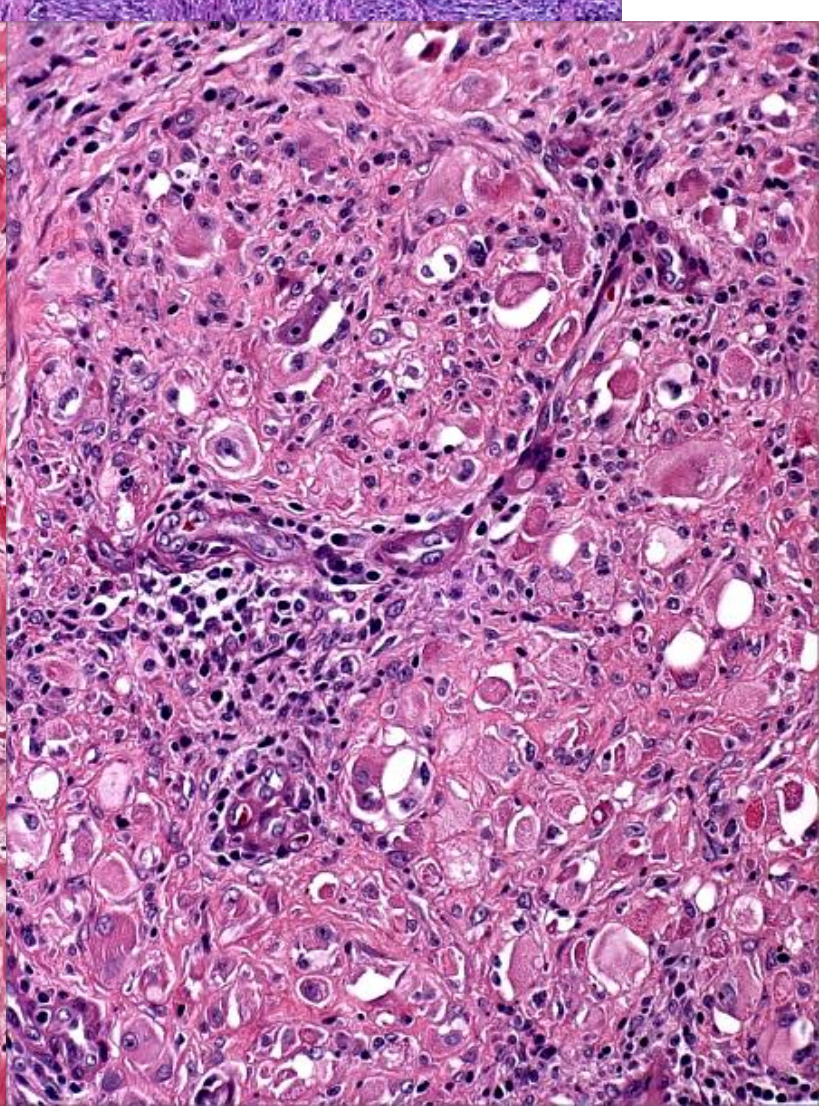


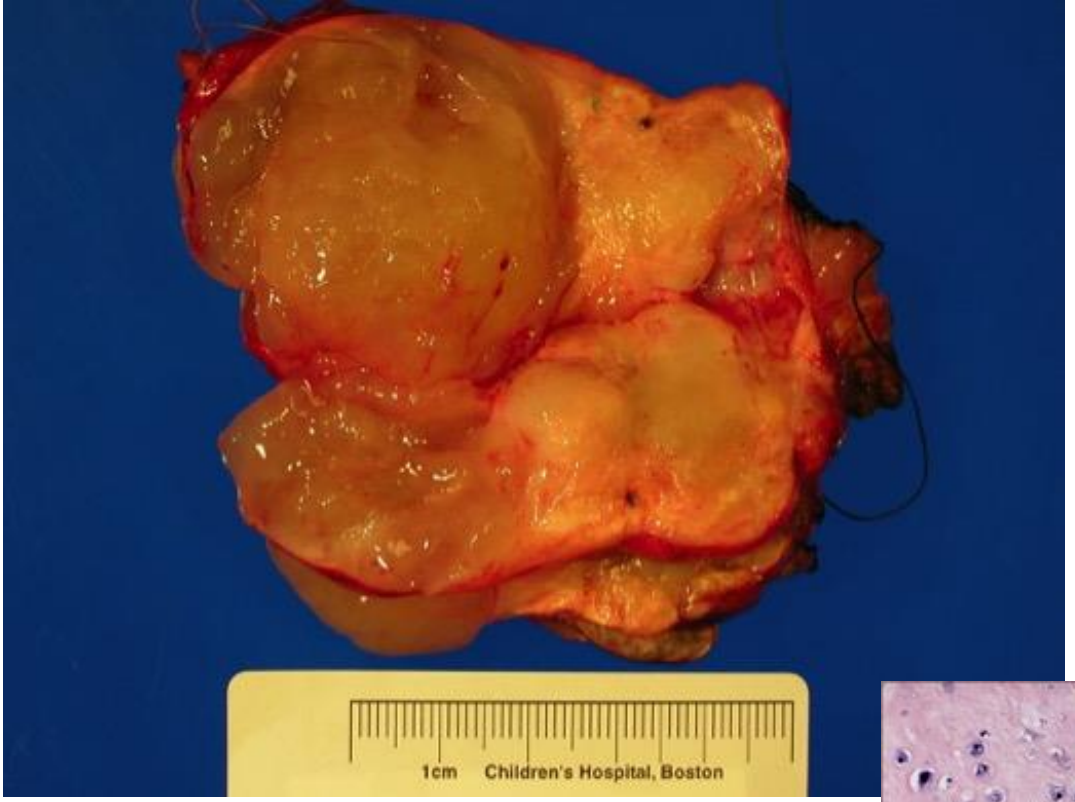


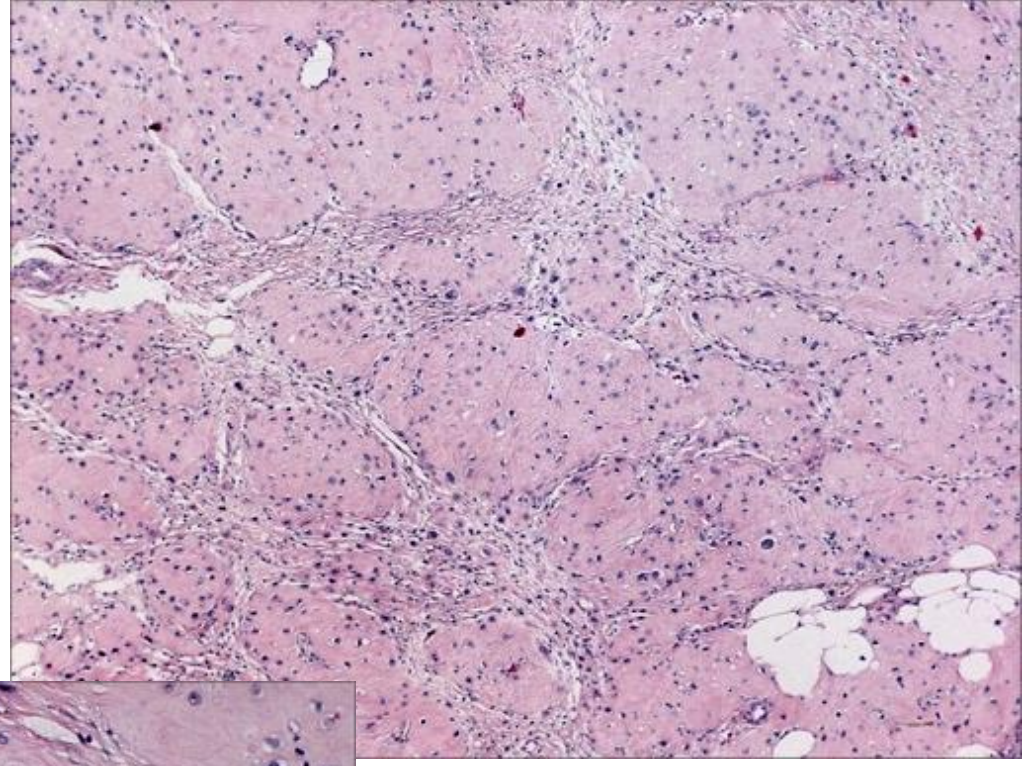

LABORATORY APPARATUS, FURNITURE
SCIENTIFIC INSTRUMENTS & CHEMICALS
VWR

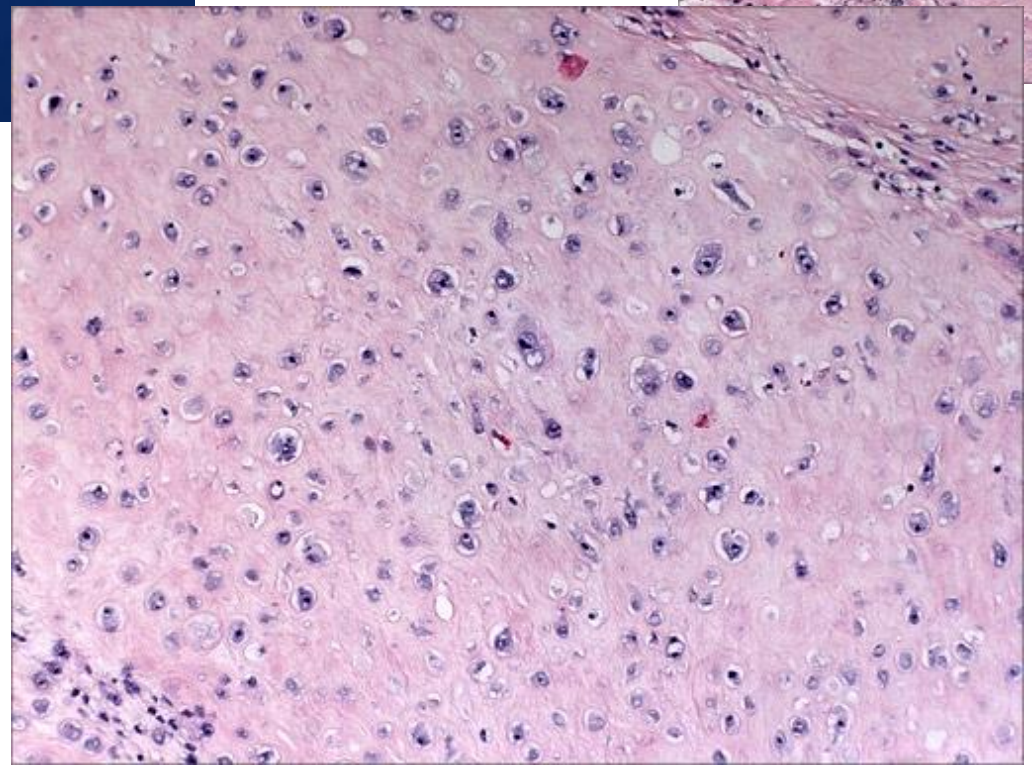


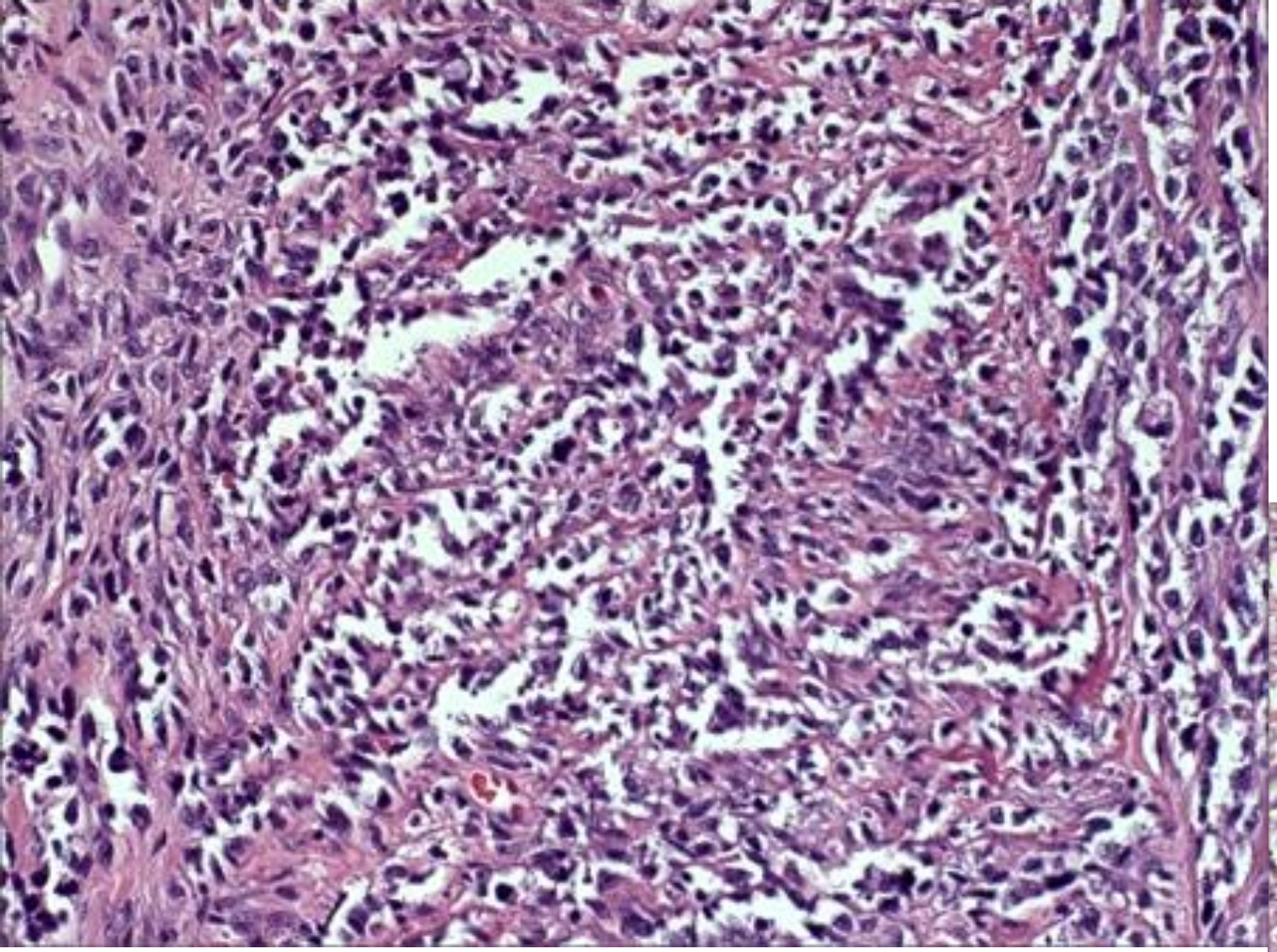


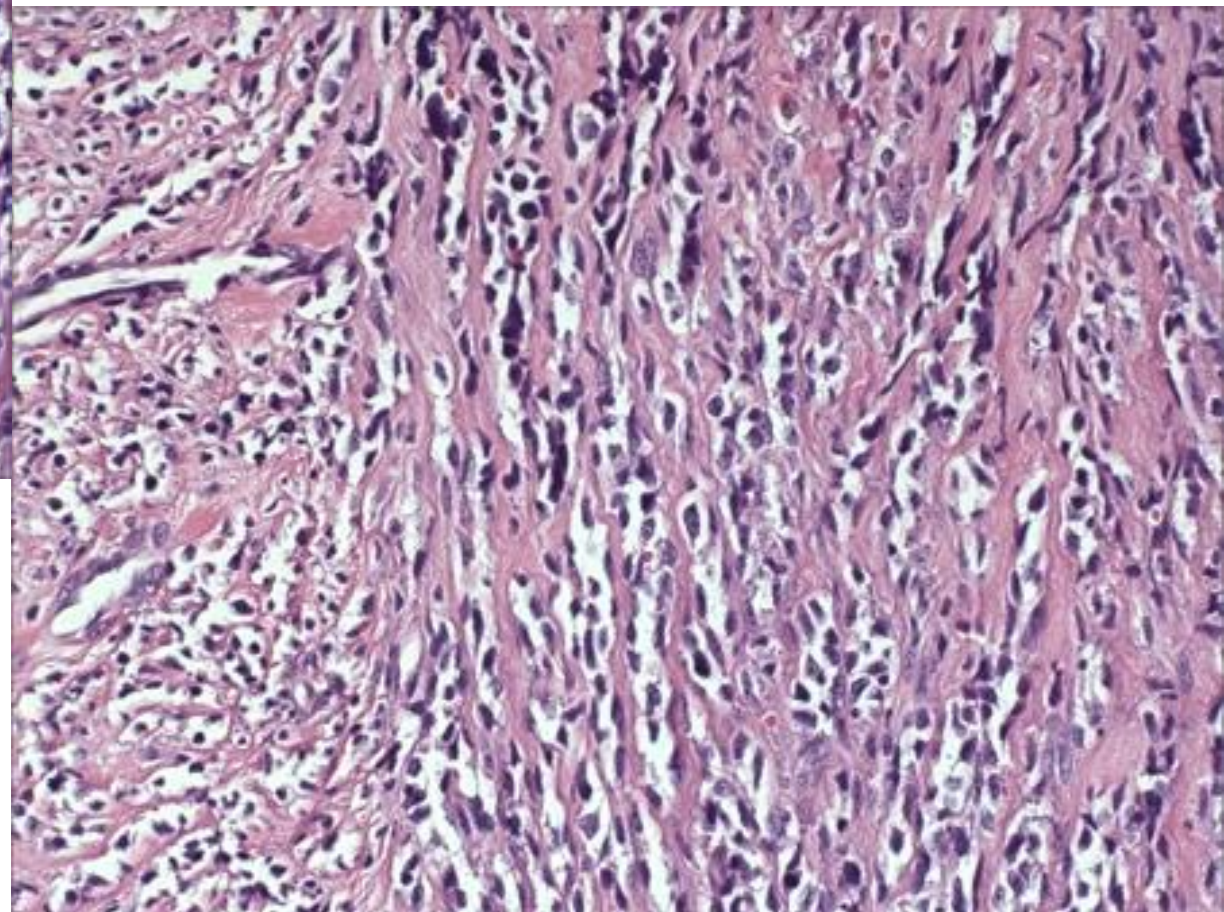



1cm
Children's Hospital, Boston









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Volume 14 Number 3
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Pediatric Sclerosing Rhabdomyosarcoma

Eduardo Zambrano, MD, MSc, Antonio R Pérez-Atayde, MD,
William Ahrens, MD, Miguel Reyes-Múgica, MD

Sclerosing rhabdomyosarcoma, a particular phenotypic variant of rhabdomyosarcoma initially described in the adult population, has emerged as a potential pitfall in the evaluation of pediatric sarcomas. Because of its densely hyalinized collagenous matrix and its occasional expression of a pseudovascular pattern of growth, sclerosing rhabdomyosarcoma has been at times misdiagnosed as chondrosarcoma, osteosarcoma, or angiosarcoma. We describe 3 pediatric patients with sclerosing rhabdomyosarcoma and provide a detailed description of its distinguishing pathologic features. Awareness about this rhabdomyosarcoma variant and careful immunophenotypical evaluation are necessary to establish the correct diagnosis. Although no specific genetic aberrations have been yet recognized, the cytogenetic findings in 2 tumors of this series suggest a link with embryonal rhabdomyosarcoma. It is likely that further genotyping will result in better nosologic delineation of sclerosing rhabdomyosarcoma and that it will uncover pathogenetically and prognostically relevant genes.

Keywords: sclerosing rhabdomyosarcoma, sarcomas in children; hyalinized collagenous matrix

Am J Surg Pathol • Volume 00, Number 00, ■■ 2015

ORIGINAL ARTICLE

A Molecular Study of Pediatric Spindle and Sclerosing Rhabdomyosarcoma

Identification of Novel and Recurrent VGLL2-related Fusions in Infantile Cases

Rita Alaggio, MD, Lei Zhang, MD,† Yun-Shao Sung, MSc,† Shih-Chiang Huang, MD,† Chun-Liang Chen, MSc,† Gianni Bisogno, MD,‡ Angelica Zin, PhD,§ Narasimhan P. Agaram, MD,† Michael P. LaQuaglia, MD,‖ Leonard H. Wexler, MD,¶ and Cristina R. Antonescu, MD†*

TABLE 1. Clinicopathologic and Molecular Features of Pediatric SRMS/ScRMS

RMS#	Age/Sex	Site	Diagnosis	Molecular Results	FU (y)	IRS	Status
1*	0.7/M	Post-neck	SRMS	SRF-NCOA2†	3	I	NED, CR2
2*	4W/M	Chest wall	SRMS	TEAD1-NCOA2	3	IIa	NED
3*,‡	0.3/F	Chest wall	SRMS	VGLL2-NCOA2	13	III	NED, CR4
4	0/M	Calf	SRMS	TEAD1-NCOA2	NA	NA	NA
5	0.2/F	Back	SRMS	VGLL2-NCOA2	NA	NA	NA
6	0/F	Back	SRMS	VGLL2-CITED2†	9	III	NED, CR
7	0/F	Back	SRMS	VGLL2-CITED2†	6	III	NED, CR
8	0.7/F	Back	SRMS	VGLL2-CITED2	8	II	NED, CR
9	0/F	Lower neck/back	SRMS	VGLL2-CITED2	Recent case	I	In therapy
10	0.8/M	Chest wall	SRMS	VGLL2	NA	NA	NA
11	0.4/M	Paravertebral	SRMS	—	NA	NA	NA
12§	10/F	Paraspinal	SRMS	MyoD1 (L122R)‖	3	III	DOD
13§	2/F	Buttock	SRMS	MyoD1 (L122R)	1	IIa	DOD
14	17/M	Paravertebral	ScRMS	MyoD1 (L122R)‖	2	III	DOD
15§	15/F	Infratemporal	ScRMS	MyoD1 (L122R)‖,¶	1	III	DOD
16§	13/F	Back	ScRMS	MyoD1 (L122R)‖,¶	2	III	DOD
17	10/F	Buttock	ScRMS	MyoD1 (L122R) ¶,† FGFR4 (V548M)	0.5	III	DOD
18	8/M	Thigh	ScRMS	MyoD1 (L122R)‖	1	III	NED, CR1
19	11/F	H&N	ScRMS	MyoD1 (L122R)‖,¶	Recent case	I	In therapy
20	9/M	H&N	SRMS	MyoD1 (L122R)‖	3	III	AWD (2nd LR)
21	9/F	H&N	SRMS	MyoD1 (L122R)‖	1	III	DOD
22	3/M	Intra-abd	SRMS	—	13	I	NED, CR2
23	16/M	Paratesticular	SRMS	—	1	I	NED, CR
24	5/F	Intra-abd	SRMS	FGFR4 (V550L)	NA	NA	NA
25	2.8/F	Ovary/salpinx	SRMS	—	2	III	DOD
26	11/M	Paratesticular	ScRMS	—	1	II	NED, CR

- Grupo genética y clínicamente heterogéneo de enfermedades con 3 subtipos moleculares distintos:

1. **Tumores que presentan al nacimiento o durante el primer año de vida:** predilección en tronco; están asociados a fusiones recurrentes de genes involucrados en la activación transcripcional de genes músculo-específicos, tales como *VGLL2, TEAD1, NCOA2* y *SRF*. Curso clínico favorable sin potencial metastástico.
2. **Tumores MYOD1-mutantes:** ocurren en pacientes mayores de un año (y adultos) y siguen un curso altamente agresivo con alto índice de mortalidad y resistencia a terapia multimodal.
3. Existe un grupo de tumores predominantemente intra-abdominales o genito-urinarios en los que no se han identificado fusiones génicas o mutaciones de MYOD1. Este grupo sigue un curso clínico favorable.

Genes Chromosomes Cancer. 2021;60:687–694.

RESEARCH ARTICLE

Novel fusion genes in spindle cell rhabdomyosarcoma: The spectrum broadens

Diego M. Montoya-Cerrillo | Julio A. Diaz-Perez | Jaylou M. Velez-Torres | Elizabeth A Montgomery | Andrew E. Rosenberg

Nuevas fusiones genéticas en 3 casos de SRMS:

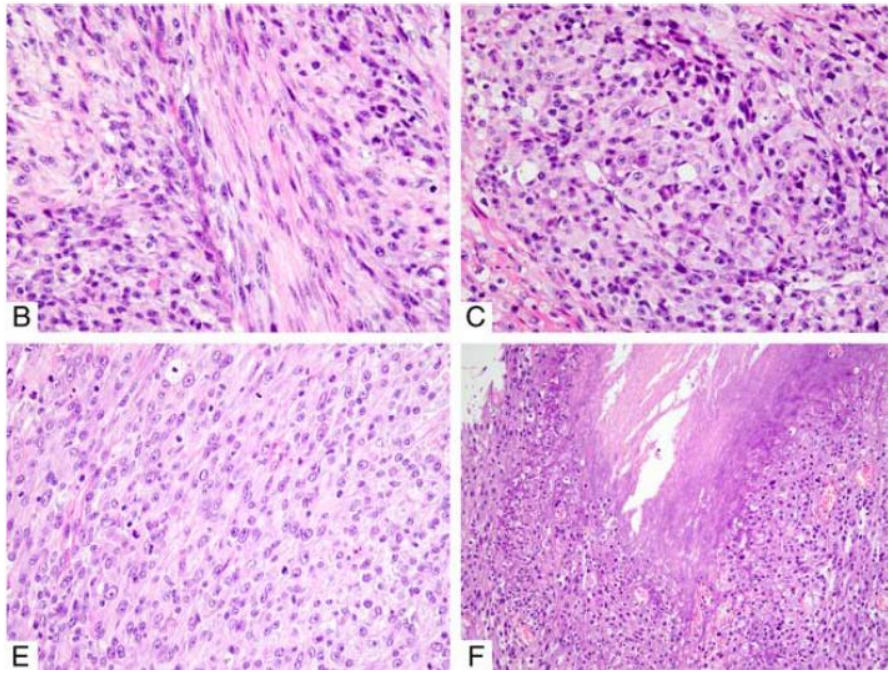
- *EP300-VGLL3*
- *NCOA2-MEIS1* y *CAV1-MET*
- *HMGA2-NEGR1* con múltiples gene amplificados

Am J Surg Pathol • Volume 43, Number 5, May 2019

Expanding the Spectrum of Intraosseous Rhabdomyosarcoma

Correlation Between 2 Distinct Gene Fusions and Phenotype

Narasimhan P. Agaram, MBBS, Lei Zhang, MD,* Yun-Shao Sung, MSc,* Marcela S. Cavalcanti, MD,† Dianne Torrence, MD,‡ Leonard Wexler, MD,§ Glenn Francis, MD,‖ Scott Sommerville, MD,¶ David Swanson, BSc,# Brendan C. Dickson, MSc, MD,# Albert J.H. Suurmeijer, MD, PhD,** Richard Williamson, MD,†† and Cristina R. Antonescu, MD**



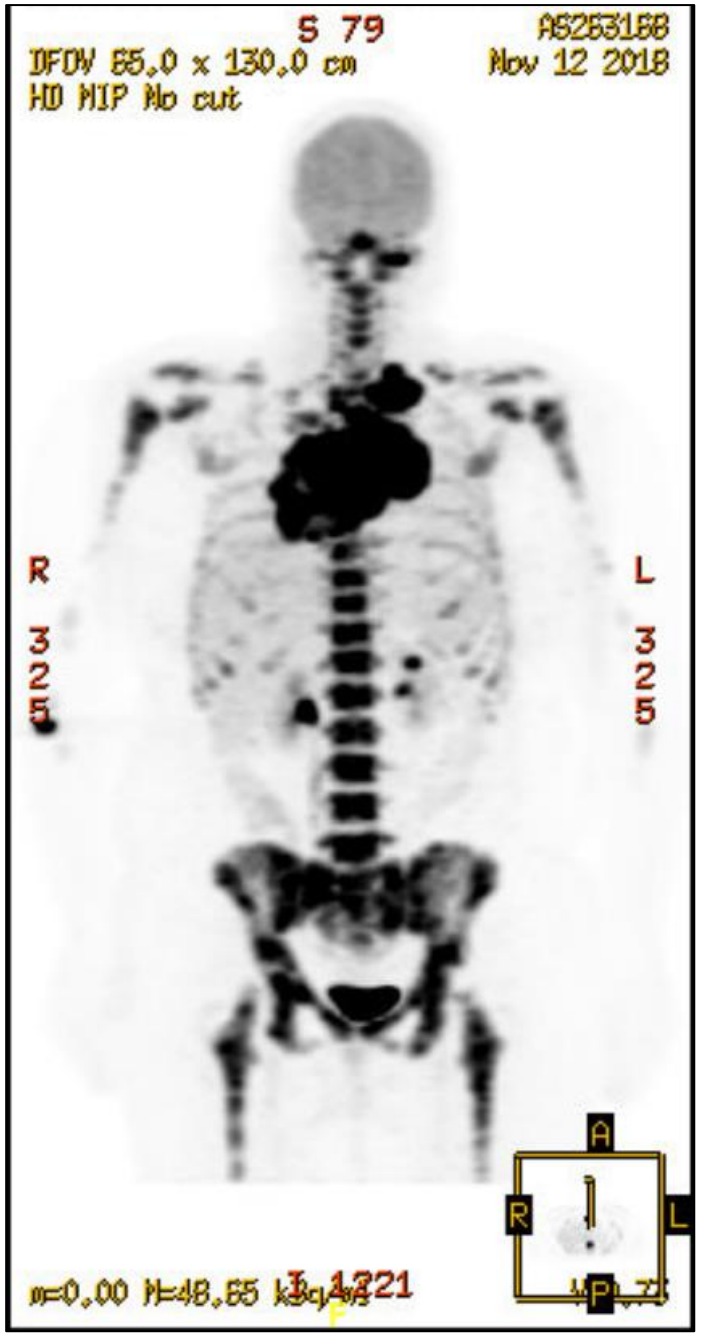
- Edad: 16-72 años
- Pelvis, fémur, huesos del cráneo, pared torácica
- Morfología fusocelular y/o epitelioide
- *EWSR1-TFCP2, FUS-TFCP2, MEIS1-NCOA2*

RMS – Diágnosticos Diferenciales

- Tumores que expresan desmina:
  - Tumor tenosinovial de células gigantes
  - Fibrohistiocitoma angiomatoide
  - Tumor desmoplásico de células pequeñas redondas
  - Tumores de músculo liso
- Tumores que además expresan myogenina y/o MyoD1
  - Tumor maligno de vaina de nervio periférico (Tritón)
  - Ectomesenquimoma
  - Sarcoma indiferenciado de células redondas *EWSR1-PATZ1*

Historia Clínica

- Mujer de 22 años quien presenta por linfadenopatía supraclavicular dolorosa (3 cm).
- Pérdida de peso de 30 lbs y letargo
- Imágenes: múltiples linfadenopatías, anormalidades óseas difusas y masa mediastinal 12 x 10 cm; sospechoso para linfoma.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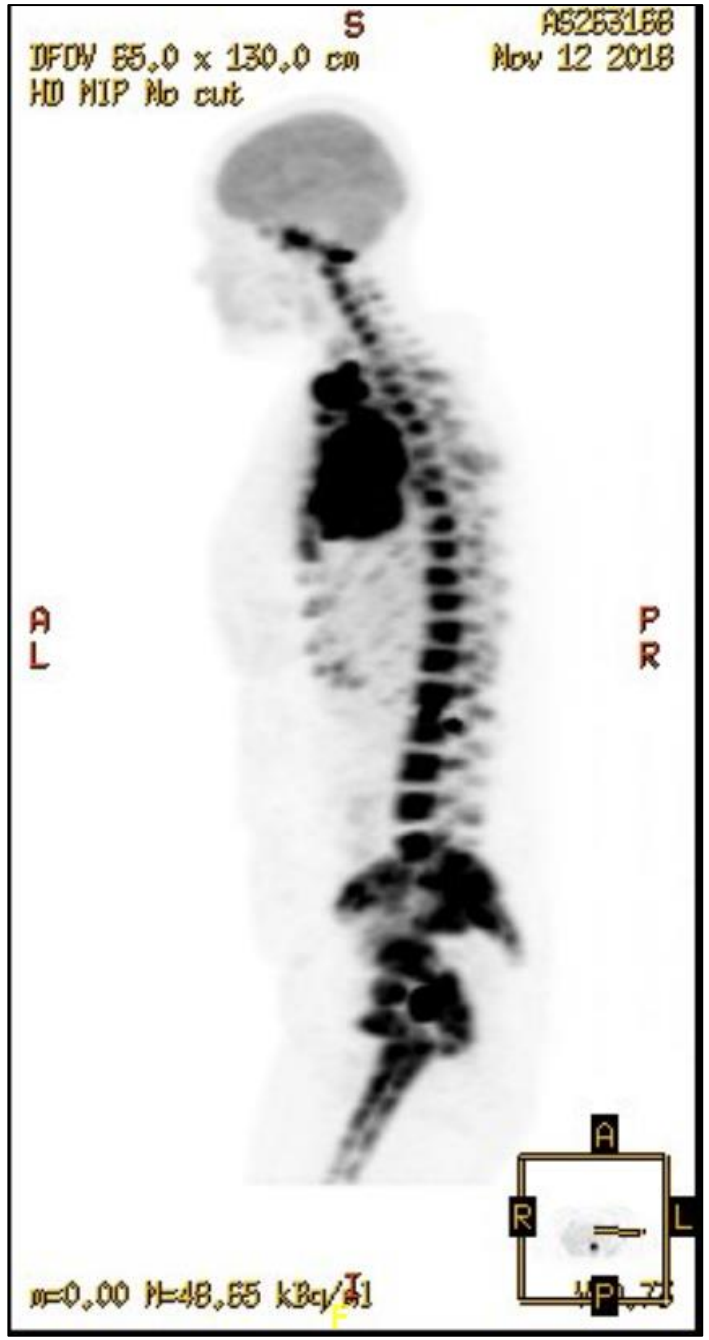
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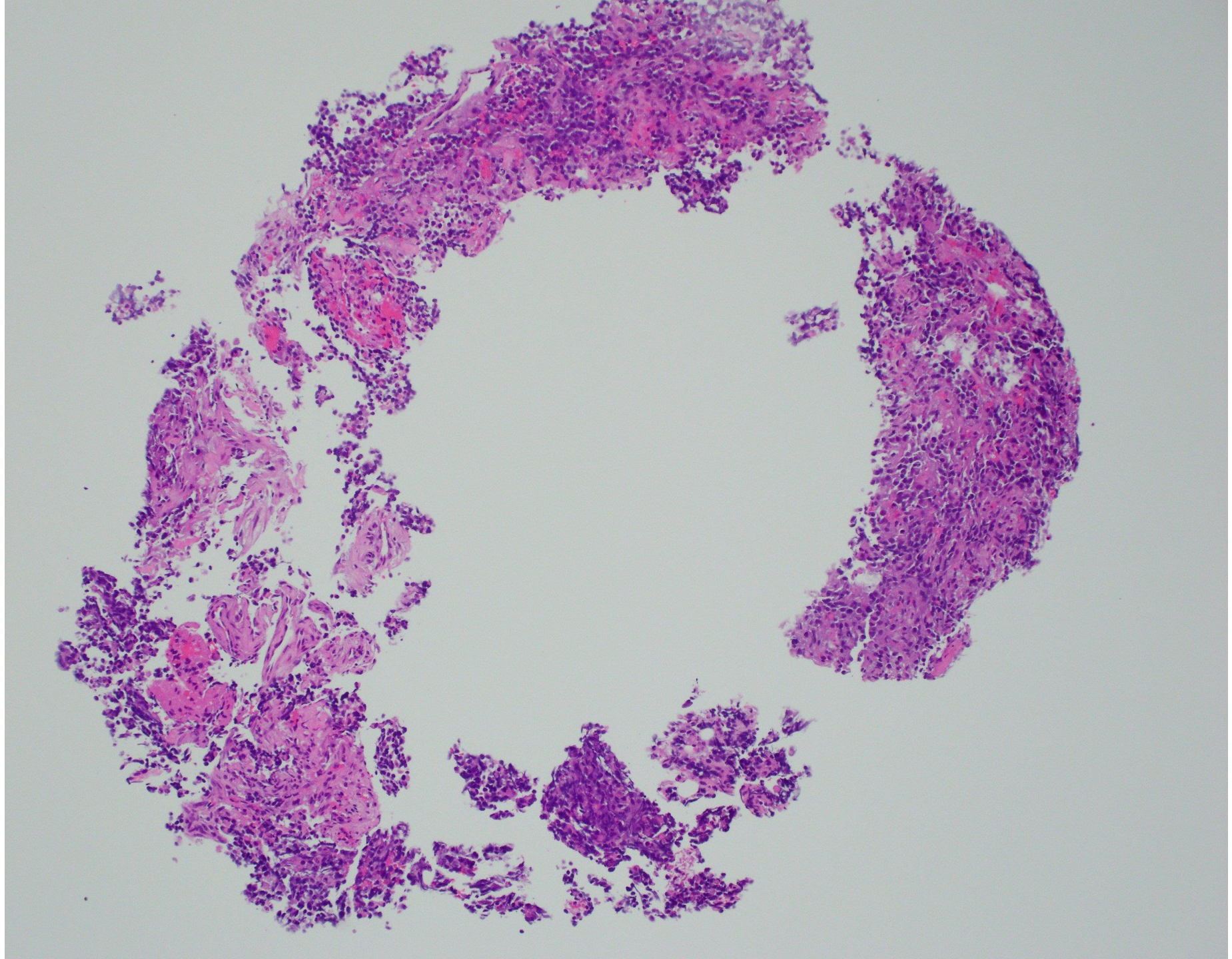
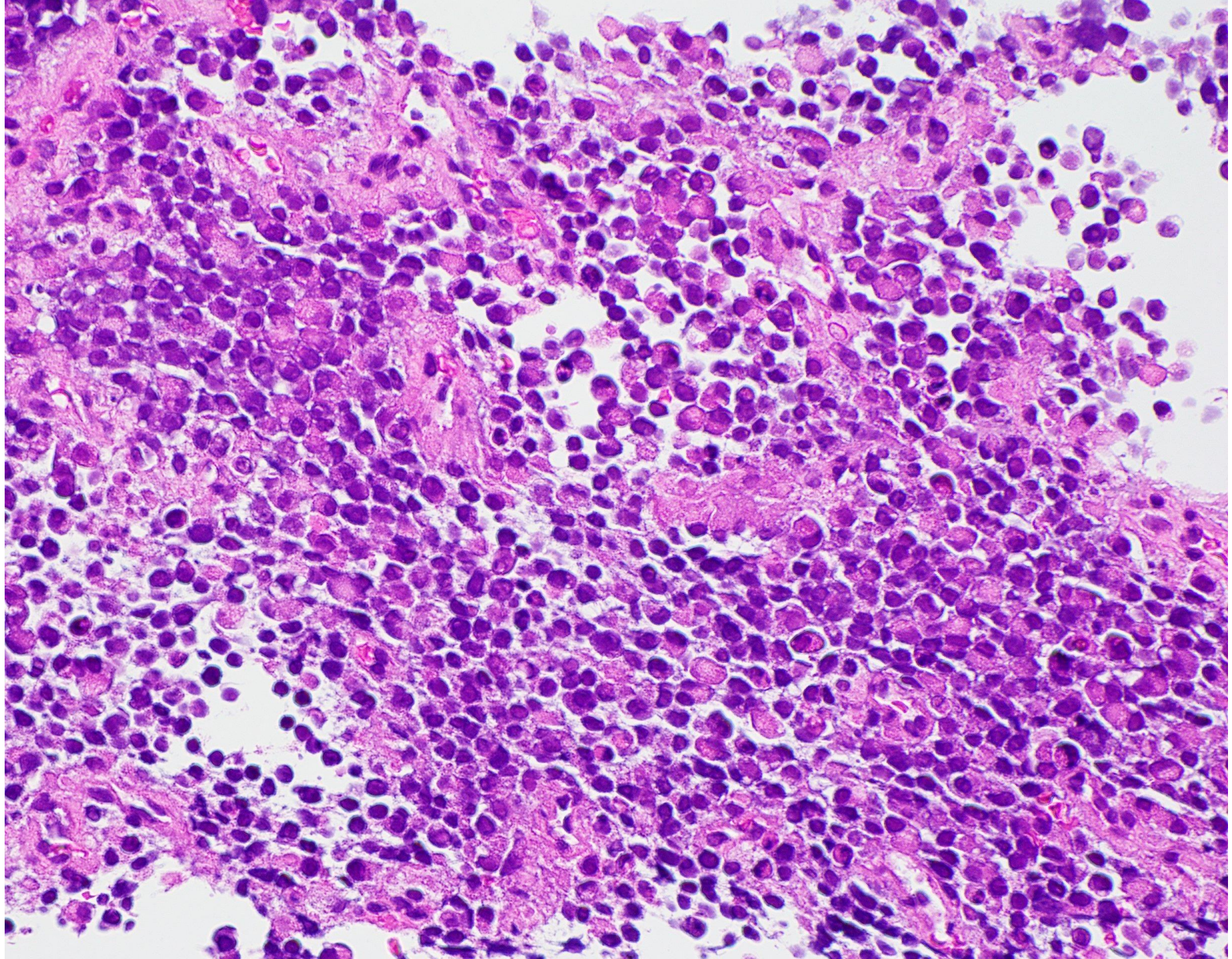
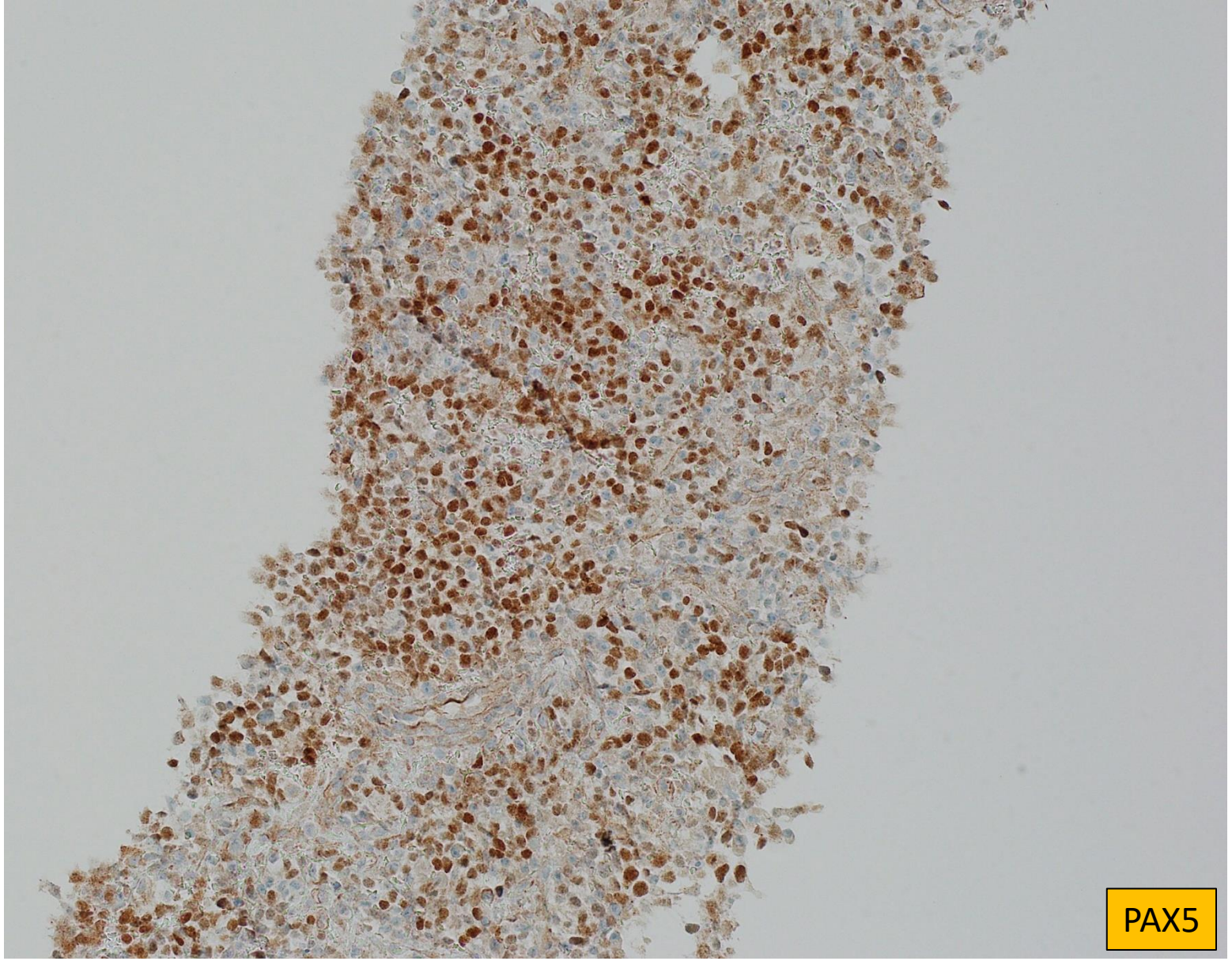






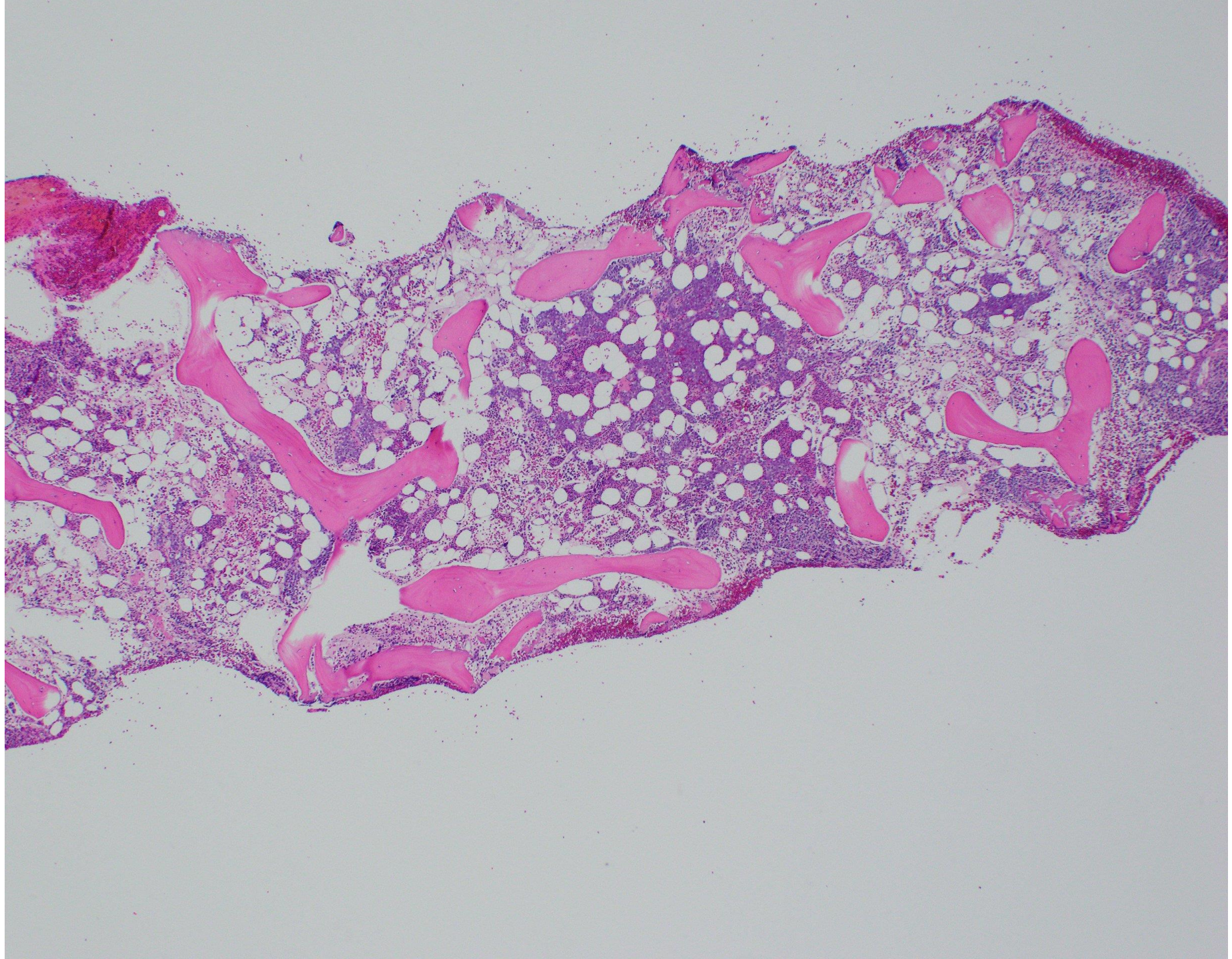
Results

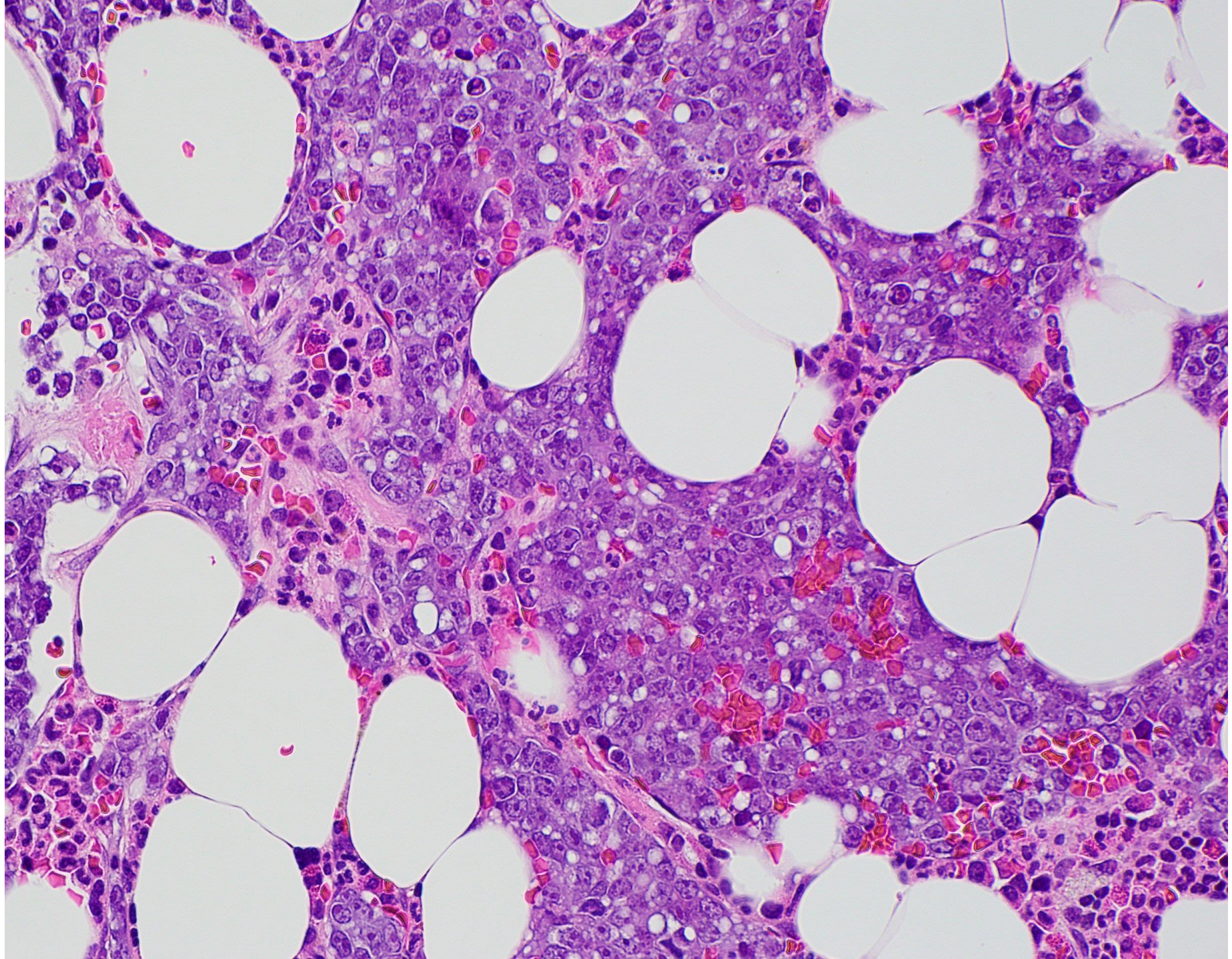
CD19	cMyc	TdT
Negative	Positive	Negative

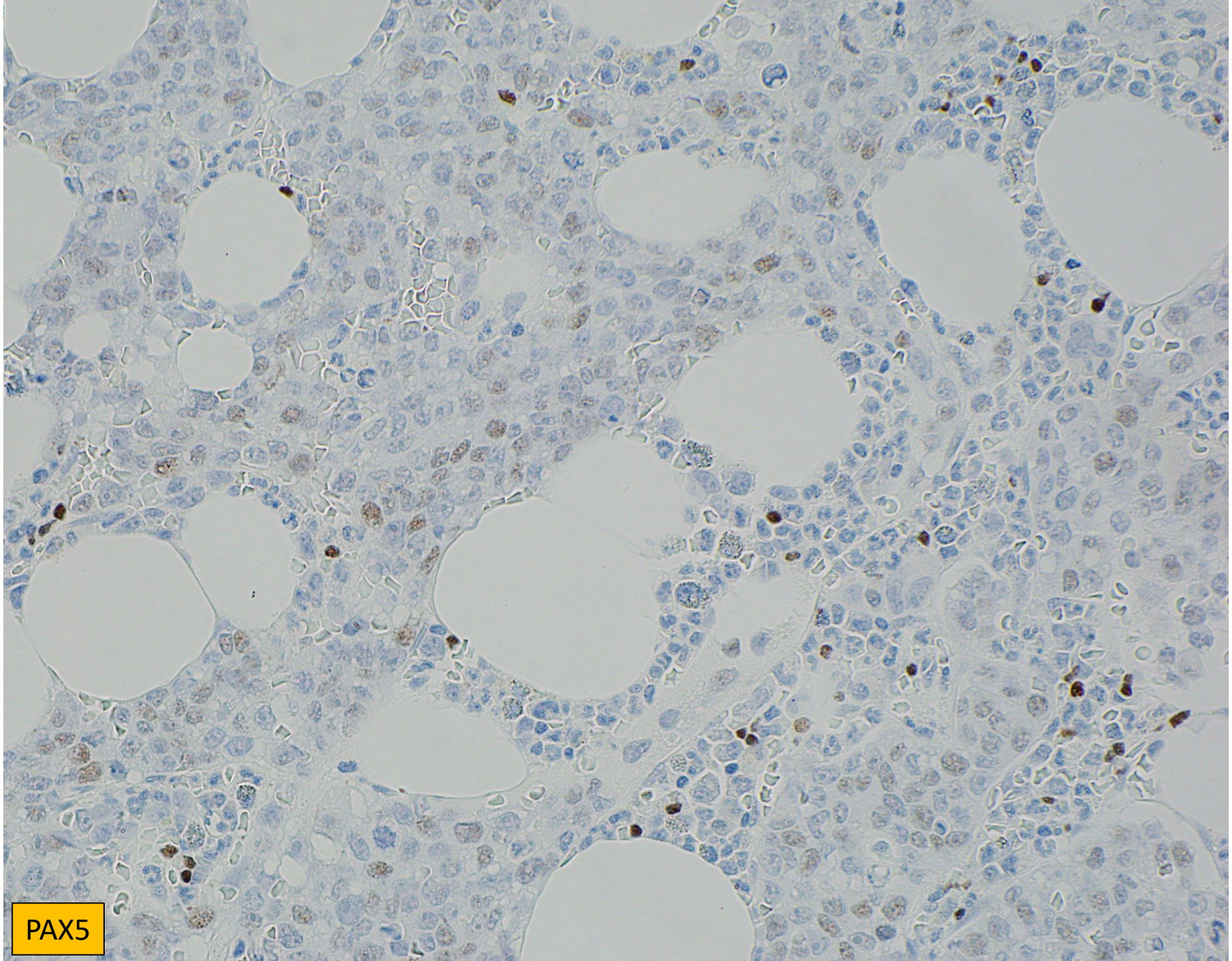
Lymph node, left supraclavicular, ultrasound-guided needle core biopsy:

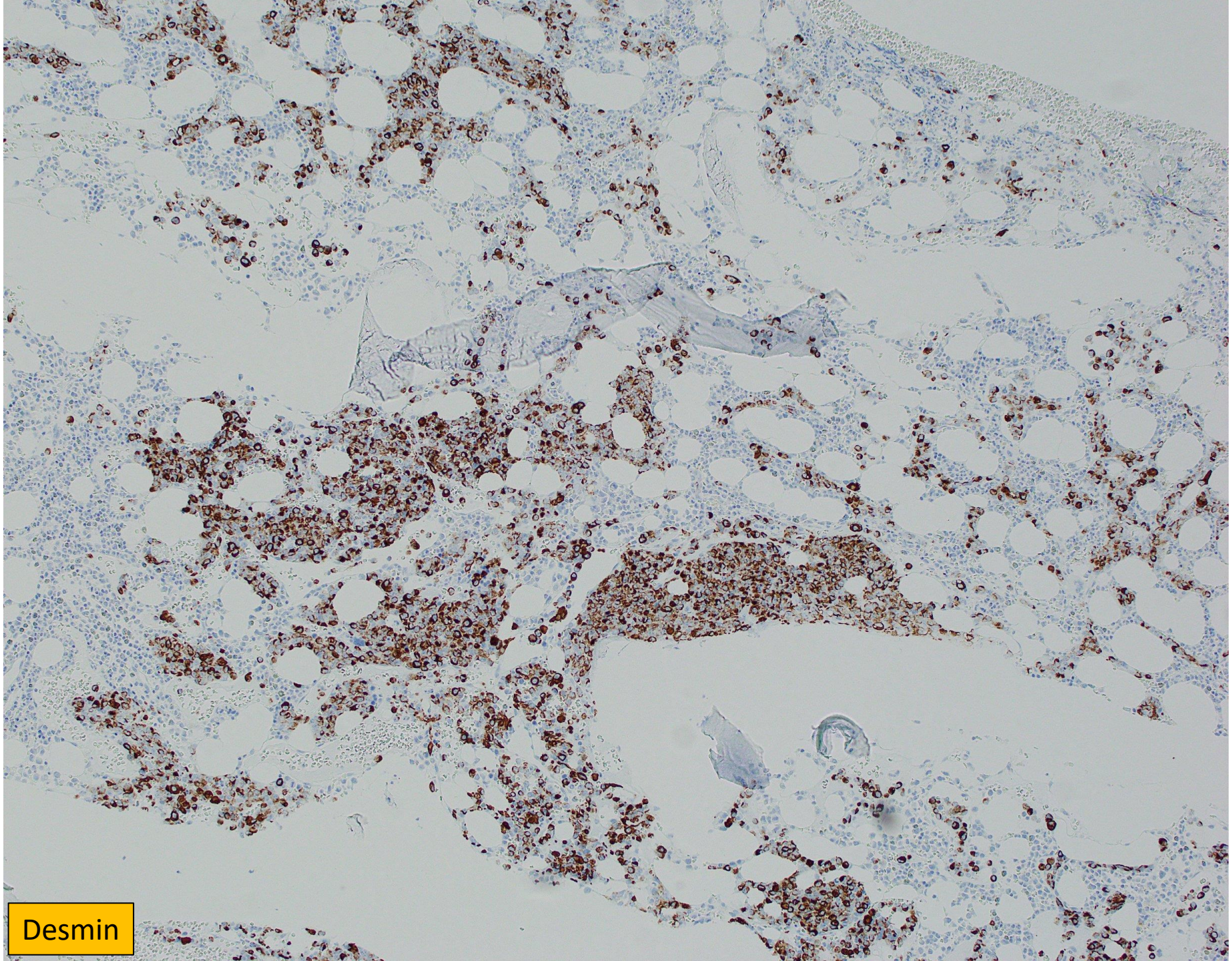
- Poorly differentiated, necrotic malignancy, most suggestive of a B lymphoproliferative neoplasm, see comment.

COMMENT: The findings are highly concerning for a B lymphoblastic lymphoma/leukemia, given the patient's age and mediastinal mass(...) Because of the extensive necrosis, definitive diagnosis may not be attainable with this biopsy(…)






PAX5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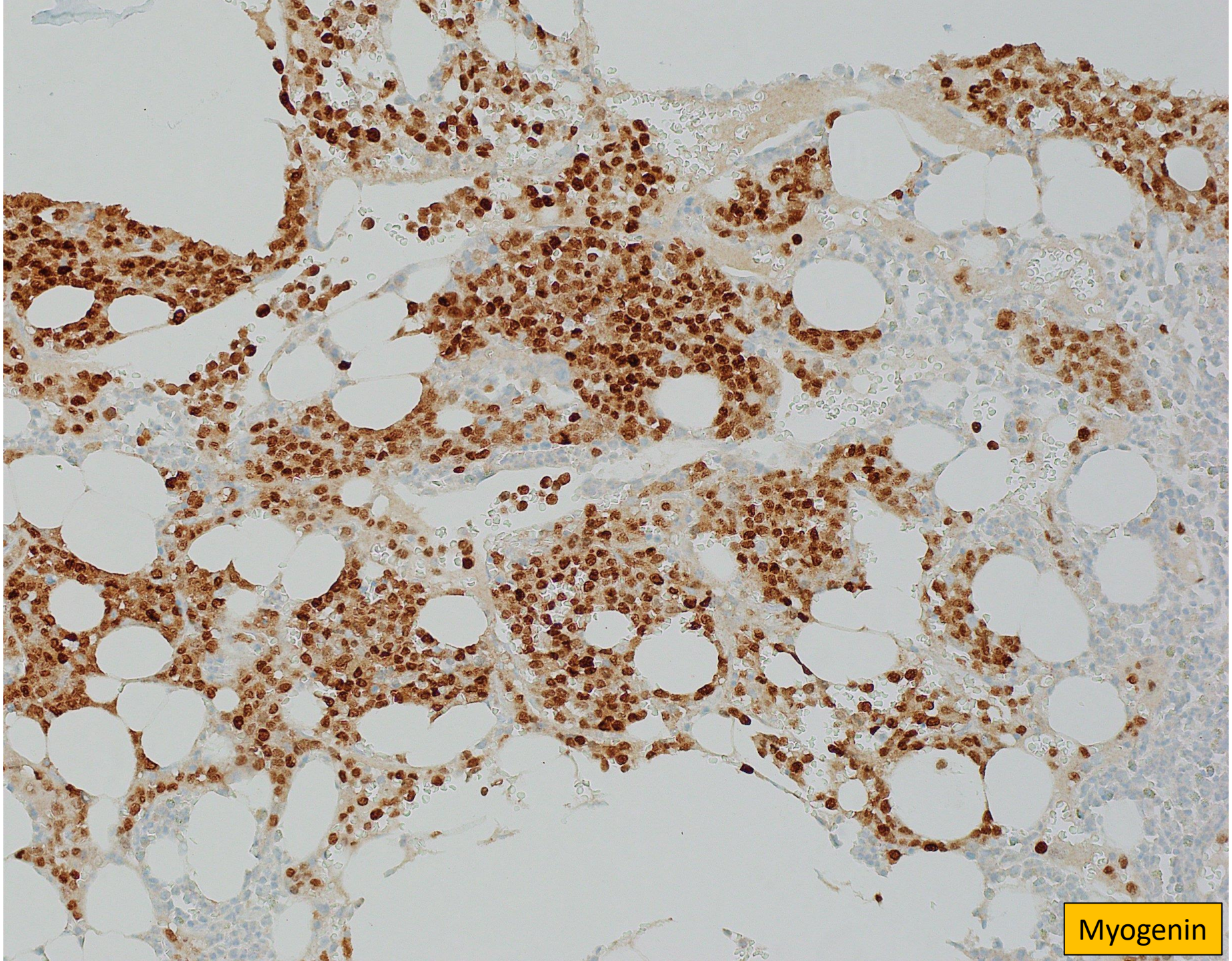
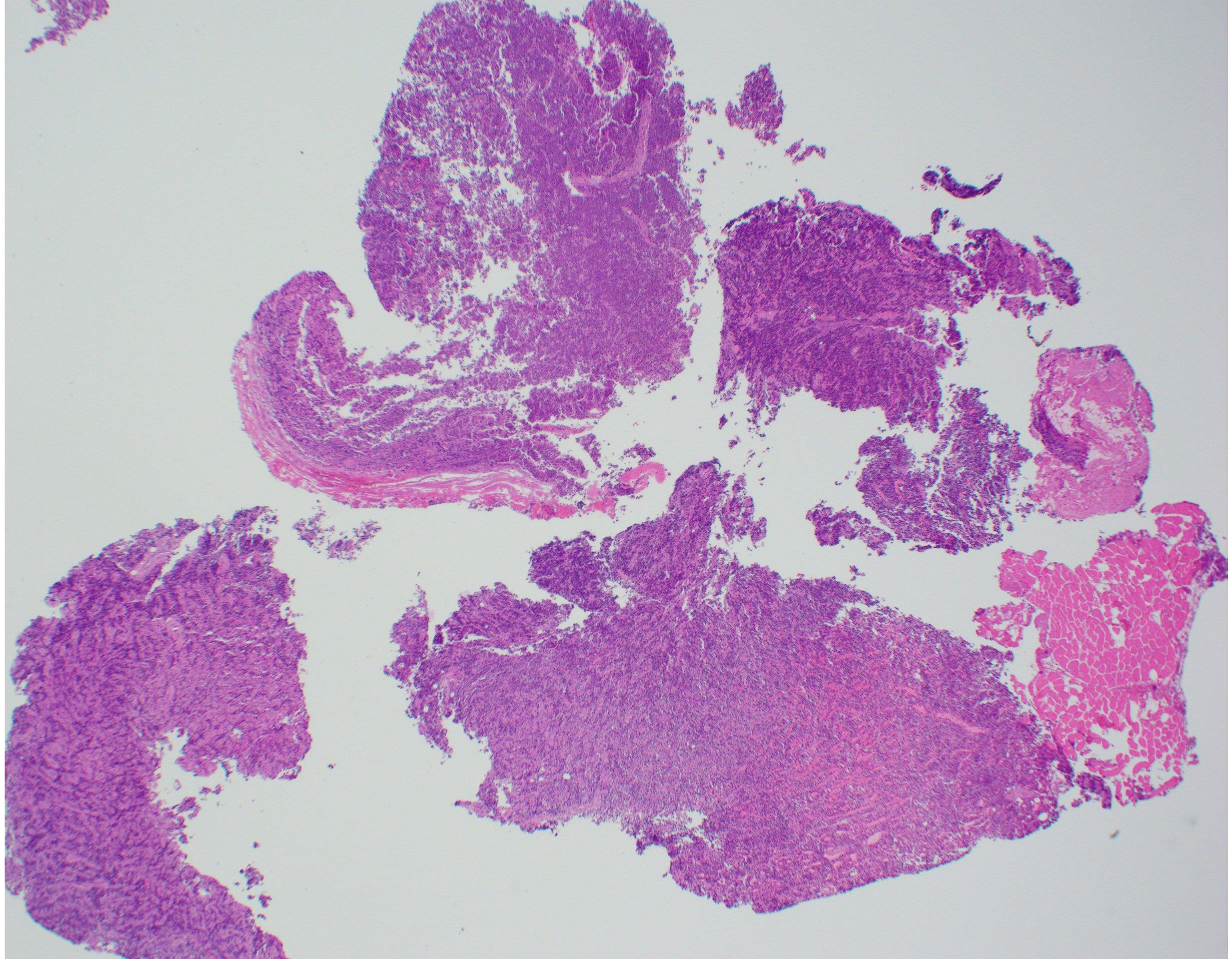
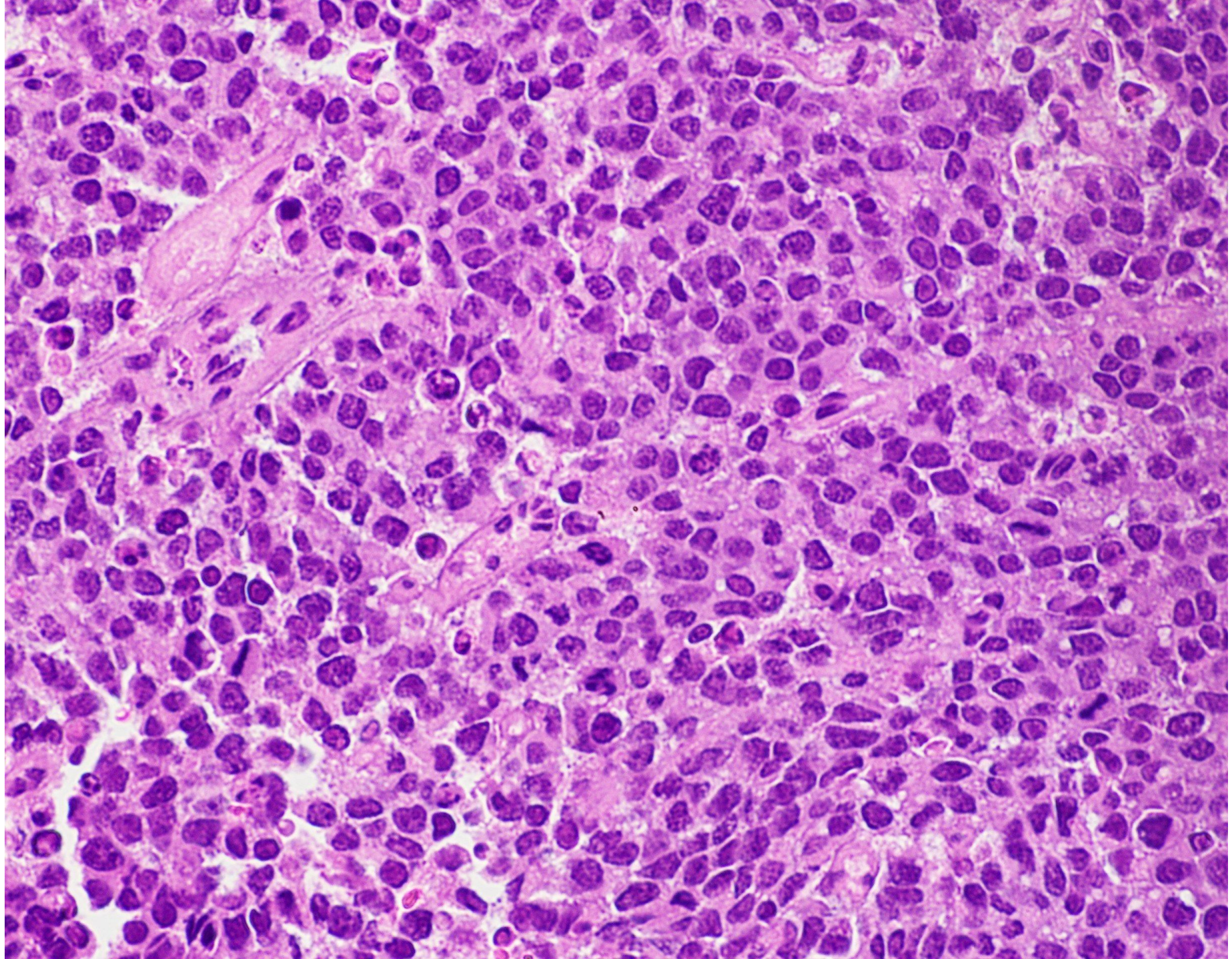
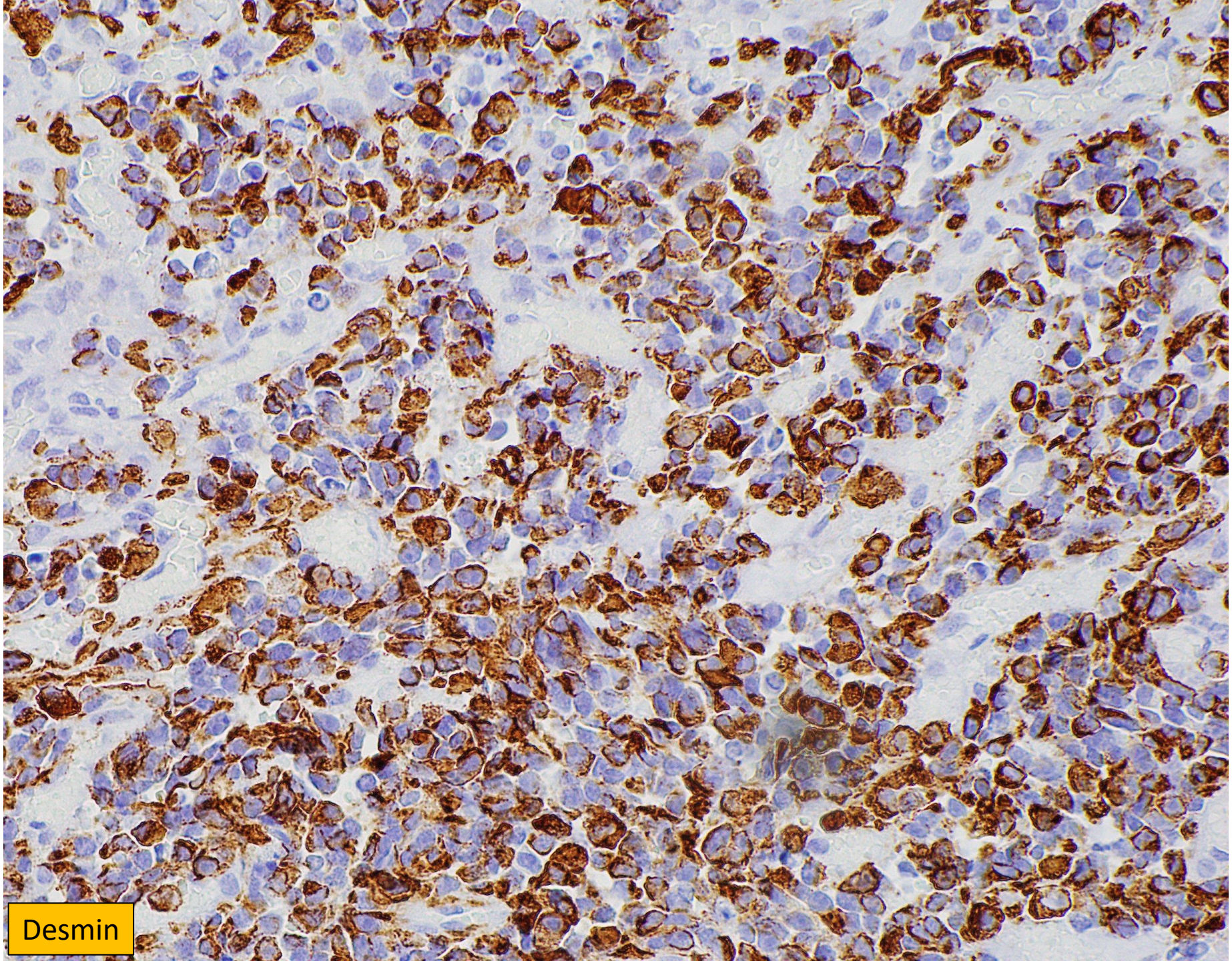

Myogenin

Lymph node, supraclavicular, biopsy:



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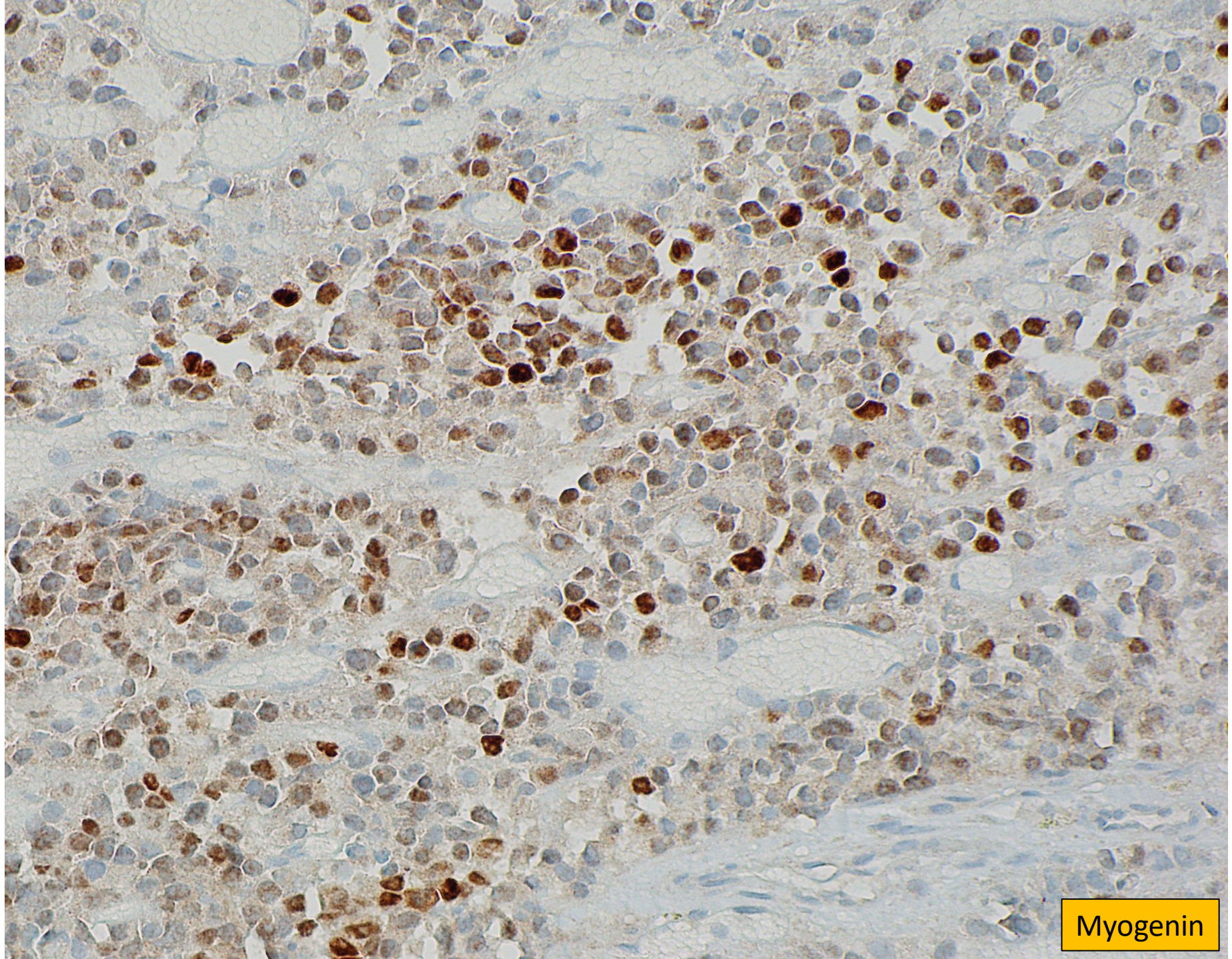

Myogenin

Left supraclavicular node and bone marrow biopsies:

- Rhabdomyosarcoma.

Comment: Additional studies pending for further classification.

American Journal of Hematology 68:51–57 (2001)

Hematologic Masquerade of Rhabdomyosarcoma

Avery A. Sandberg,[1]* John F. Stone,[1] Lawrence Czarnecki,[2] and Jesse D. Cohen[3]

[1]Department of DNA Diagnostics, St. Joseph's Hospital and Medical Center, Phoenix, Arizona
[2]Department of Pathology, St. Joseph's Hospital and Medical Center, Phoenix, Arizona
[3]Department of Pediatrics, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

Eur J Pediatr (2007) 166:505–506
DOI 10.1007/s00431-006-0269-y

SHORT REPORT

Alveolar rhabdomyosarcoma mimicking lymphoma with bone marrow involvement

Christof Andreas Hanke · Jochen Roessler · Sabine Stegmaier · Eva Koscielniak · Charlotte Marie Niemeyer · Udo Kontny

Imataki *et al. Diagnostic Pathology* (2017) 12:77
DOI 10.1186/s13000-017-0667-7

Diagnostic Pathology

CASE REPORT Open Access

Complete mimicry: a case of alveolar rhabdomyosarcoma masquerading as acute leukemia

Osamu Imataki[1,4*], Makiko Uemura[1], Shumpei Uchida[1], Shigeyuki Yokokura[1], Akihiro Takeuchi[2], Ryo Ishikawa[3], Akihiro Kondo[2], Kayoko Seo[2] and Norimitsu Kadowaki[1]

RMS Subtyping

Alveolar RMS

- Age
- Strong diffuse myogenin staining on BM Bx
- Round cell morphology
- Aggressive, hematological malignancy-like clinical presentation

Embryonal RMS

- Patchy myogenin staining on supraclavicular Bx
- No alveolar architecture

5'FOX01/3'FOX01 (FKHR, 13q14)	Negative rearrangement	100.0	200

KARYOTYPE:
47,XX,+X,8~91dmin[13]/49,sl,+4,+17,80~100dmin[2]/48,XX,+6,+17,4~51dmin[3]/
46,XX[3]

INTERPRETATION:
Cytogenetic studies of a bone marrow aspirate specimen revealed three related abnormal clones in eighteen of twenty one metaphase spreads examined, as described in the karyotype result. Notable abnormalities include a hyperdiploid (>46) chromosome count with gain of chromosomes X, 4, 6, 8, 17 and the presence of multiple copies of double minute (dmin) or small chromosome fragments. Three cells with a normal karyotype were observed.

Next Generation Sequencing

1719 E. 19th Avenue
Denver, CO 80218
Phone: (720) 754-6851
Fax: (303) 839-6907

Specimen Type: **Paraffin Tissue**
Body Site: **Lymph Node Biopsy**
Specimen ID: **IS-5395 (30433343-A1)**
MRN: **30433343**
Reason for Referral: **Mediastinal Mass**

Collection Date: **11/08/2018**
Received Date: **11/16/2018 02:27:00 AM PST**
Report Date: **12/04/2018 03:33:49 PM EST**

Results:

Fusion	Results	Fusion Partner	Fusion Read (%)	Mutation in Fused genes
FOXO1	Not Detected	Not Detected	Not Detected	Not Detected
NCOA2	Not Detected	Not Detected	Not Detected	Not Detected
TFE3	Not Detected	Not Detected	Not Detected	Not Detected

Interpretation:
THERE IS NO EVIDENCE OF EXPRESSION OF FUSION RNA OR MUTATION INVOLVING FOXO1, NCOA2 AND TFE3 GENES BY NEXT GENERATION SEQUENCING.

GENOMIC FINDINGS:	THERAPIES WITH CLINICAL BENEFIT (IN PT. TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
PIK3CA-H1047R	None	Everolimus Temsirolimus

Clin Cancer Res. 2012 February 1; 18(3): 748–757. doi:10.1158/1078-0432.CCR-11-2056.

ONCOGENE MUTATION PROFILING OF PEDIATRIC SOLID TUMORS REVEALS SIGNIFICANT SUBSETS OF EMBRYONAL RHABDOMYOSARCOMA AND NEUROBLASTOMA WITH MUTATED GENES IN GROWTH SIGNALING PATHWAYS

Neerav Shukla[1], **Nabahet Ameur**[2], **Ismail Yilmaz**[3], **Khedoudja Nafa**[3], **Chyau-Yueh Lau**[3], **Angela Marchetti**[3], **Laetitia Borsu**[3], **Frederic G. Barr**[4], and **Marc Ladanyi**[2,3]

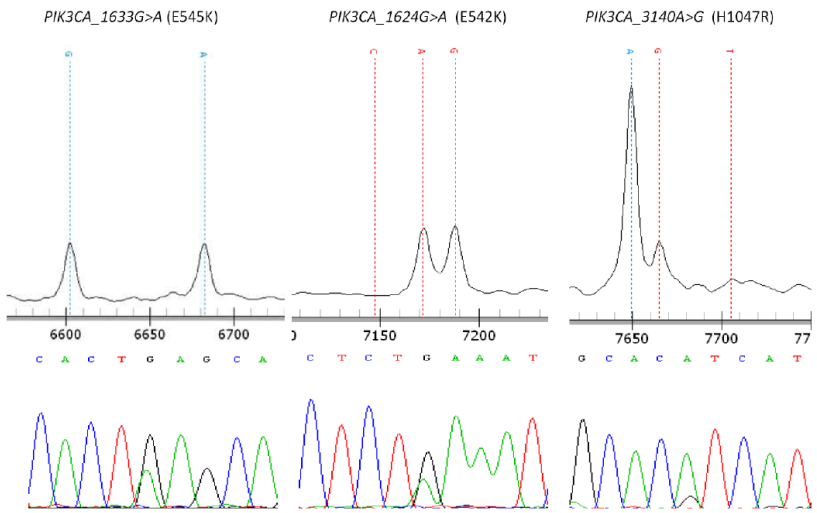


Figure 1. *PIK3CA* mutations in rhabdomyosarcoma
3 mutations were identified by Sequenom analysis and verified by direct sequencing. E542K and E545K mutations involve the helical domain of PIK3CA. The H1047R mutation involves the kinase domain of PIK3CA.

- *PIK3CA* mutations were identified in 5% (3/60) of ERMS cases, but were not seen in any other tumor type.
- Two of the 3 mutations were in the helical domain of the gene (E542K and E545K). The other mutation was located in the kinase domain (H1047R).
- All 3 *PIK3CA*-mutant ERMS patients died of relapsed disease suggesting a more aggressive phenotype than is typical for ERMS. An expanded RMS sample set will be necessary to rigorously assess the impact of *PIK3CA* mutations on outcomes.

Cancer Discov. 2014 February ; 4(2): 216–231. doi:10.1158/2159-8290.CD-13-0639.

Comprehensive genomic analysis of rhabdomyosarcoma reveals a landscape of alterations affecting a common genetic axis in fusion-positive and fusion-negative tumors

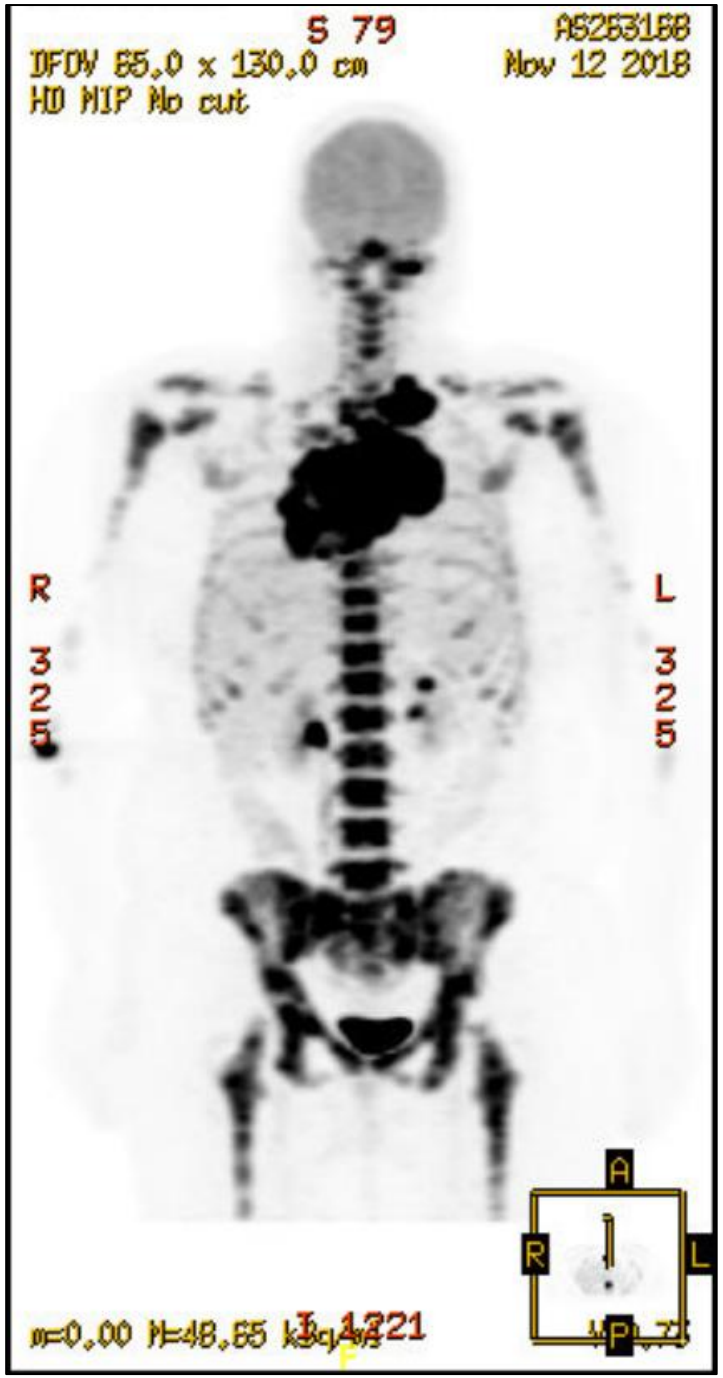
Jack F. Shern[1,*], Li Chen[1,*], Juliann Chmielecki[2,3], Jun S. Wei[1], Rajesh Patidar[1], Mara Rosenberg[2], Lauren Ambrogio[2], Daniel Auclair[2], Jianjun Wang[1], Young K. Song[1], Catherine Tolman[1], Laura Hurd[1], Hongling Liao[1], Shile Zhang[1], Dominik Bogen[1], Andrew S. Brohl[1], Sivasish Sindiri[1], Daniel Catchpoole[4], Thomas Badgett[1], Gad Getz[2], Jaume Mora[5], James R. Anderson[6], Stephen X. Skapek[7], Frederic G. Barr[8], Matthew Meyerson[2,3,9], Douglas S. Hawkins[10], and Javed Khan[1,#]

RAS/PIK3CA/Tyrosine Kinase Mutations predominately affect PAX fusion-negative tumors

- Mutations affecting the receptor tyrosine kinase/RAS/PIK3CA pathway were the most common mutations observed in the study.
- *PIK3CA* mutations (7.4%) occurred at the known oncogenic codons Q546 or H1047 affecting the helical and the kinase domain, respectively.
- Despite a predilection for ERMS tumors (6/7), one fusion positive ARMS tumor also harbored a mutation in *PIK3CA*.

Diagnosis:

- Fusion-negative Rhabdomyosarcoma.
- Embryonal, dense pattern histologic subtype.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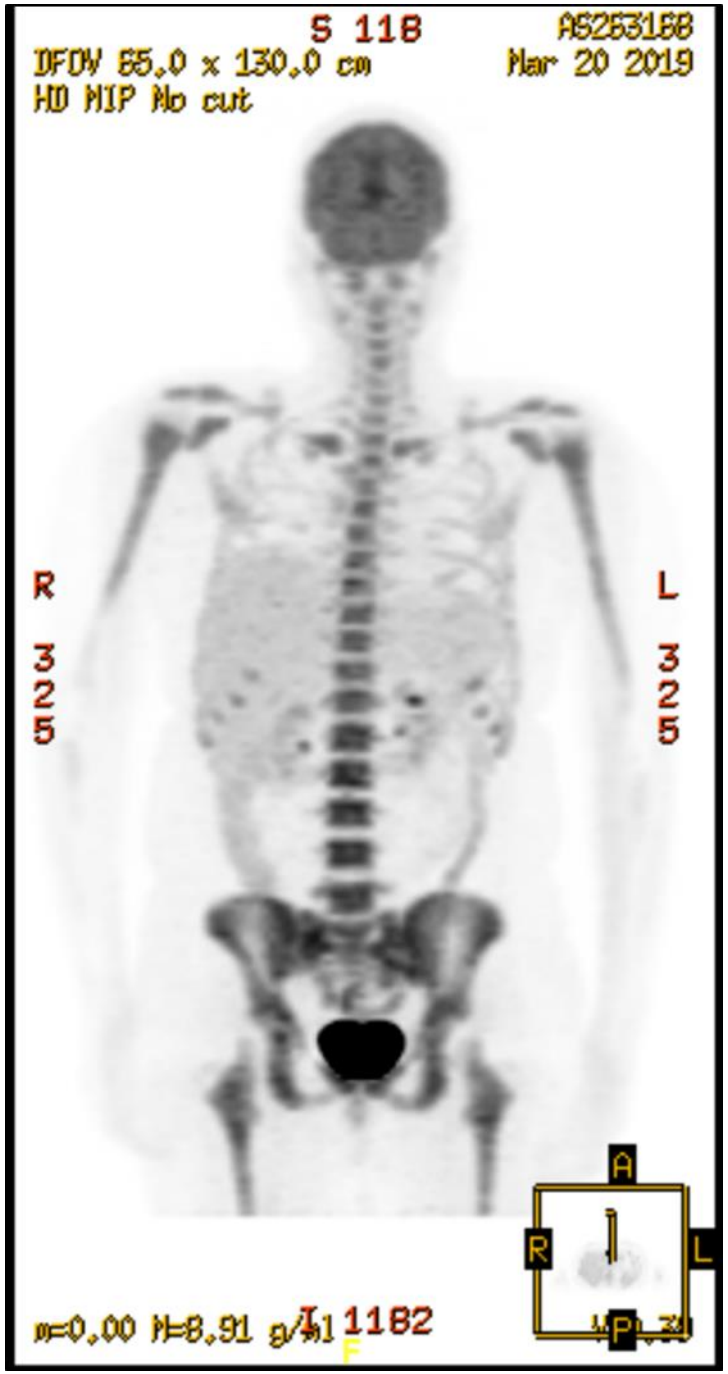
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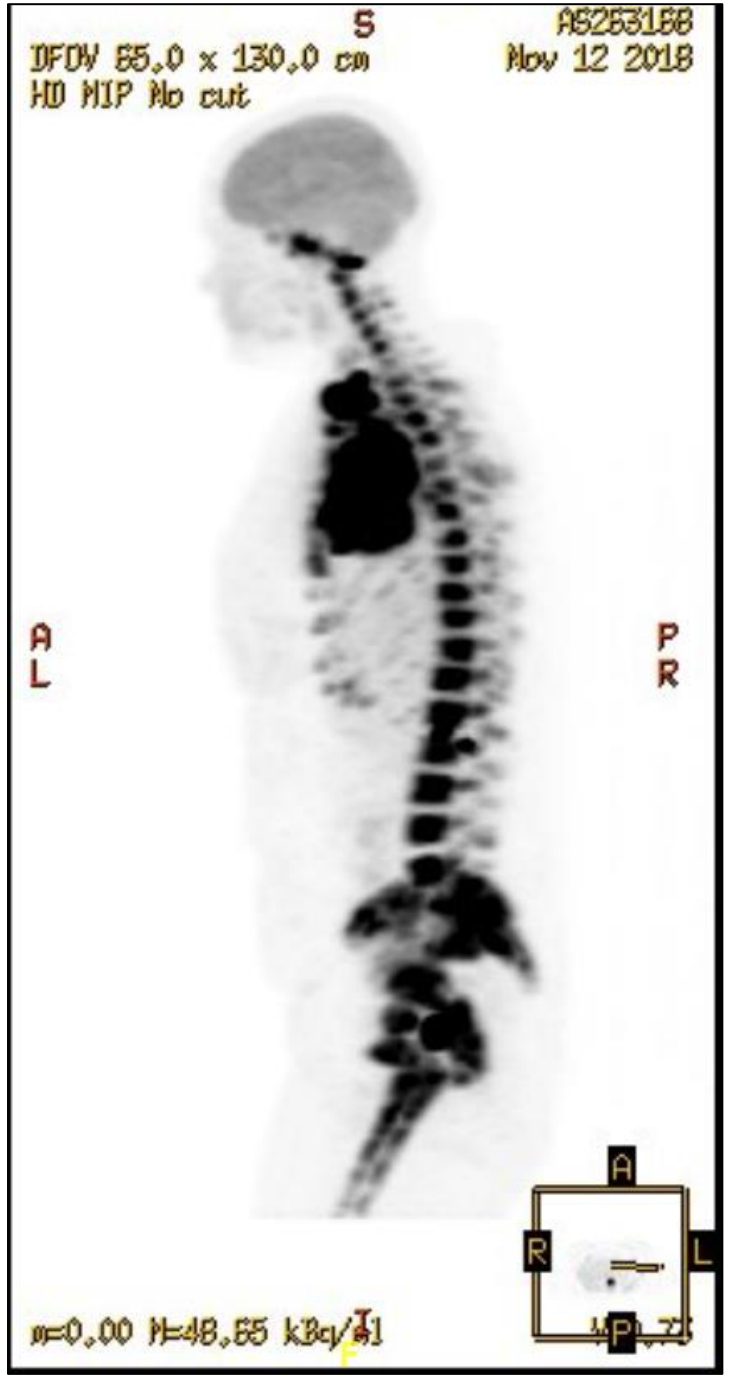
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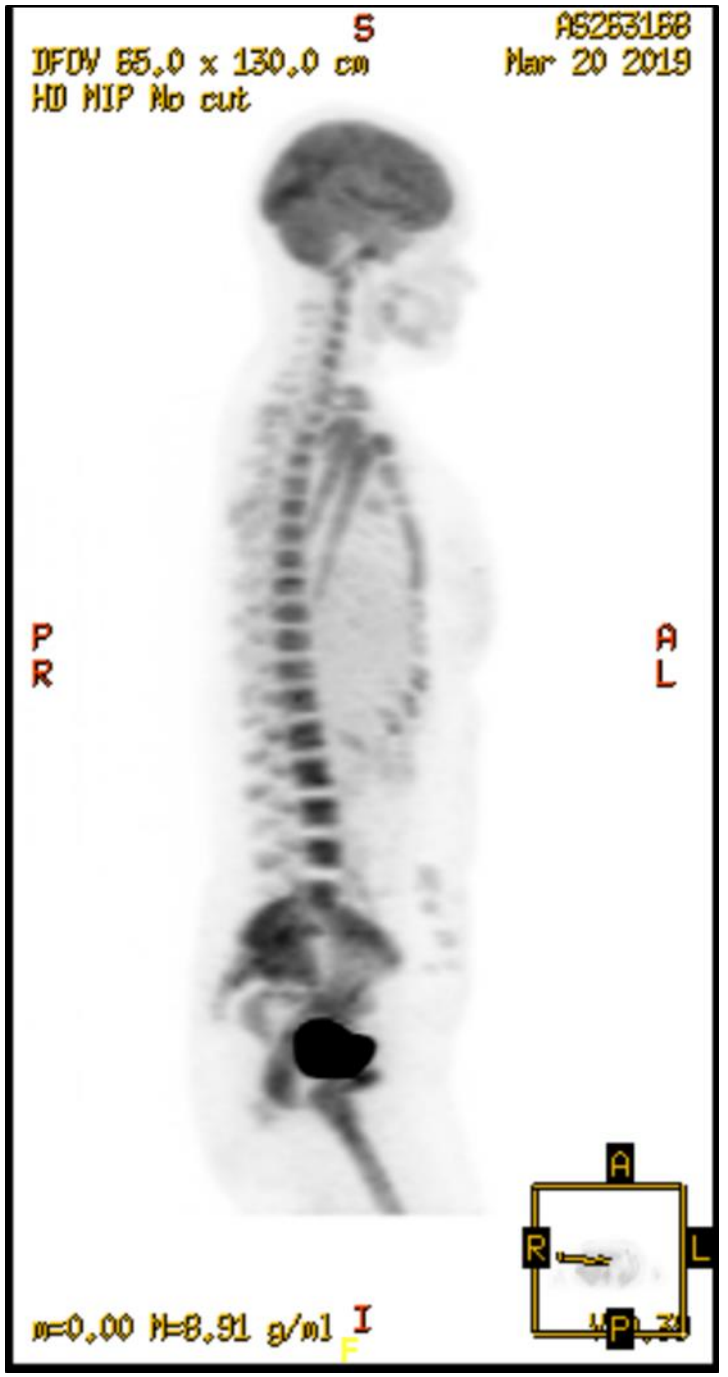
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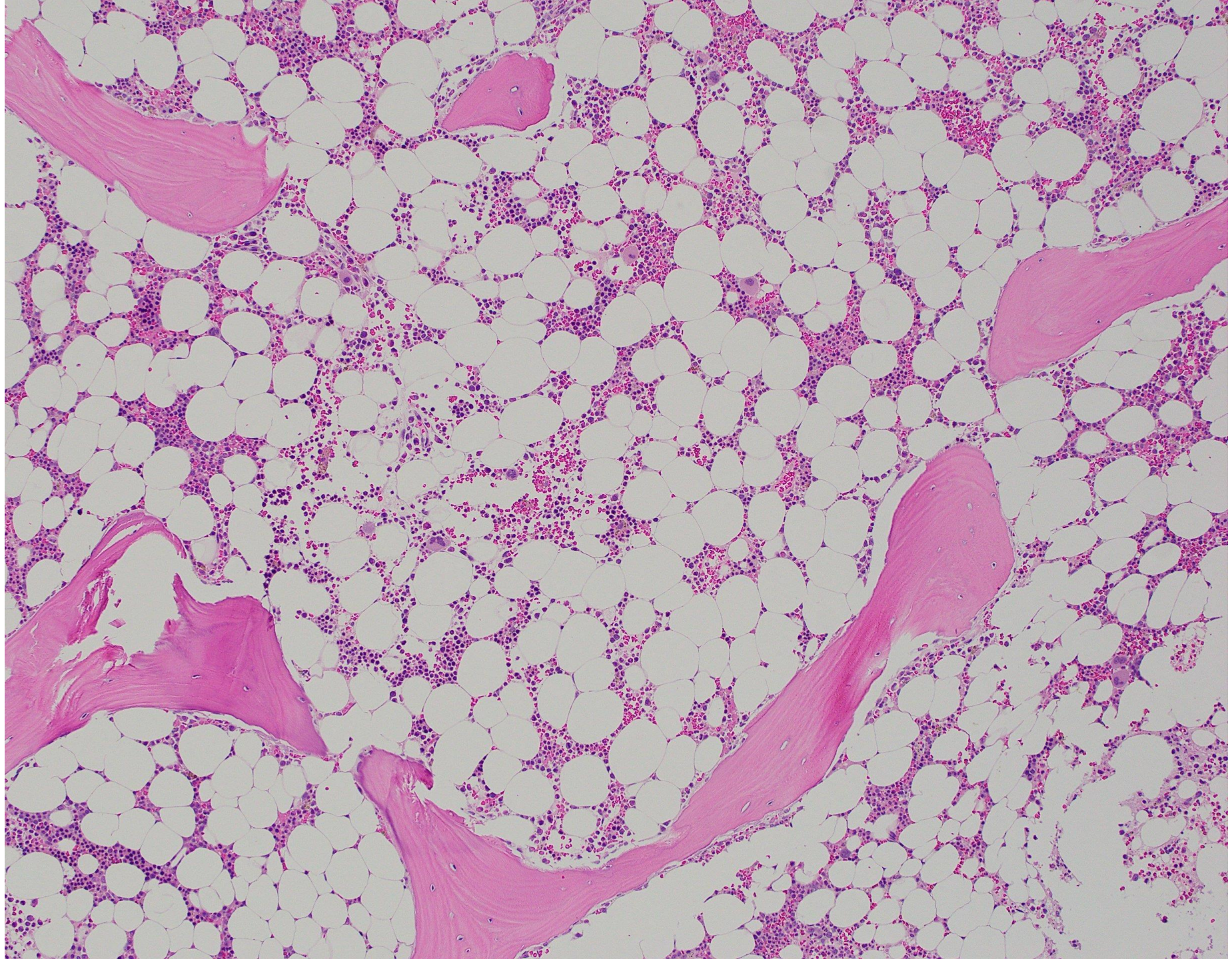

Conclusiones

- Un diagnóstico y subtipificación precisos se requieren para una adecuada estratificación y tratamiento del RMS.
- Correlación de las caracteristicas clínicas, histológicas, inmunohistoquímicas y moleculares son necesarias para llegar a un diagnóstico preciso.
- En ocasiones, estudios más extensos que incluyan NGS pueden ser necesarios.

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