in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 1

Biopsy of an inoperable, rapidly enlarging, 10 cm mass infiltrating the left thyroid lobe with extension to the adjacent soft tissues. Clinical diagnosis: lymphoma. The patient is a 62 year-old woman

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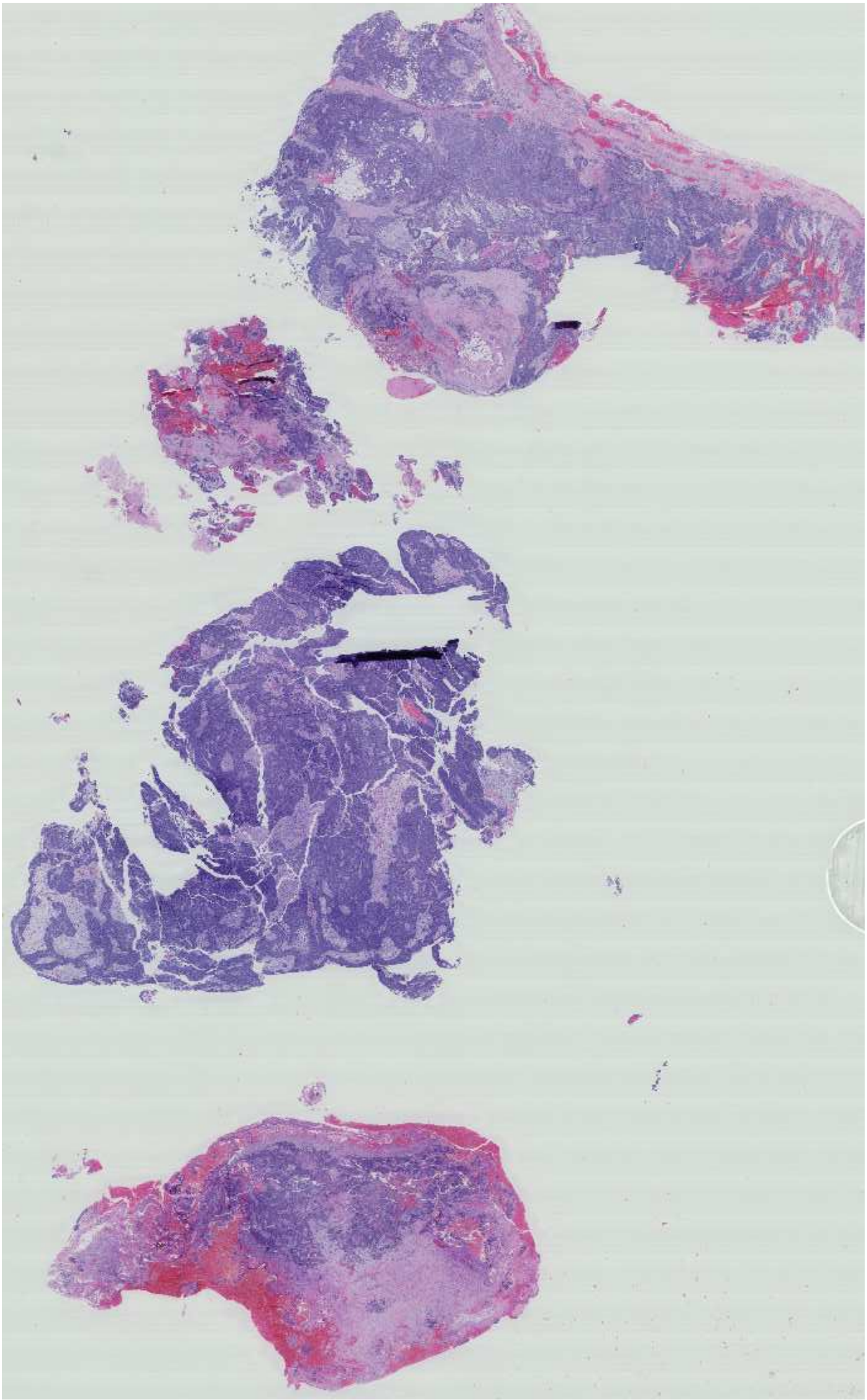

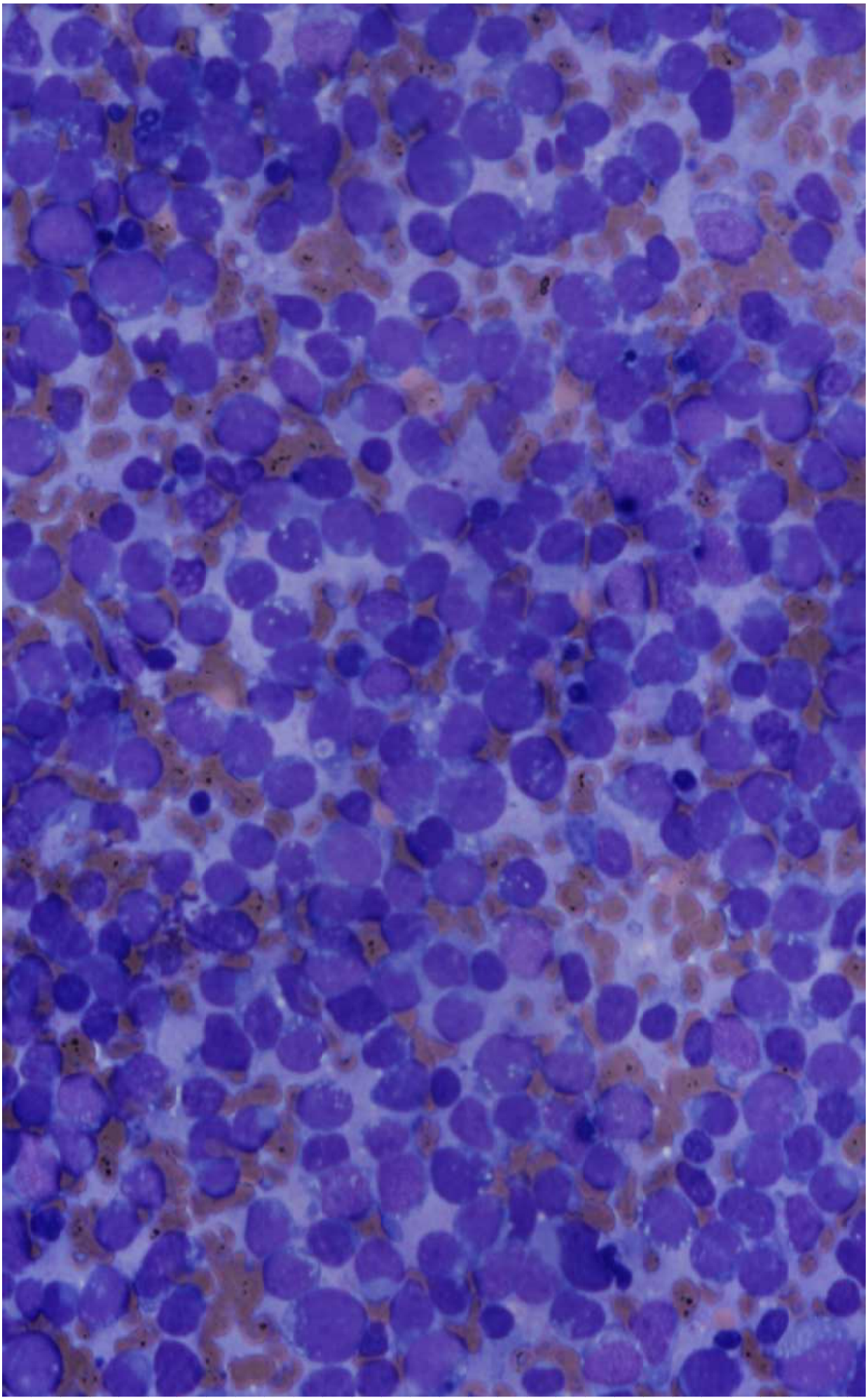

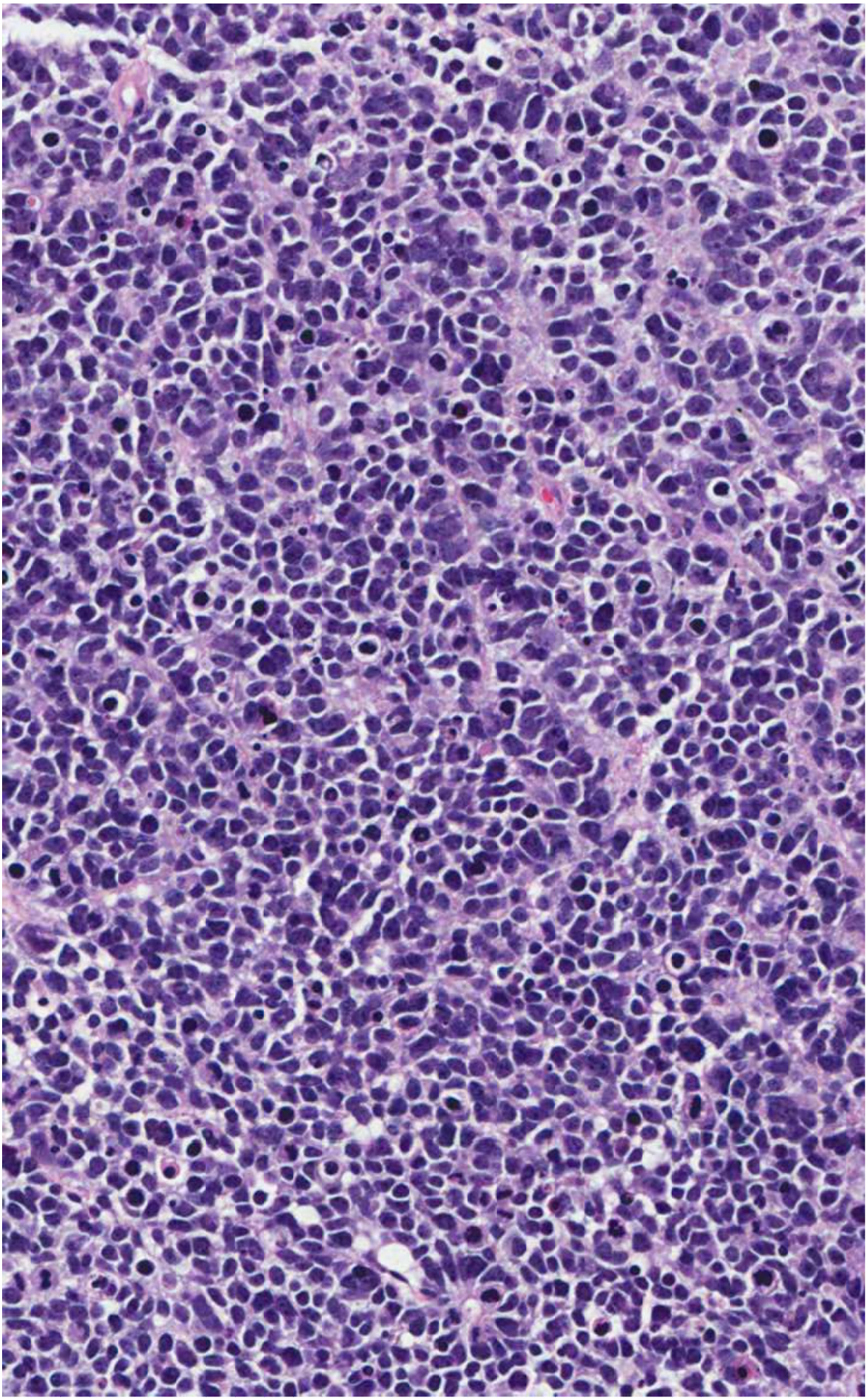

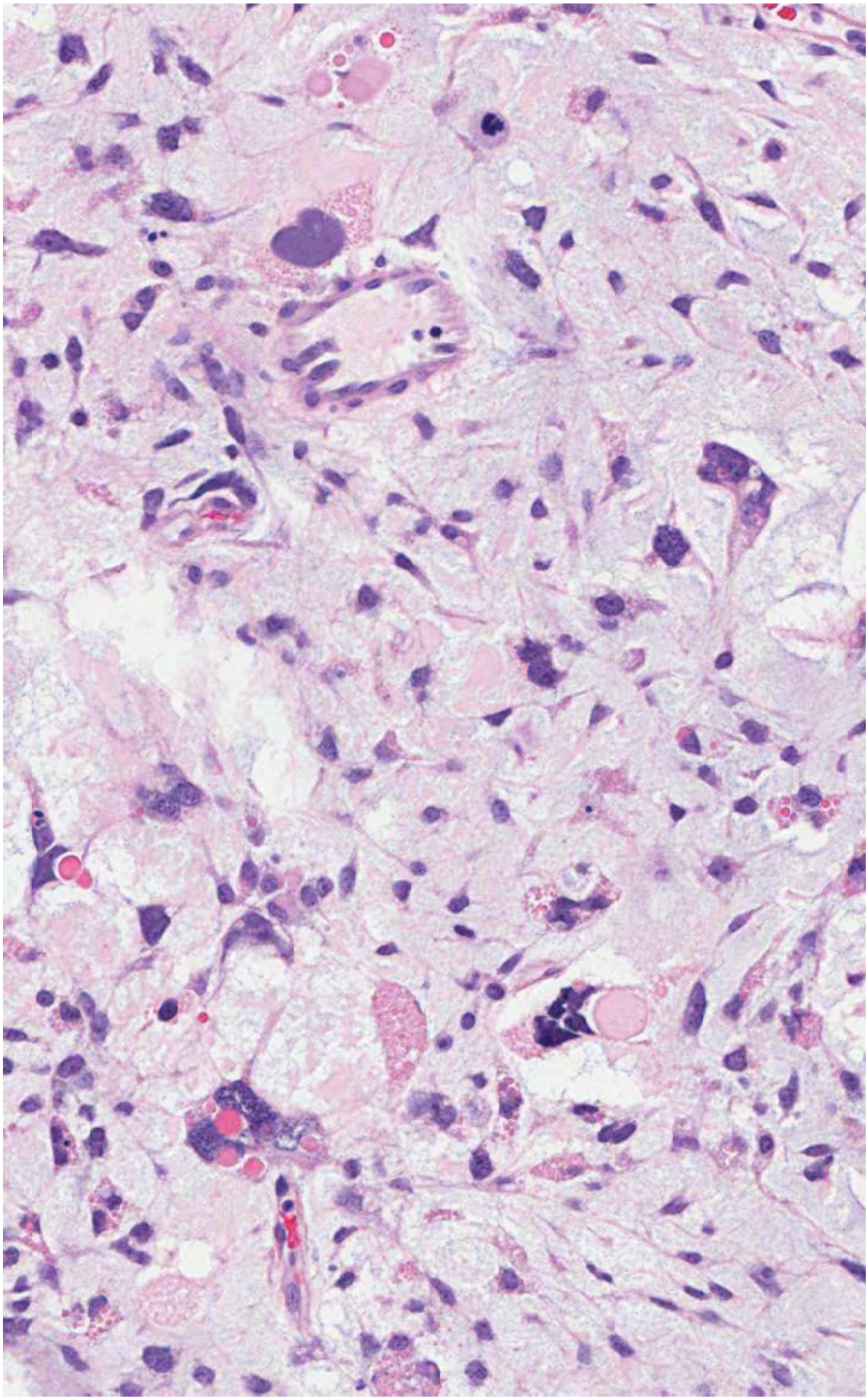

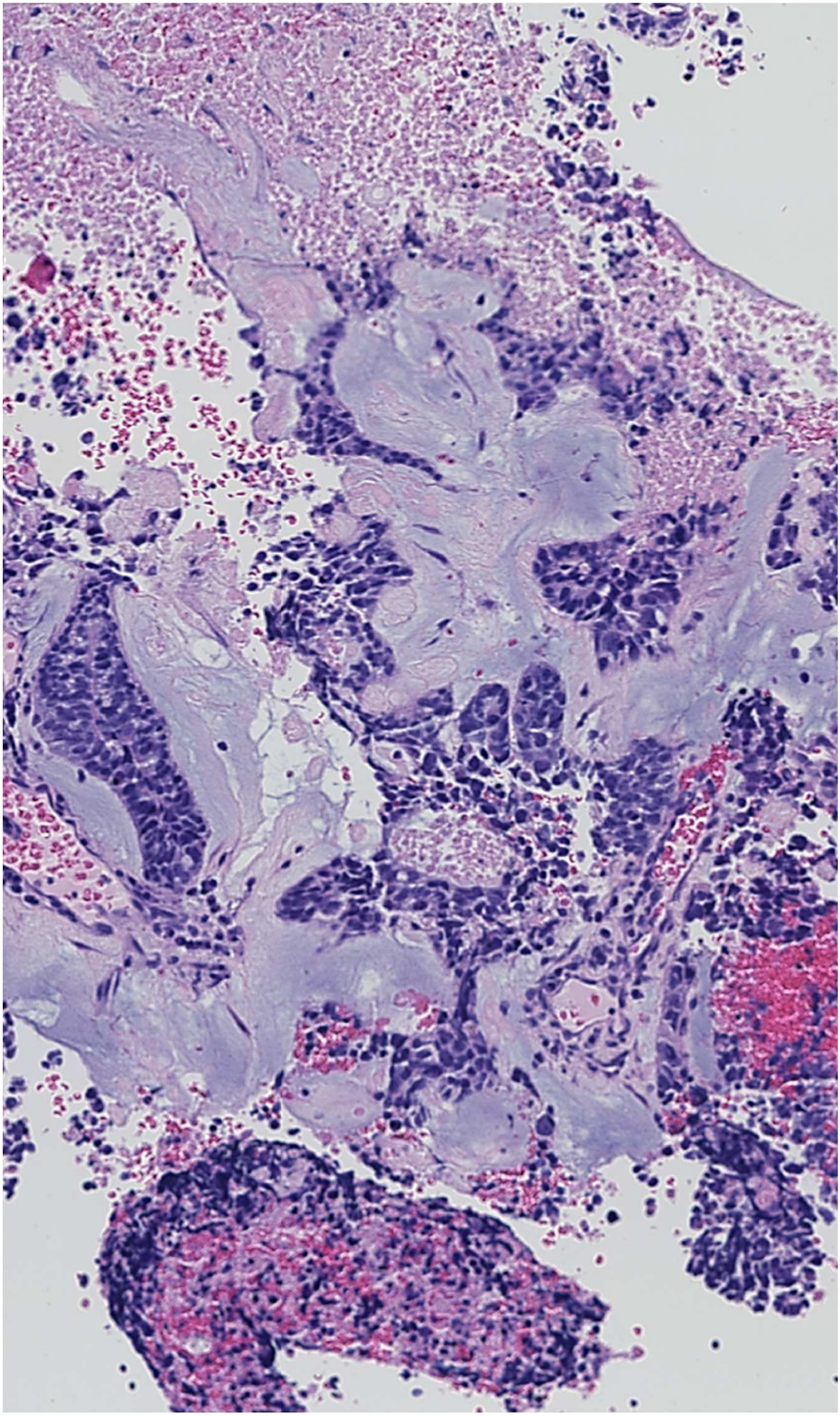

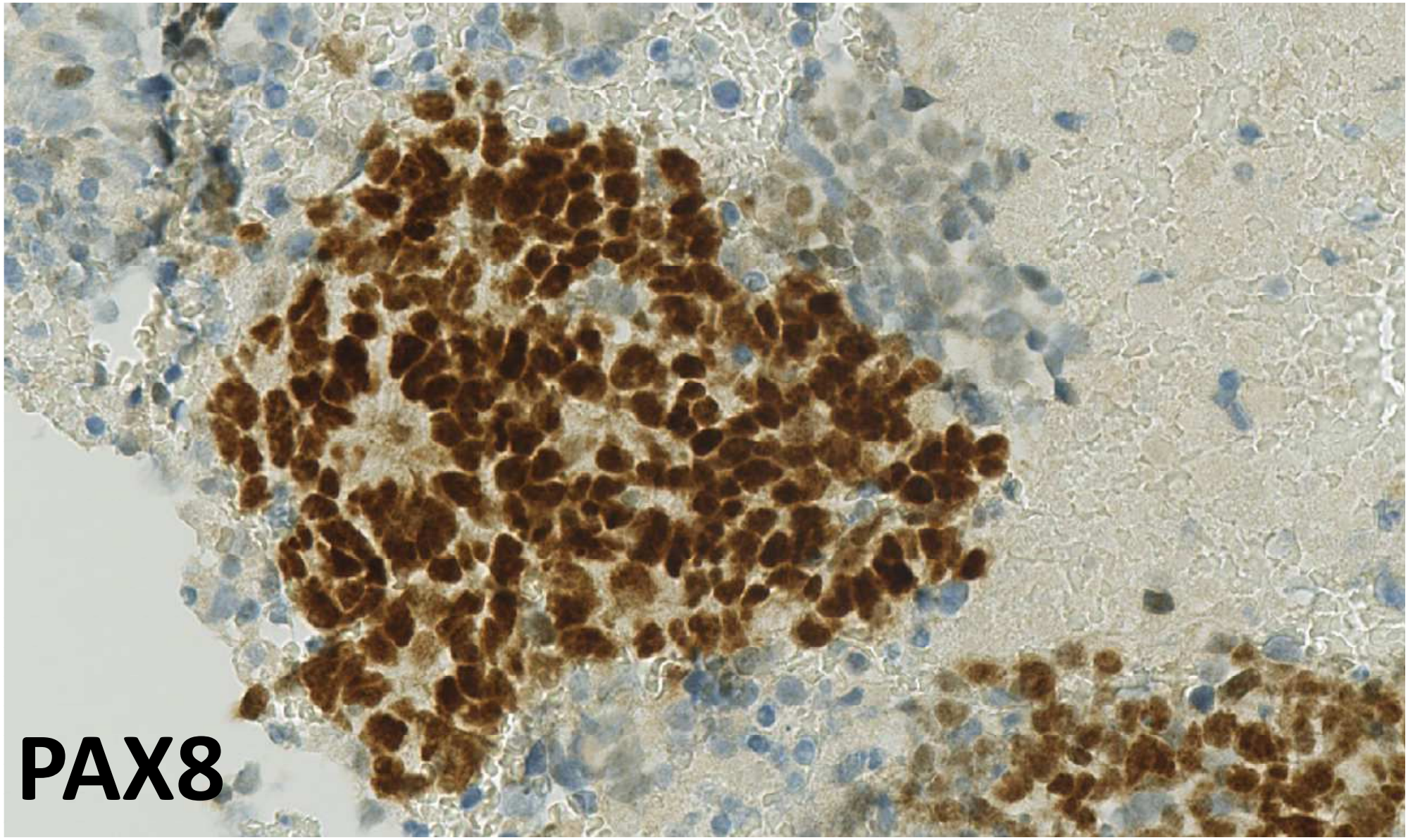
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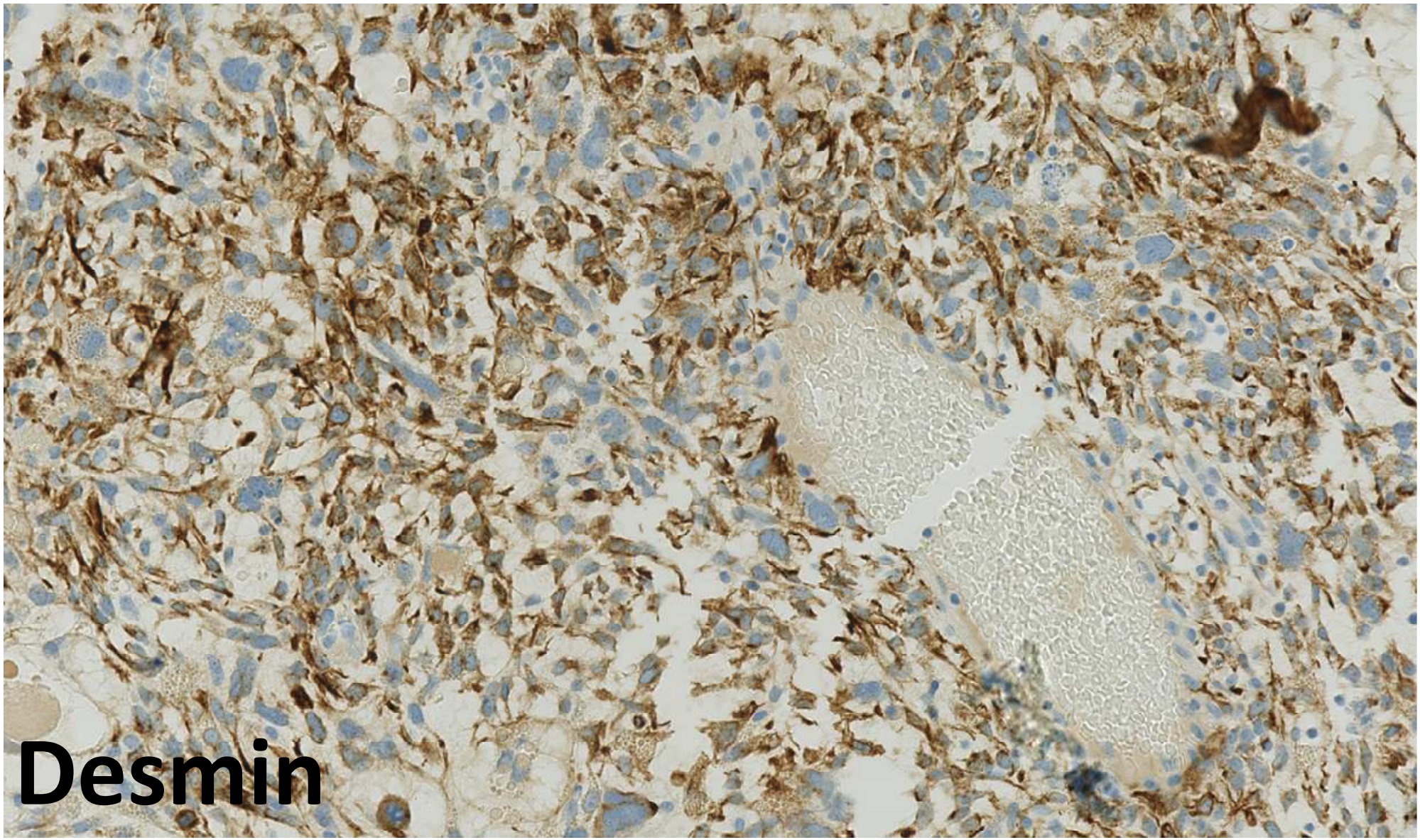
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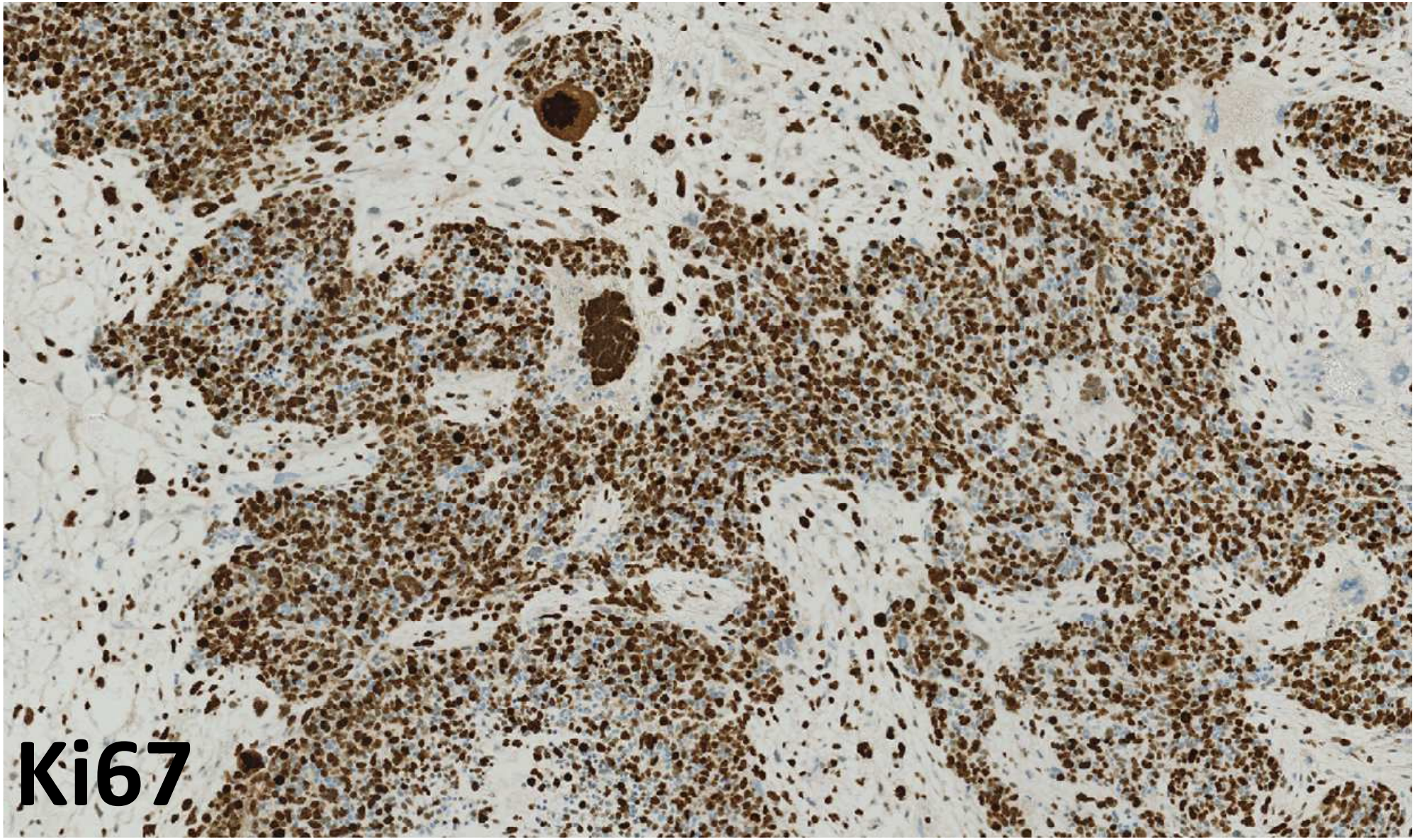
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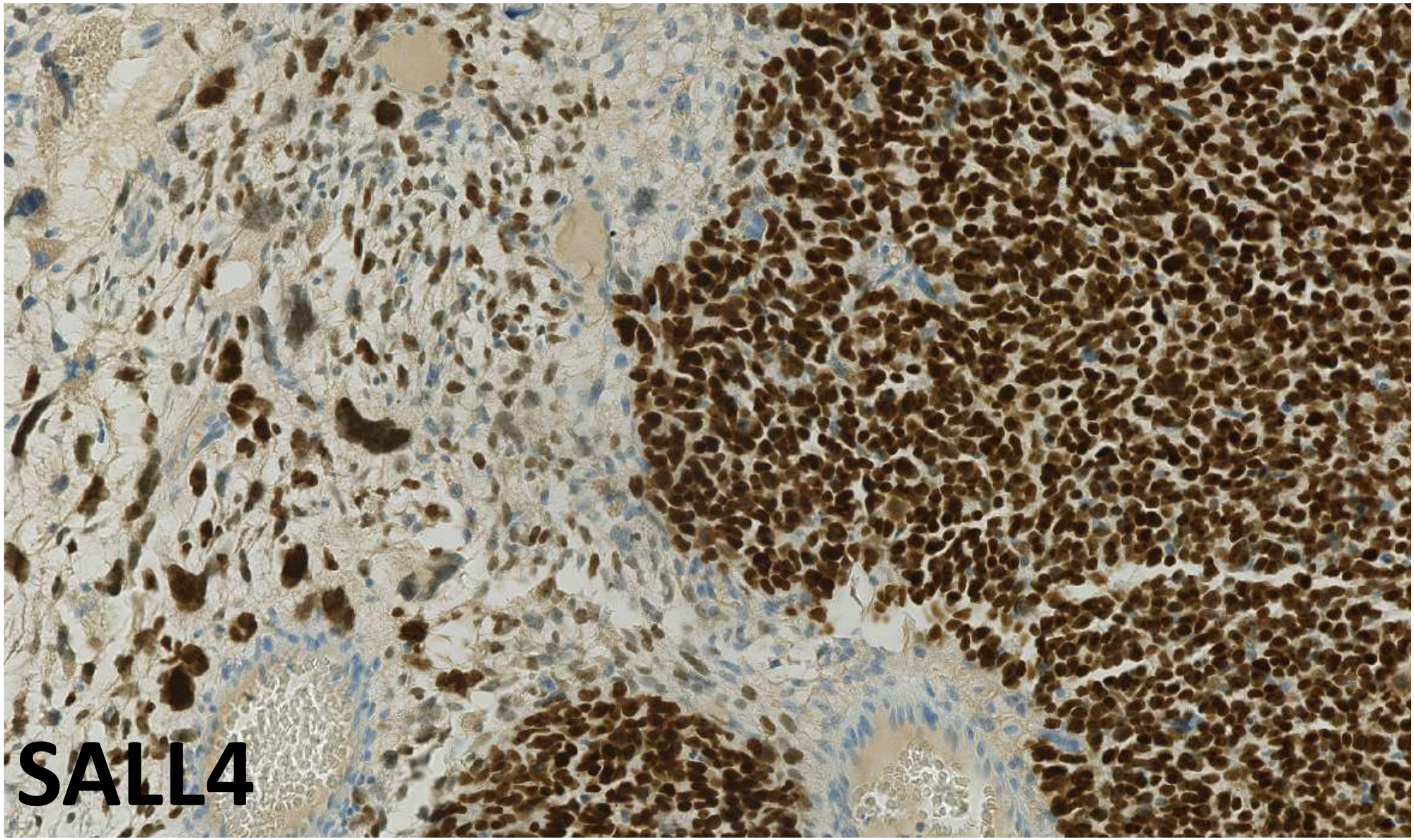
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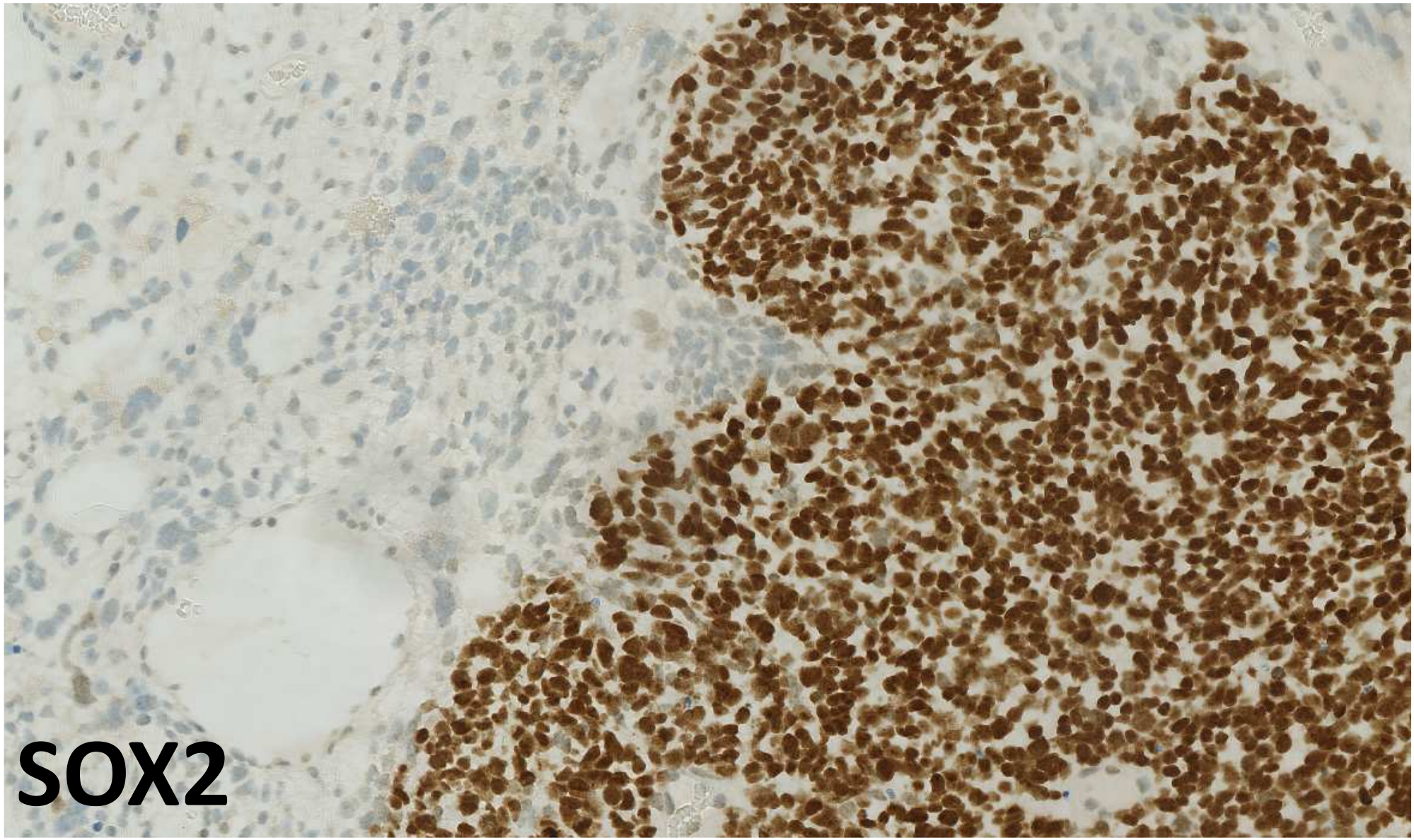
SOX2

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CASE 1
Thyroblastoma

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CASE 1

The patient had distant metastases at presentation (lung and bone), was treated with a neuroendocine carcinoma regimen chemotherapy. After a good initial response (~12 months), the tumor underwent rapid progression and the patient died due to local disease with diffuse tracheal stenosis

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CASE 1

Points for discussion

- What is Thyroblastoma?
- What is its relationship with germ cell tumors and teratomas of the Thyroid and Head and Neck?

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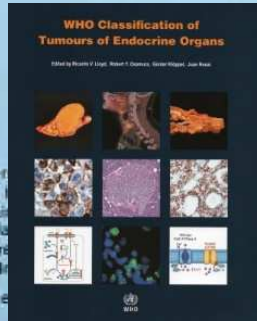
Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1*
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1*
Well-differentiated tumour of uncertain malignant potential	8348/1*
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features	8349/1*
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
Follicular thyroid carcinoma (FTC), NOS	8330/3
FTC, minimally invasive	8335/3
FTC, encapsulated angioinvasive	8339/3*
FTC, widely invasive	8330/3
Hürthle (oncocytic) cell tumours	
Hürthle cell adenoma	8290/0
Hürthle cell carcinoma	8290/3
Poorly differentiated thyroid carcinoma	8337/3
Anaplastic thyroid carcinoma	8020/3
Squamous cell carcinoma	8070/3
Medullary thyroid carcinoma	8345/3
Mixed medullary and follicular thyroid carcinoma	8346/3
Mucoepidermoid carcinoma	8430/3
Sclerosing mucoepidermoid carcinoma with eosinophilia	8430/3
Mucinous carcinoma	8480/3
Ectopic thymoma	8580/3
Spindle epithelial tumour with thymus-like differentiation	8588/3
Intrathyroid thymic carcinoma	8589/3
Paraganglioma and mesenchymal/stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours (PNSTs)	
Schwannoma	9560/0
Malignant PNST	9540/3
Benign vascular tumours	
Haemangioma	9120/0
Cavernous haemangioma	9121/0
Lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1
Haematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma (grade 0 or 1)	9080/0
Immature teratoma (grade 2)	9080/1
Malignant teratoma (grade 3)	9080/3
Secondary tumours	

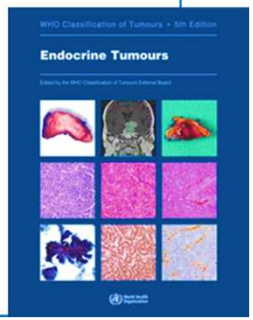
The morphology codes are from the Inter
for Oncology (ICD-O) (898A). Behaviour
/1 for unspecified, borderline, or uncerta
situ and grade III intraepithelial neoplasi
The classification is modified from the pr
into account changes in our understandi

*These new codes were approved by the



tumourclassification.iarc.who.int/chapters/53

3. Thyroid gland



WHO 5TH edition: Thyroblastoma

Thyroblastoma is an embryonal high-grade thyroid neoplasm composed of primitive thyroid-like follicular cells surrounded by a primitive small cell component and mesenchymal stroma with variable differentiation

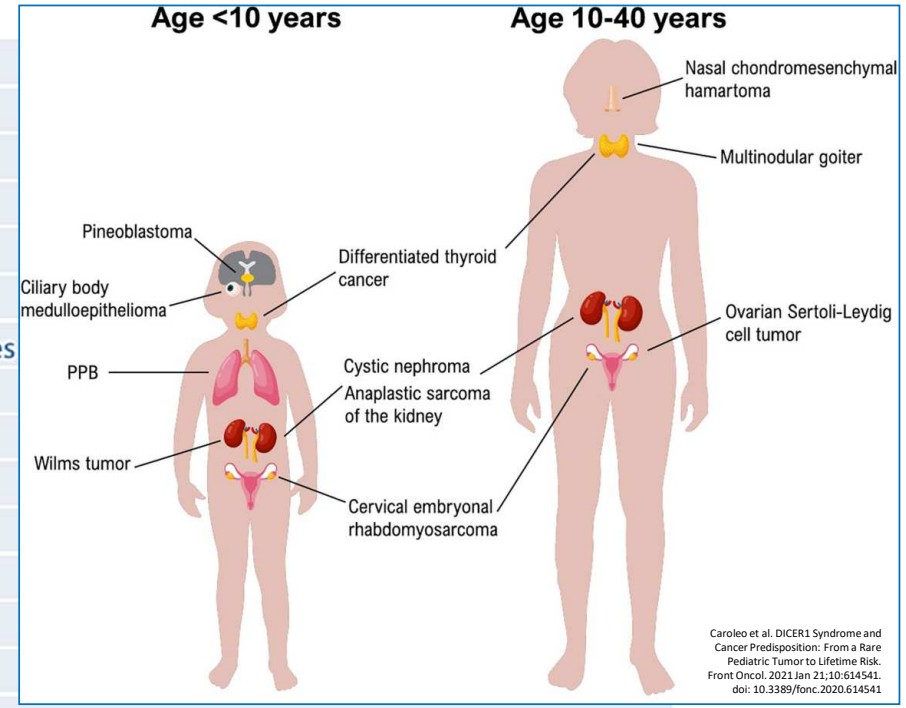
- Endocrine organ teratomas graded with criteria for ovarian teratoma (quantity of immature neuroectodermal tissue)
- Grade 0: benign (only mature elements); Grade 1: immature (little immature neuroectodermal tissue); Grade 2: immature (intermediate amount of immature neuroectodermal tissue); Grade 3: malignant (mitoses, and/or pleomorphism) →**Malignant teratomas of the thyroid gland now reclassified as Thyroblastoma based on recurrent somatic DICER1 mutations**
- Female predilection (3: 1); median age: 43 years (range: 17-65 years)
- Somatic DICER1 mutations detected in all cases tested
- ✓Cases should be tested for germ line DICER1 mutations: conventional benign and malignant thyroid nodules/tumors, but not thyroblastoma, are typical of DICER1 syndrome
- Very rare, likely under-recognized (eight recently reported and molecularly verified cases)

[Rabinowits et al. Successful Management of a Patient with Malignant Thyroid Teratoma. Thyroid. 2017 Jan;27(1):125-128][Yang et al. A rare malignant thyroid carcinosarcoma with aggressive behavior and DICER1 gene mutation: a case report with literature review. Thyroid Res. 2018 Jul 31;11:11] [Rooper et al. Recurrent DICER1 Hotspot Mutations in Malignant Thyroid Gland Teratomas: Molecular Characterization and Proposal for a Separate Classification. Am J Surg Pathol. 2020 Jun;44(6):826-833][Agaimy et al. Malignant teratoid tumor of the thyroid gland: an aggressive primitive multiphenotypic malignancy showing organotypical elements and frequent DICER1 alterations-is the term "thyroblastoma" more appropriate? Virchows Arch. 2020 Dec;477(6):787-798]

DICER1 Syndrome

Table 1. *DICER1*-associated neoplasms.

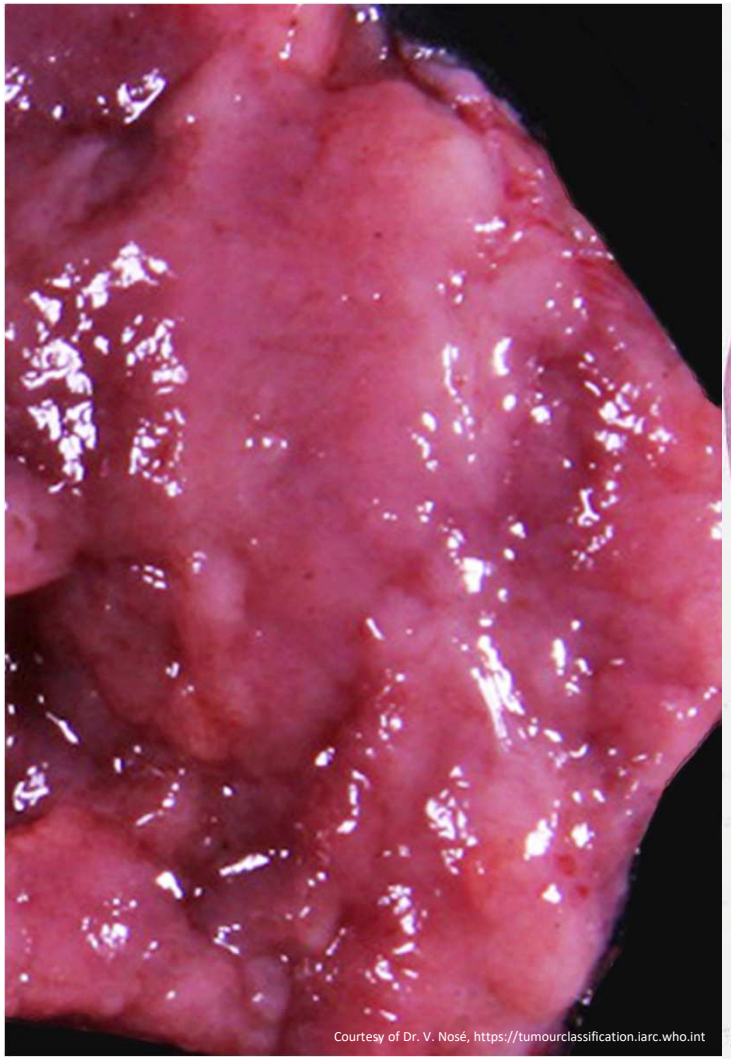
Pleuropulmonary blastoma (PPB) and PPB-like neoplasms
Pleuropulmonary blastoma, type I, IR, II, III
PPB-like Sertoli-Leydig cell tumor of lung
Pediatric cystic neoplasms and *DICER1*-sarcoma (anaplastic sarcoma of kidney)
Nasal chondromesenchymal hamartoma
Central nervous system sarcoma with rhabdomyosarcoma/PPB III-like features
Sertoli-Leydig cell tumor with and without heterologous features and type I PPB-like features
Peritoneal, ovarian and fallopian tube sarcoma with PPB-like features
DICER1-associated cystic hepatic neoplasm with type I PPB-like features
Cervical embryonal rhabdomyosarcoma
Teratoid and primitive neuroepithelial neoplasms
Cervical-thyroid teratoma
Malignant teratoid neoplasm of sacrococcygeal region
Ciliary body medulloepithelioma
Pituitary blastoma
Pineoblastoma
Embryonal tumor with multilayered rosettes
Thyroid
Multinodular hyperplasia (goiter)
Papillary thyroid carcinoma, invasive follicular variant
Follicular carcinoma, pediatric type
Poorly differentiated thyroid carcinoma, pediatric type
Intestine
Hamartomatous polyp with juvenile polyp-like features

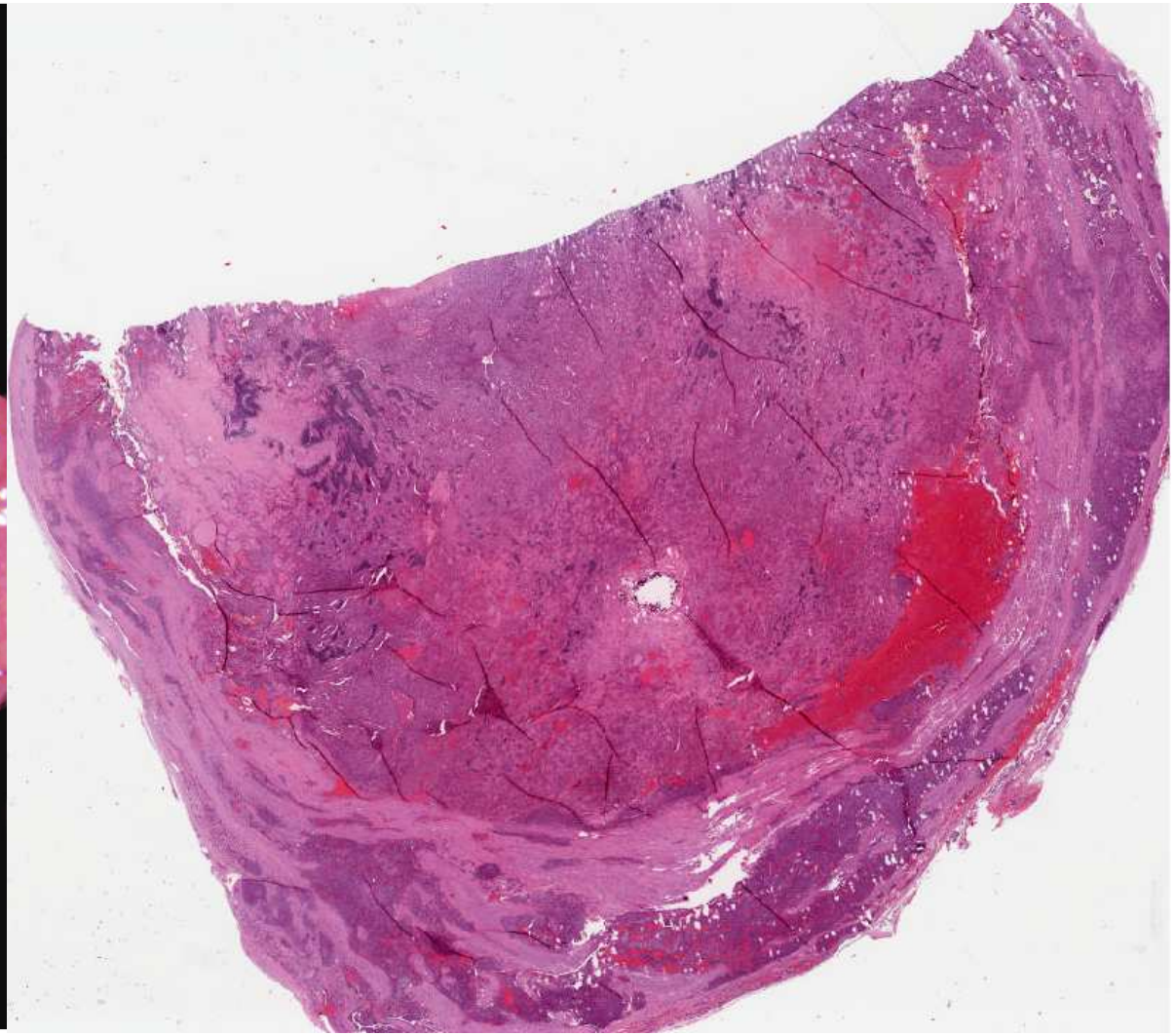


- DICER1 syndrome (OMIM 606241, 601200) is an autosomal dominant familial tumor predisposition disorder with a heterozygous DICER1 germline mutation
- *DICER1* on chromosome 14q32.13 encodes an RNA endonuclease (Dicer) involved in the post-transcriptional gene expression of over 30% of protein-coding genes by modulating microRNAs
- Reduced penetrance, which likely decreases the rate of familial cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

González IA, Stewart DR, Schultz KAP, Field AP, Hill DA, Dehner LP. DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma. Mod Pathol. 2022 Jan;35(1):4-22

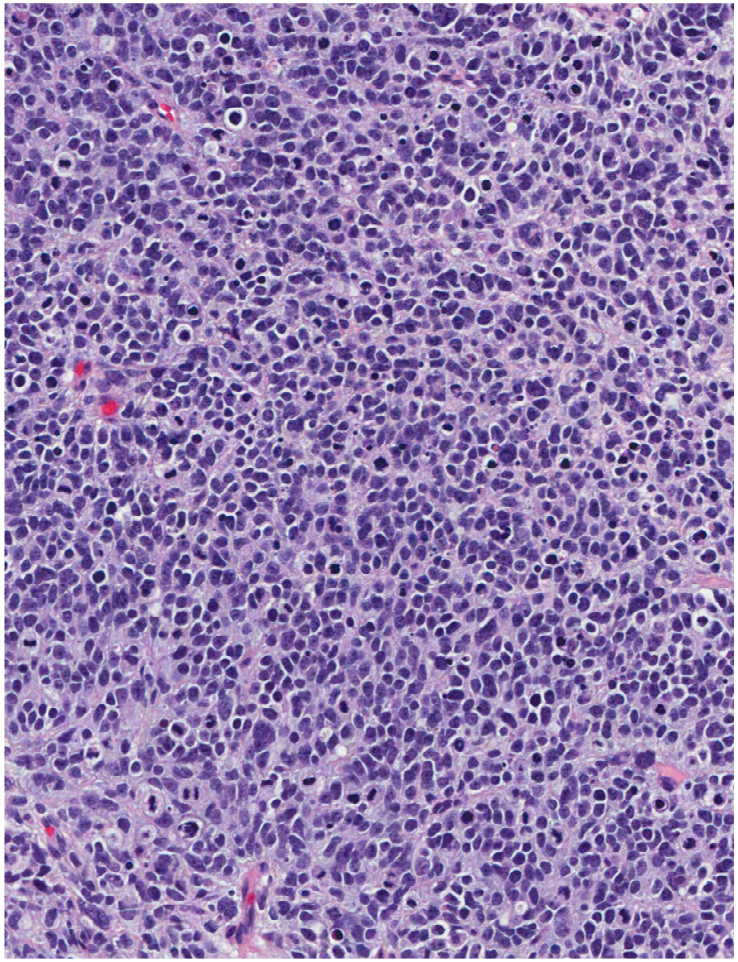
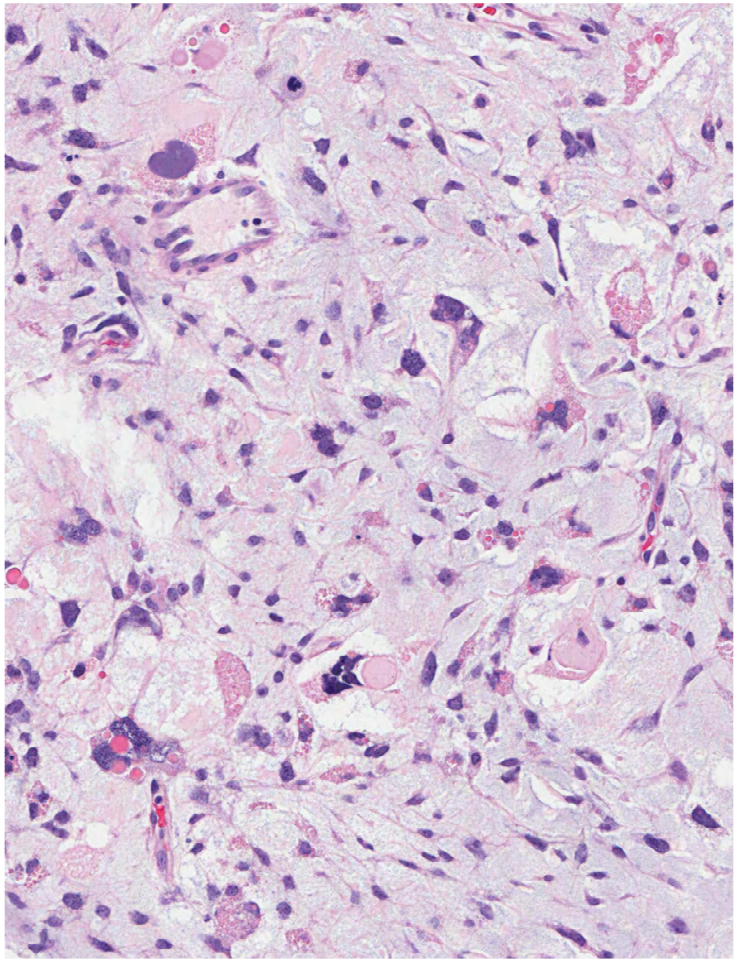
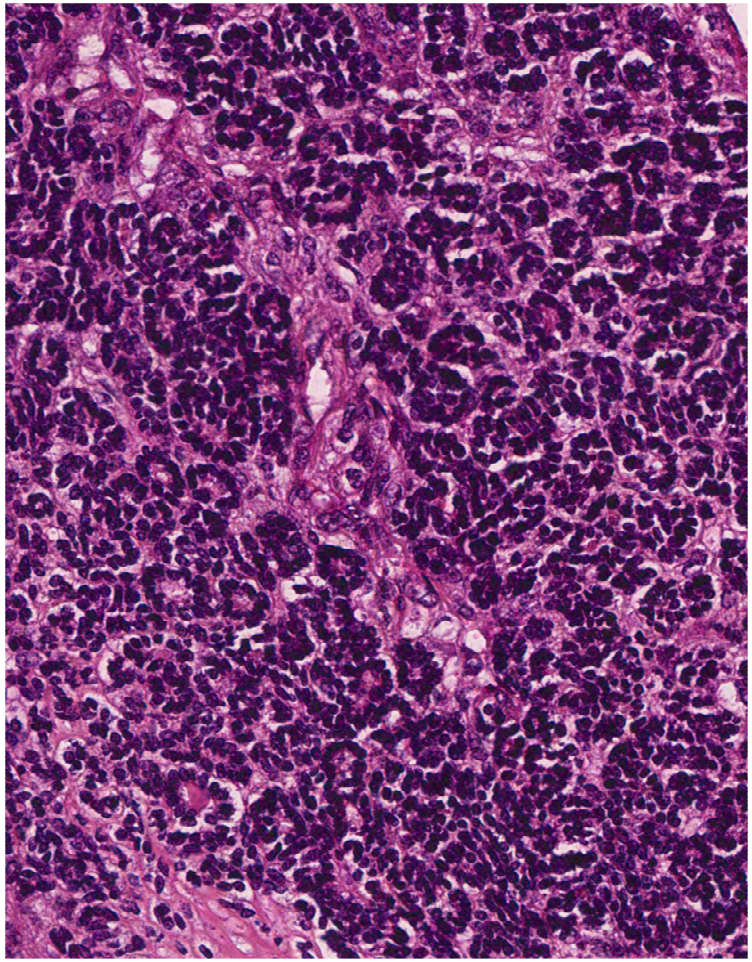
WHO 5TH edition: Thyroblastoma





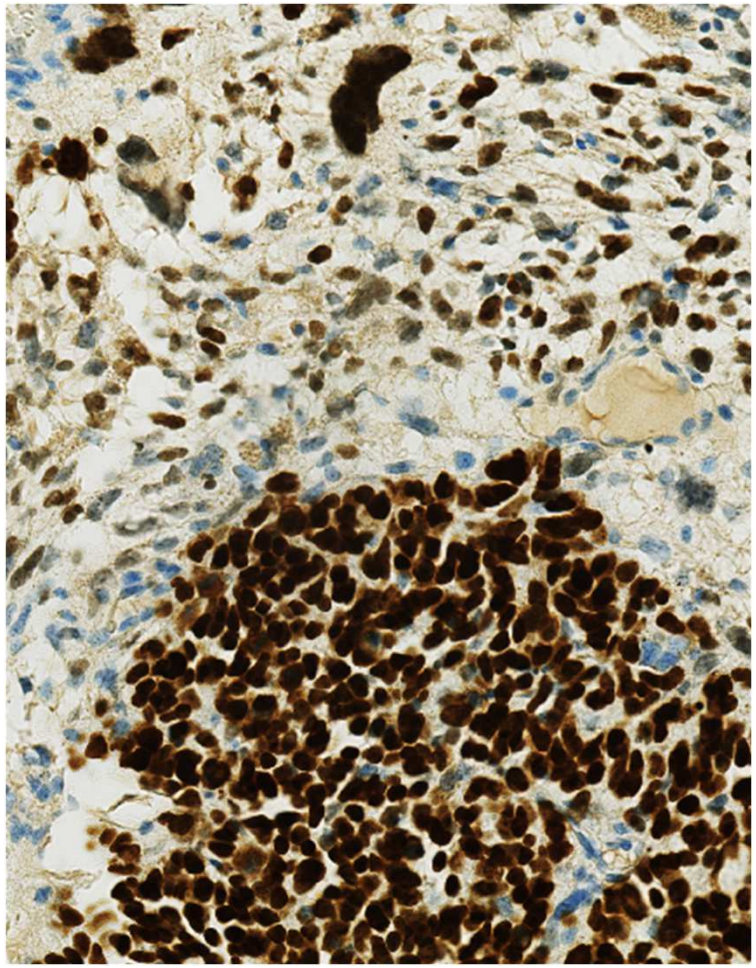
- Rapidly growing infiltrative thyroid mass up to 10 cm in diameter, highly aggressive (>50% of patients die within 1 year)

WHO 5TH edition: Thyroblastoma

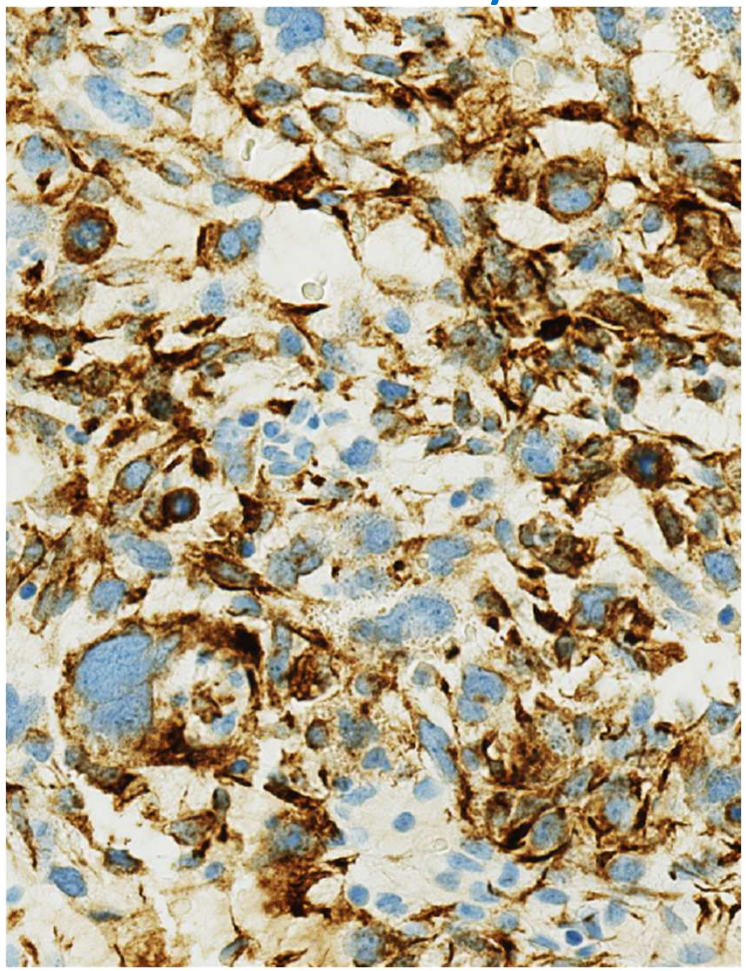




- Histologically, three cellular components: undifferentiated small round/oval cells with foci of necrosis and brisk mitotic activity, primitive spindle cell stroma with variable differentiation (rhabdomyoblastic with smooth muscle actin+/focal desmin+ and myogenin+, cartilaginous), immature epithelial structures and thyroid follicles (TTF1+/PAX8+/focal thyroglobulin+), similar to first trimester prenatal thyroid; rare cases have well differentiated adult-type organoid structures

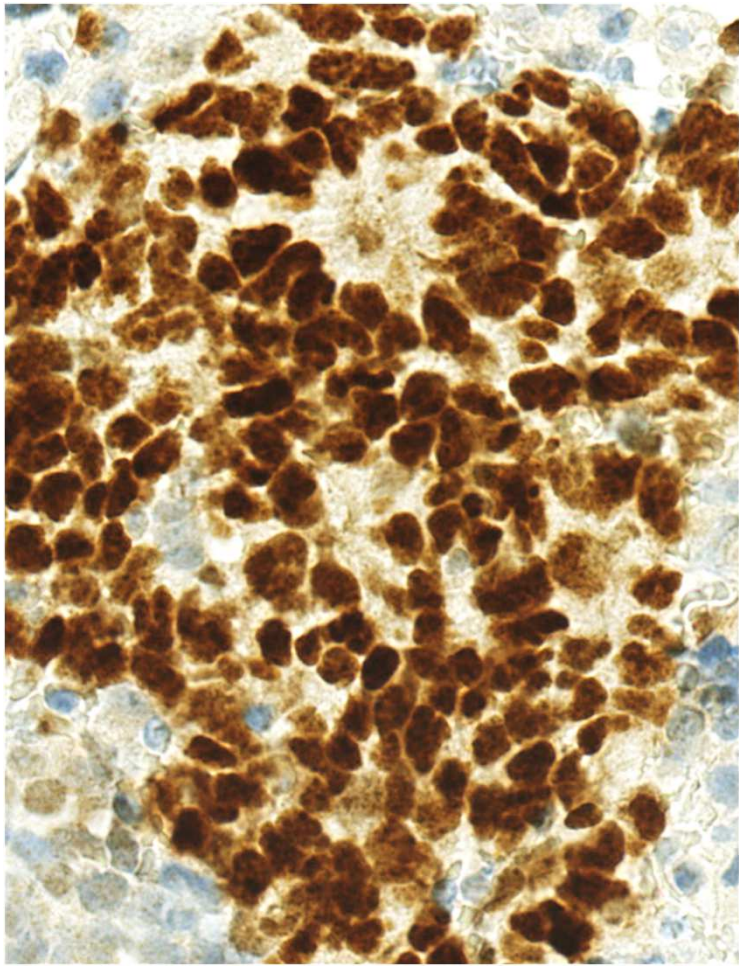
WHO 5TH edition: Thyroblastoma



Primitive embryonal cell marker SALL4 (and SOX2, Glypican-3): positive – while germ cell markers OCT3/4 or PLAP are negative



Stromal cells are Desmin positive



Primitive thyroid follicles are PAX8 (and TTF1) positive

Germ cell tumors of Thyroid and Head and Neck

- Germ cell tumors
- Seminoma
- Embrional carcinoma
- Yolk sac tumor
- Choriocarcinoma
- Teratoma

In the head and neck region and in the thyroid gland malignant extragonadal germ cell tumors are extremely rare, yolk sac tumour being the one more commonly reported

- **Diagnosed** [Thompson LD, Rosai J, Heffess CS. Primary thyroid teratomas: a clinicopathologic study of 30 cases. Cancer. 2000 Mar 1;88(5):1149-58] as : (i) mature; (ii) immature or (iii) malignant - based on the amount of immature components: blastema, primitive neuroepithelium; (iv) with malignant transformation - due to somatic malignancy
- **Graded** following the criteria for ovarian teratoma [Norris HJ, Zirkin HJ, Benson WL. Immature (malignant) teratoma of the ovary: a clinical and pathologic study of 58 cases. Cancer. 1976 May;37(5):2359-72] as:
  - Grade 0 – benign: mature elements only, no pleomorphism
  - Grade 1 – immature: primitive neuroepithelium in < 1 low-power field (4x) only
  - Grade 2 – immature: primitive neuroepithelium in 1 -4 low-power field (4x) only
  - Grade 3 – malignant: primitive neuroepithelium in > 4 low-power field (4x) and/or pleomorphism

Recurrent DICER1 Hotspot Mutations in Malignant Thyroid Gland Teratomas: Molecular Characterization and Proposal for a Separate Classification

Rooper LM, Bynum JP, Miller KP, Lin MT, Gagan J, Thompson LDR, Bishop JA

Am J Surg Pathol. 2020 Jun;44(6):826-833

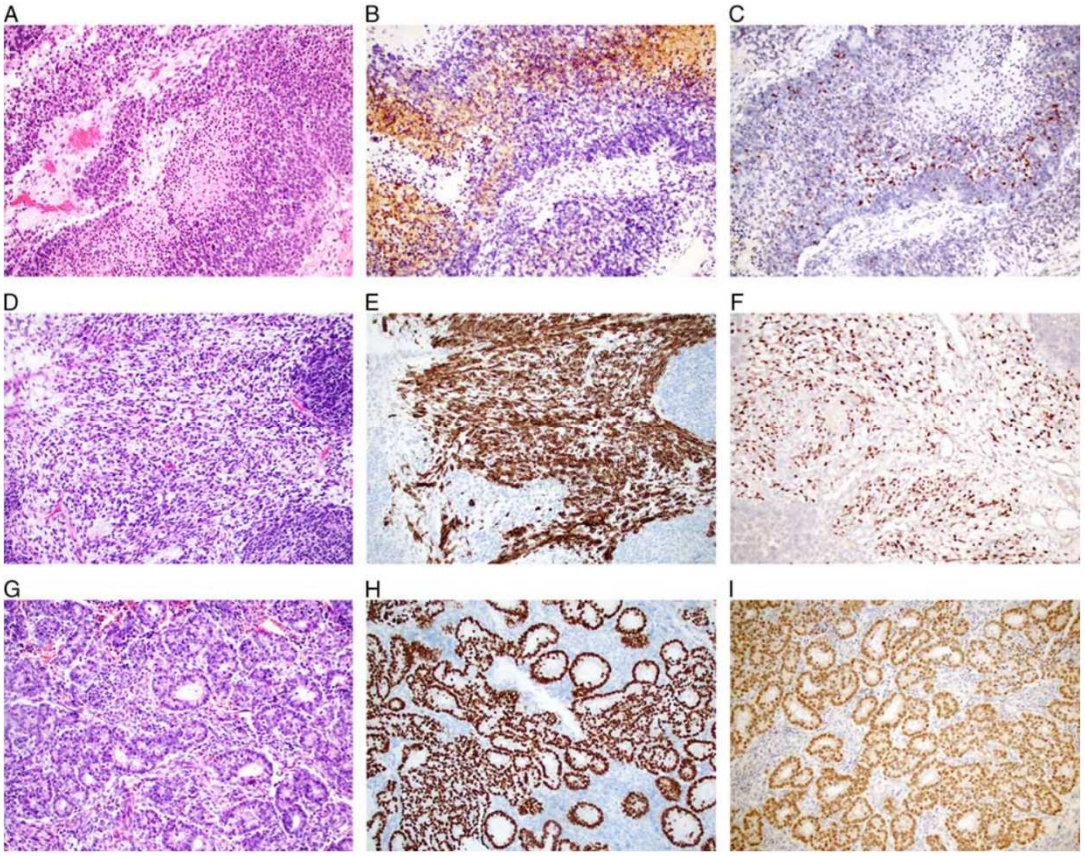


FIGURE 2. The **malignant teratomas** contained **immature neural tissues** with sheets and rosettes of hyperchromatic cells embedded in scant neuropil (A) and were positive for synaptophysin (B) and INSM1 (C). They also contained **primitive spindle cell elements** with variable amounts of eosinophilic cytoplasm (D) that showed rhabdomyoblastic differentiation with positivity for desmin (E) and myogenin (F). In addition, there were proliferations of bland cuboidal to columnar epithelial cells that formed glandular and cribriform structures (G) and were positive for TTF-1 (H) and PAX8 (I), consistent with **thyroid follicular cell differentiation**

TABLE 2. NGS Results

	Case No.	*DICER1* Hotspot (Variant Allele Frequency)	*DICER1* Nonhotspot (Variant Allele Frequency)	Other Mutations (Variant Allele Frequency)
Thyroblastoma (Malignant teratoma)	1	p.E1705K (42.9%)	p.Y819fs (46.8%)	*BRD4* p.V350D (49.8%) *FGFR3* p.S779R (46.5%) *FBN2* p.A731G (39.2%) Chromosome 1p loss and 1q gain
	2	p.E1813G (32.8%)	p.V448fs (39.5%)	*RET* p.R418X (35.4%) *NFKB2* p.Q164R (43.2%)
	3	p.E1813Q (45.5%)	p.K868X (47.8%)	*KLF4* p.V262M (47.2%) *ARID2* p.H800D (50.2%) *NTRK3* p.R138W (47.8%) Chromosome 2 amplification
	4	p.D1810H (9.4%)	None	*BCOR* p.Y755fs (14.7%) *BRD4* p.V1089I (49.0%) *HSP90AA1* p.G570A (43.1%) *FANCG* p.R485Q (48.1%)
Immature teratoma ←	5	None	None	*IGF1R* p.V1013fs (49.1%) *XRCC3* p.S327fs (44.8%)
Mature teratoma	6	None	None	*FLT3* p.S574N (48.4%) *KNL1* p.M788V (45.4%) *PARP4* p.A666S (9.1%) *RYR3* p.I3000V (43.5%)
	7	None	p.K1844N (22.0%)	None
	8	NP	NP	NP

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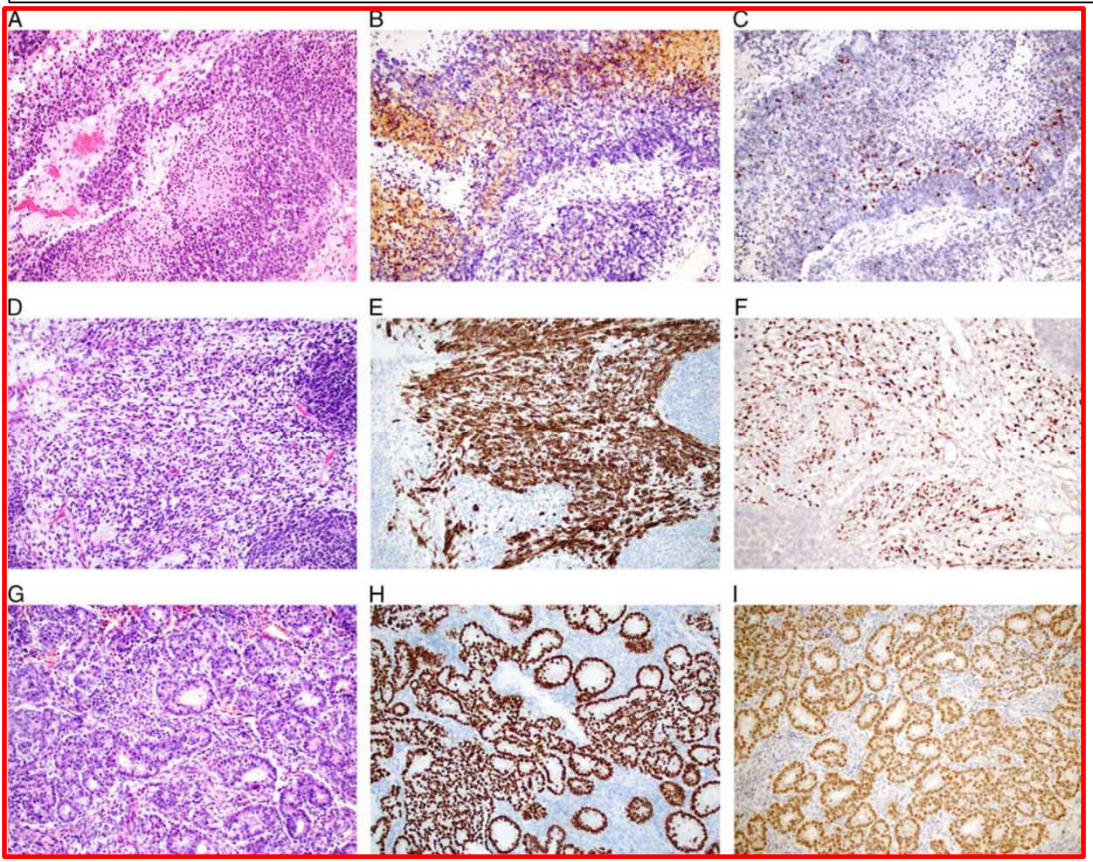

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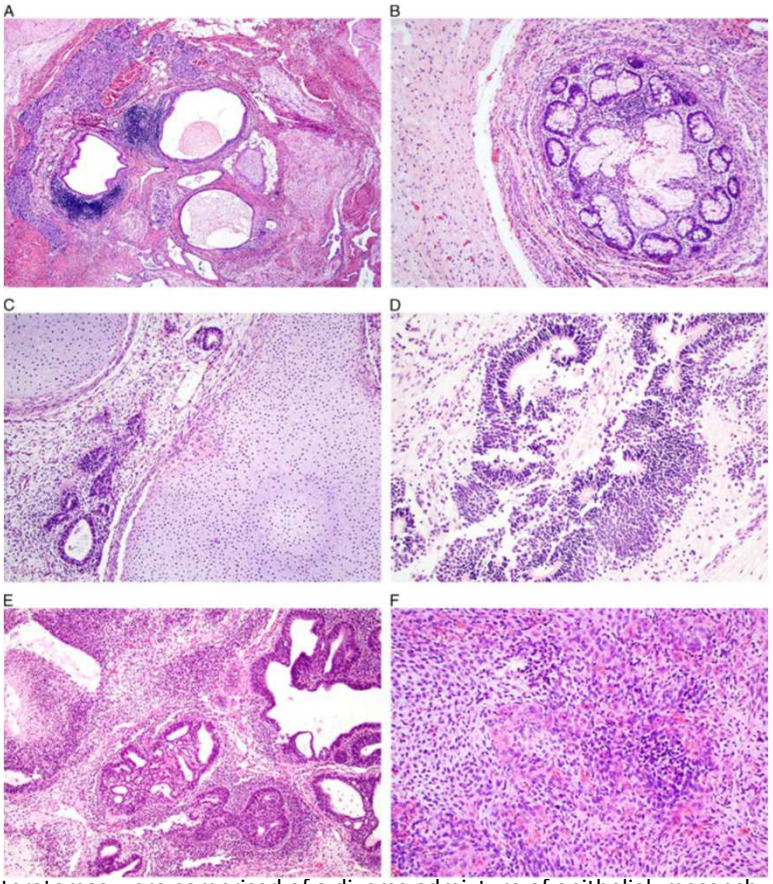

FIGURE 1. Benign teratomas were comprised of a diverse admixture of epithelial, mesenchymal, and neural tissues (A). A subset of benign teratomas displayed focal **organoid growth with recapitulation of normal tissue architecture** (B). While the single case of immature teratoma did demonstrate **immature neural elements**, they collectively **occupied <1 low-power field in a background of more differentiated tissue** (C). The immature neural tissue in the immature teratoma lacked significant cytologic atypia or necrosis (D). The malignant teratomas were composed of a mix of immature neural, spindled, and epithelial components (E). A subset of malignant teratomas showed a predominance of primitive spindled and epithelial elements rather than immature neural tissue (F)

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	2	p.E1813G (32.8%)	p.V448fs (39.5%)	*RET* p.R418X (35.4%) *NFKB2* p.Q164R (43.2%)
	3	p.E1813Q (45.5%)	p.K868X (47.8%)	*KLF4* p.V262M (47.2%) *ARID2* p.H800D (50.2%) *NTRK3* p.R138W (47.8%) Chromosome 2 amplification
	4	p.D1810H (9.4%)	None	*BCOR* p.Y755fs (14.7%) *BRD4* p.V1089I (49.0%) *HSP90AA1* p.G570A (43.1%) *FANCG* p.R485Q (48.1%)
Immature teratoma	5	None	None	*IGF1R* p.V1013fs (49.1%) *XRCC3* p.S327fs (44.8%)
Mature teratoma	6	None	None	*FLT3* p.S574N (48.4%) *KNL1* p.M788V (45.4%) *PARP4* p.A666S (9.1%) *RYR3* p.I3000V (43.5%)
	7	None	p.K1844N (22.0%)	None
	8	NP	NP	NP

Recurrent DICER1 Hotspot Mutations in Malignant Thyroid Gland Teratomas: Molecular Characterization and Proposal for a Separate Classification

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Am J Surg Pathol. 2020 Jun;44(6):826-833

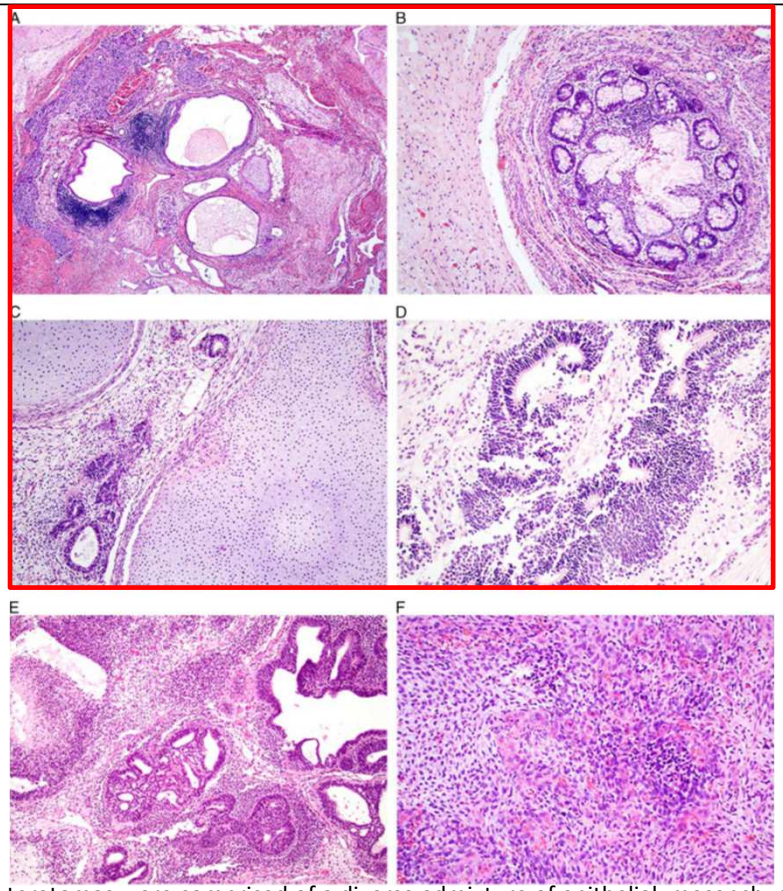

FIGURE 1. Benign teratomas were comprised of a diverse admixture of epithelial, mesenchymal, and neural tissues (A). A subset of benign teratomas displayed focal **organoid growth with recapitulation of normal tissue architecture** (B). While the single case of immature teratoma did demonstrate **immature neural elements**, they collectively **occupied <1 low-power field in a background of more differentiated tissue** (C). The immature neural tissue in the immature teratoma lacked significant cytologic atypia or necrosis (D). The malignant teratomas were composed of a mix of immature neural, spindled, and epithelial components (E). A subset of malignant teratomas showed a predominance of primitive spindled and epithelial elements rather than immature neural tissue (F)

TABLE 2. NGS Results

	Case No.	*DICER1* Hotspot (Variant Allele Frequency)	*DICER1* Nonhotspot (Variant Allele Frequency)	Other Mutations (Variant Allele Frequency)
Thyroblastoma (Malignant teratoma)	1	p.E1705K (42.9%)	p.Y819fs (46.8%)	*BRD4* p.V350D (49.8%) *FGFR3* p.S779R (46.5%) *FBN2* p.A731G (39.2%) Chromosome 1p loss and 1q gain
	2	p.E1813G (32.8%)	p.V448fs (39.5%)	*RET* p.R418X (35.4%) *NFKB2* p.Q164R (43.2%)
	3	p.E1813Q (45.5%)	p.K868X (47.8%)	*KLF4* p.V262M (47.2%) *ARID2* p.H800D (50.2%) *NTRK3* p.R138W (47.8%) Chromosome 2 amplification
	4	p.D1810H (9.4%)	None	*BCOR* p.Y755fs (14.7%) *BRD4* p.V1089I (49.0%) *HSP90AA1* p.G570A (43.1%)
Immature teratoma	5	None	None	*FANCG* p.R485Q (48.1%) *IGF1R* p.V1013fs (49.1%) *XRCC3* p.S327fs (44.8%)
Mature teratoma	6	None	None	*FLT3* p.S574N (48.4%) *KNL1* p.M788V (45.4%) *PARP4* p.A666S (9.1%) *RYR3* p.I3000V (43.5%)
	7	None	p.K1844N (22.0%)	None
	8	NP	NP	NP

Comprehensive Molecular Profiling of Sinonasal Teratocarcinosarcoma Highlights Recurrent SMARCA4 Inactivation and CTNNB1 Mutations

Rooper LM, Agaimy A, Gagan J, Simpson RHW, Thompson LDR, Trzcinska AM, Ud Din N, Bishop JA

Am J Surg Pathol. 2023 Feb 1;47(2):224-233

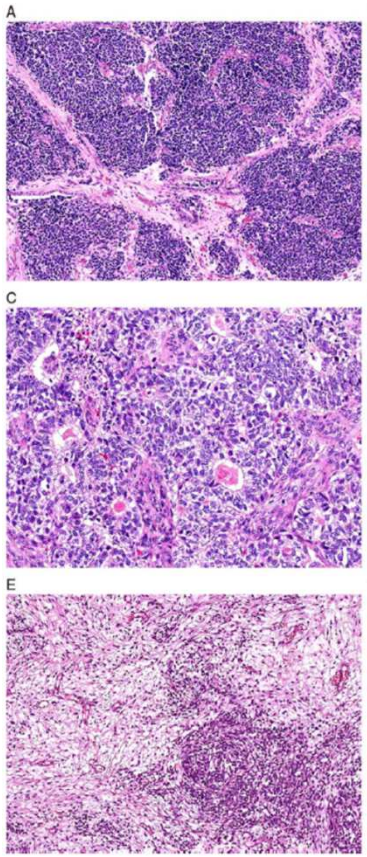

FIGURE 1. All TCS included nests and sheets **of immature neuroepithelial cells** (A) that had an overtly malignant appearance including large, hyperchromatic, and angulated nuclei (B). These primitive neuroepithelial elements showed occasional areas of clear cell change (C) with frequent prominent rosettes (D). A subset of TCS showed more mature neural elements that had prominent neurofibrillary stroma (E) and often displayed nested architecture with ganglion-like cells (F).

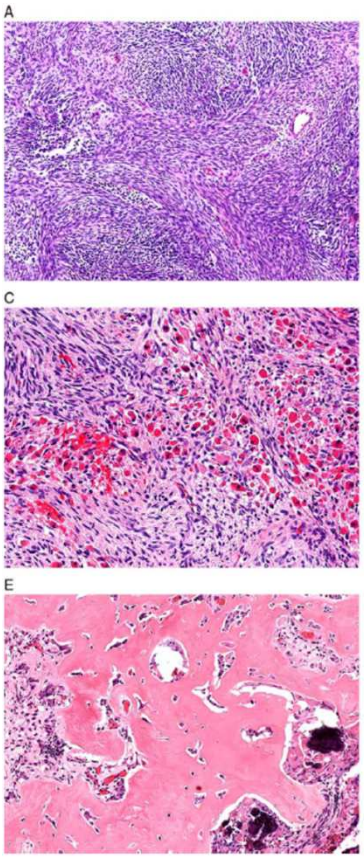

FIGURE 2. All TCS had fascicles of **undifferentiated spindle cells** that ranged from hypercellular (A) to paucicellular (B). A small subset of cases displayed heterologous differentiation, including rhabdomyoblastic elements with strap cells (C), fascicles of smooth muscle (D), and overt formation of mature bone (E) and immature cartilage (F).

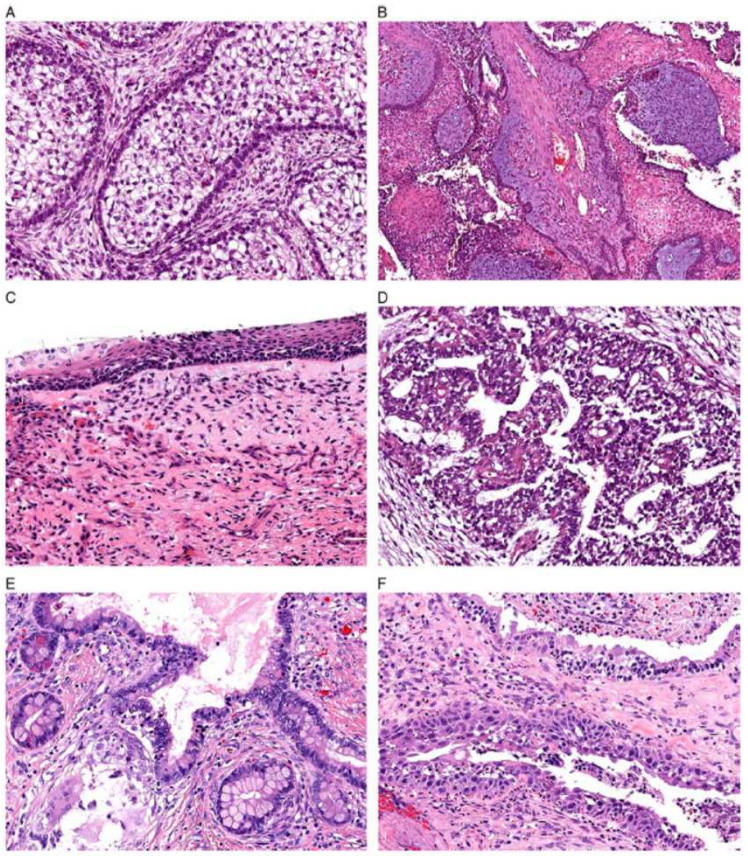

FIGURE 3. The **epithelial component** of TCS included squamous cells with glycogenated cytoplasm and prominent intracellular borders that conferred a fetal appearance (A) and in rare cases had a papillary pattern (B) or colonized surface epithelium (C). Glands also shared the clear cell fetal appearance (D) or had a highly differentiated mucinous pattern with scattered paneth-like cells (E). Rarely, the epithelial elements displayed increased cytologic atypia and mitotic activity (F).

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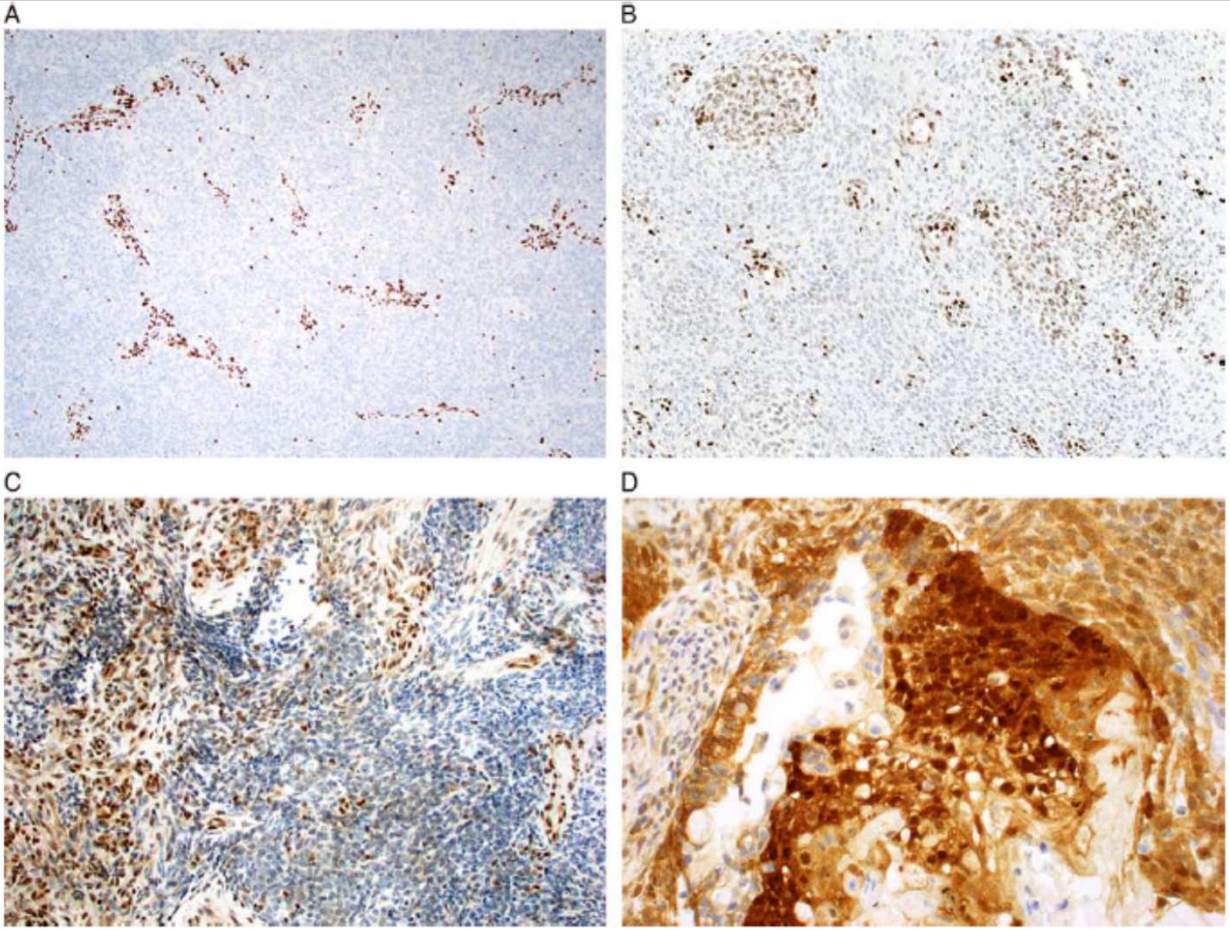

FIGURE 4. Across the entire cohort of TCS, **60% of cases showed total SMARCA4 loss in tumor cells** with retained internal control in blood vessels (A), while **13% of cases showed partial loss** with the strongest expression in neuroepithelial and epithelial components (B). There was also partial loss of SMARCB1 in 37% of cases tested (C). Focal to patchy **nuclear β-catenin localization was seen in 64% of cases**, most commonly in epithelial elements (D).

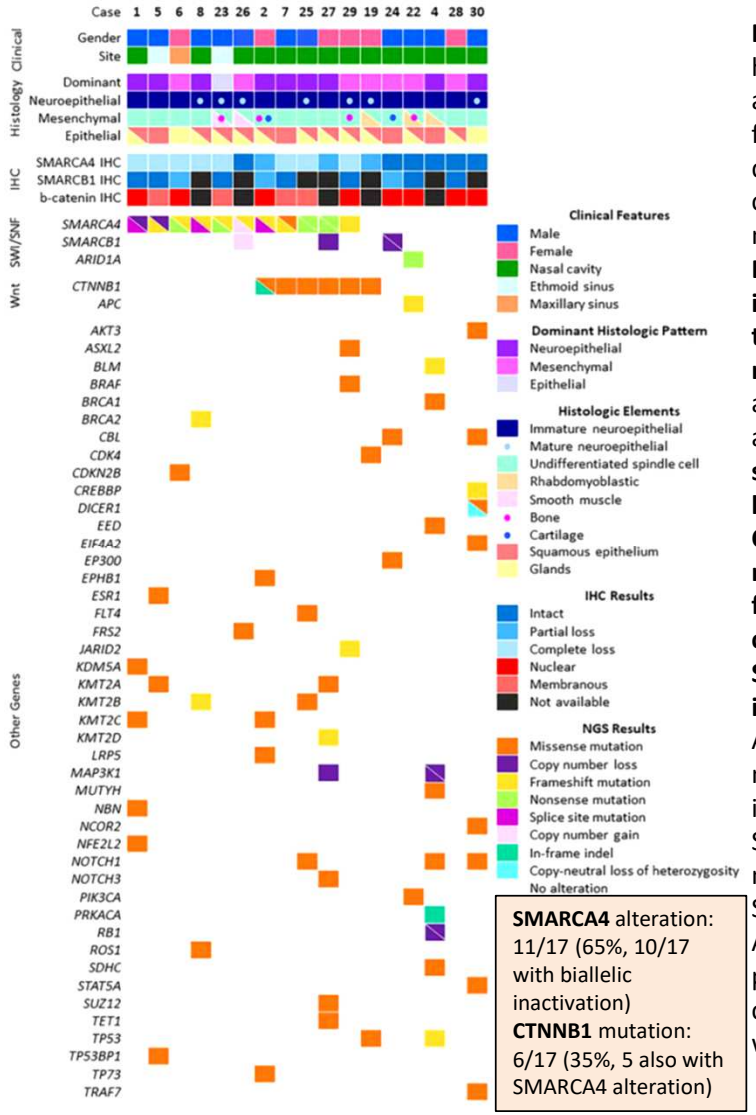

FIGURE 5. Clinical, histologic, IHC, and molecular features of TCS are depicted with cases organized by molecular findings. **Biallelic SMARCA4 inactivation was the most common molecular** alteration in TCS and **correlated strongly with IHC loss**. Activating **CTNNB1 mutations were frequently seen in combination with SMARCA4 inactivation**. Additional molecular drivers included other SWI/SNF complex members SMARCB1 and ARID1A and Wnt pathway constituent APC as well as DICER1

Teratomatous tumors of Thyroid and Head and Neck

Teratomatous tumor	Age	Sex	Site	Organoid structures/mature tissue	Primitive thyroid follicles	Somatic genetic alteration	Prognosis
Thyreoblastoma	Adult	F:75%	Distal: thyroid	Rare	Present	DICER1 mutation[e]	Poor (>50% of patients die within one year)
Teratocarcinosarcoma of the Head and Neck	Adult	M: 80%	Proximal: sinonasal tract/ skull base	May be present	Absent	SMARCA4 inactivation and/or CTNNB1 mutation[d]	Intermadiate (5-year survival rate > 50%)
Teratoma, mature and immature	Neonates /young children[a]	F=M	Proximal and Distal[b]	Present	Absent[c]	Unknown	Excellent[f]

[a]May be congenital

[b]Proximal sites (Sinonasal tract and nasopharynx) are more common than distal ones (Thyroid/perithyroidal)

[c]Organoid structures may contain developing or mature thyroid tissue

[d]DICER1 mutation is uncommon, but it has been reported: a significant subset of tumors defined by DICER1 mutations are notable for multilineage differentiation or primitive neuroepithelial components similar to teratocarcinosarcoma. Rare interchangeability between SMARCA4 and DICER1 has also been previously documented, with one case of a pleuropulmonary blastomalike neoplasm in an infant showing SMARCA4 inactivation instead of DICER1 mutation [Rooper LM et al. Comprehensive Molecular Profiling of Sinonasal Teratocarcinosarcoma Highlights Recurrent SMARCA4 Inactivation and CTNNB1 Mutations. Am J Surg Pathol. 2023 Feb 1;47(2):224-233]

[e]No germline mutation reported to date

[f]In the absence of overtly malignant component; may cause death due to mass effect with impairement of vital structures (e.g. *airways)*

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- Agaimy A, Witkowski L, Stoehr R, Cuenca JCC, González-Muller CA, Brütting A, Bährle M, Mantsopoulos K, Amin RMS, Hartmann A, Metzler M, Amr SS, Foulkes WD, Sobrinho-Simões M, Eloy C. Malignant teratoid tumor of the thyroid gland: an aggressive primitive multiphenotypic malignancy showing organotypical elements and frequent DICER1 alterations-is the term "thyroblastoma" more appropriate? Virchows Arch. 2020 Dec;477(6):787-798
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