American Association of Neuropathologists Diagnostic Slide Session 2018 Case #2

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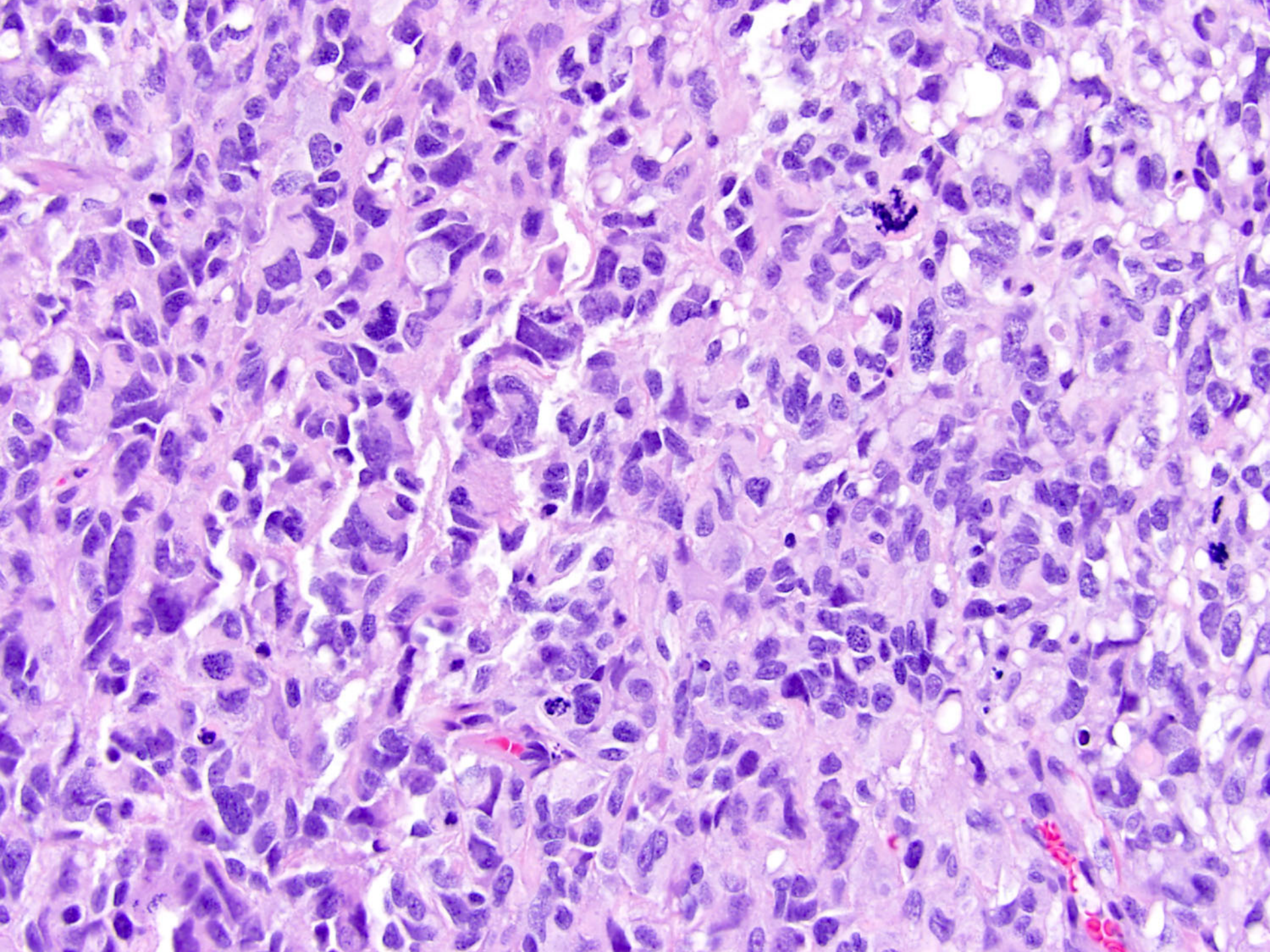
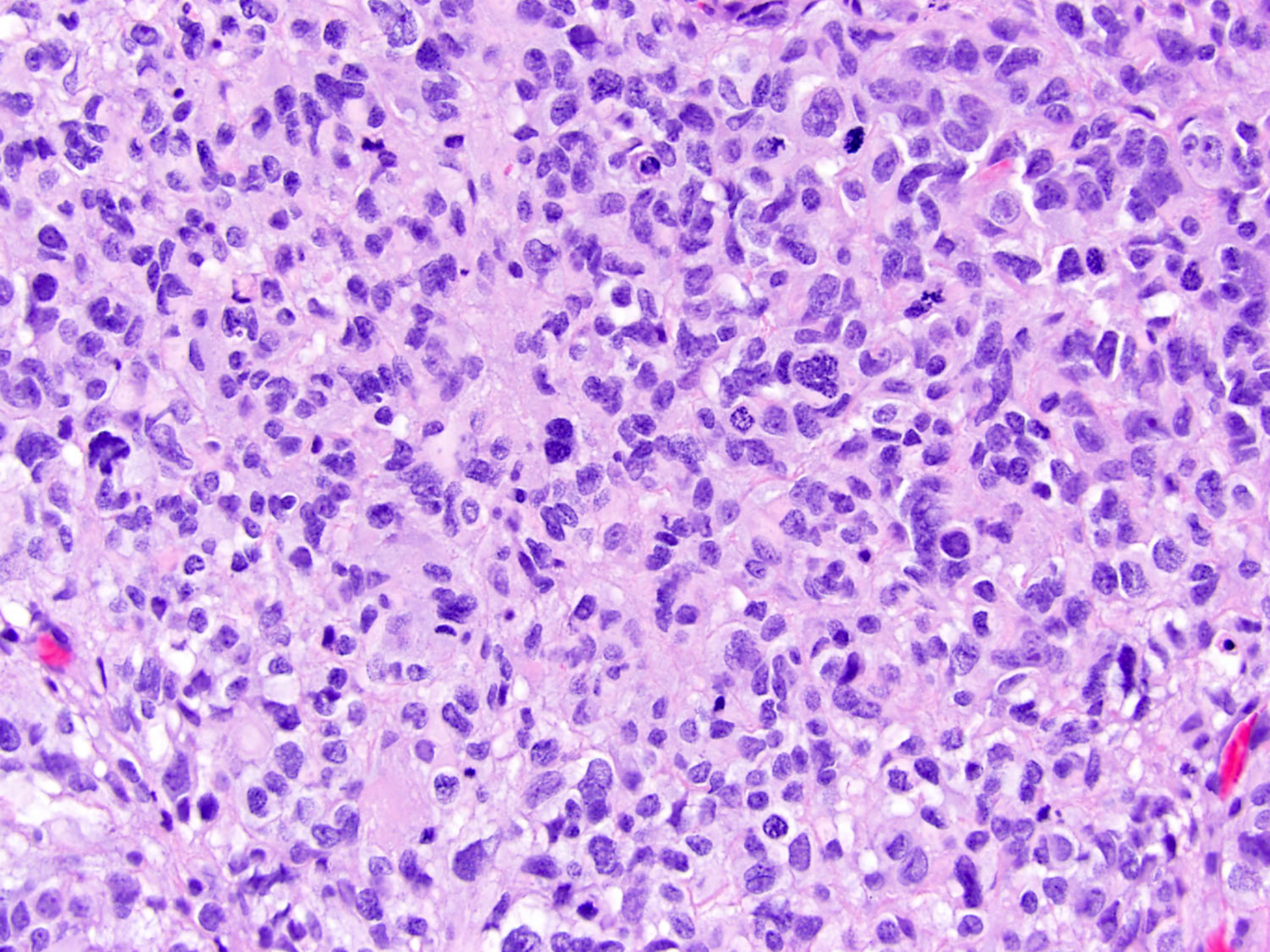
I have nothing to disclose

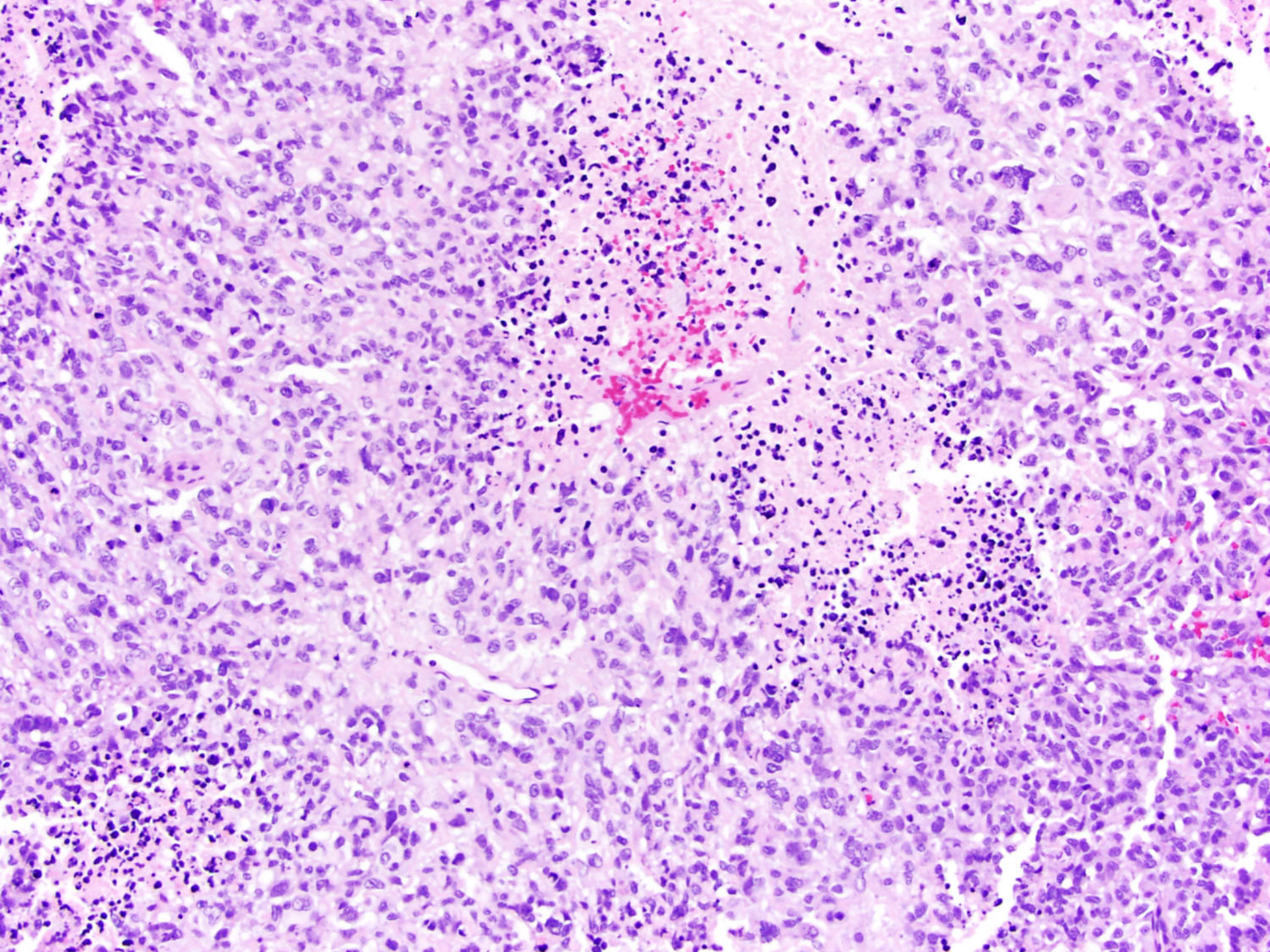
The patient is a 25-year-old-male who presented with left hand numbness and headaches.

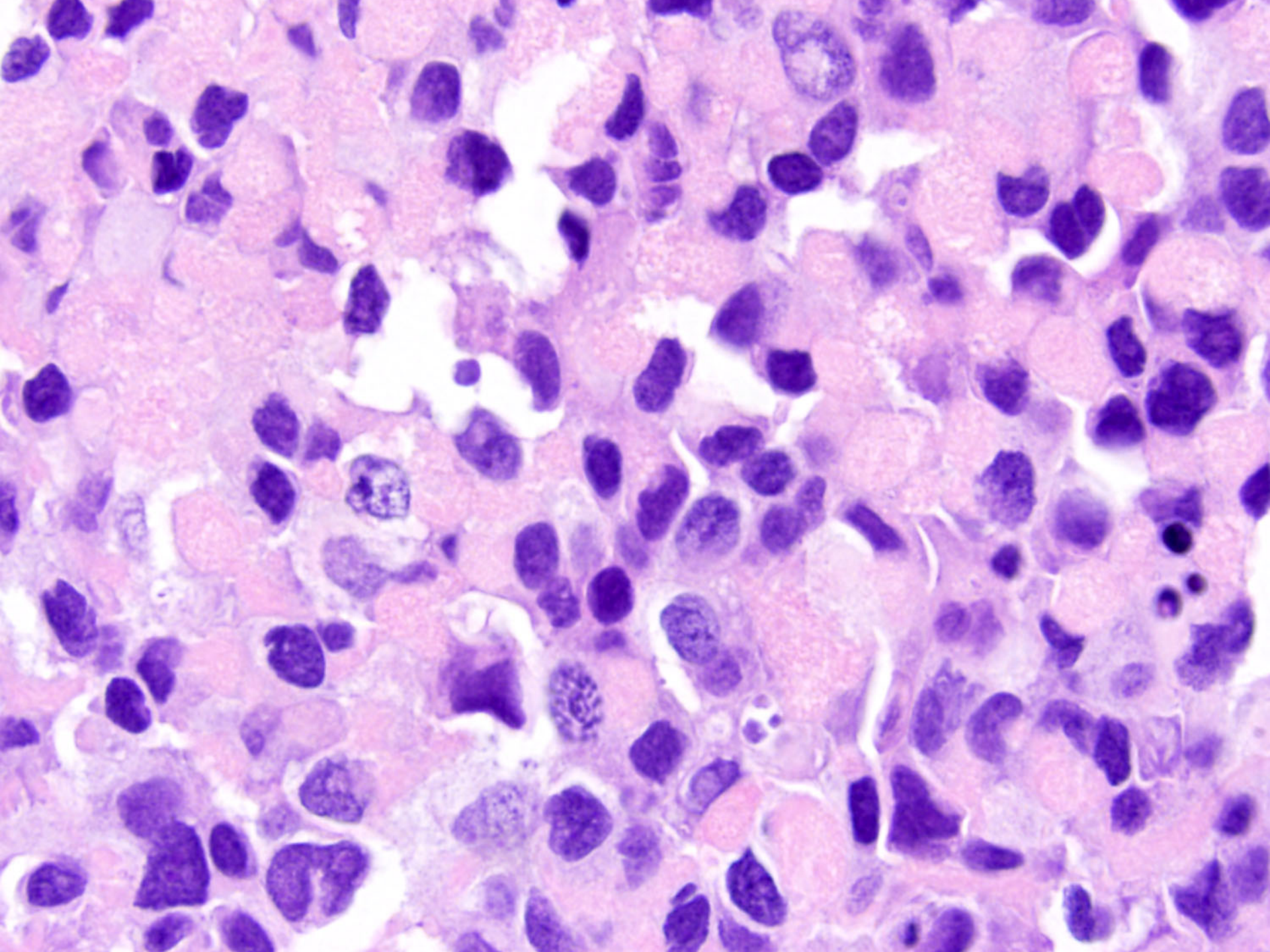
He was found to have a 4.7 cm heterogeneously enhancing intra-axial mass in the left cerebellar hemisphere, with mass effect on the fourth ventricle.

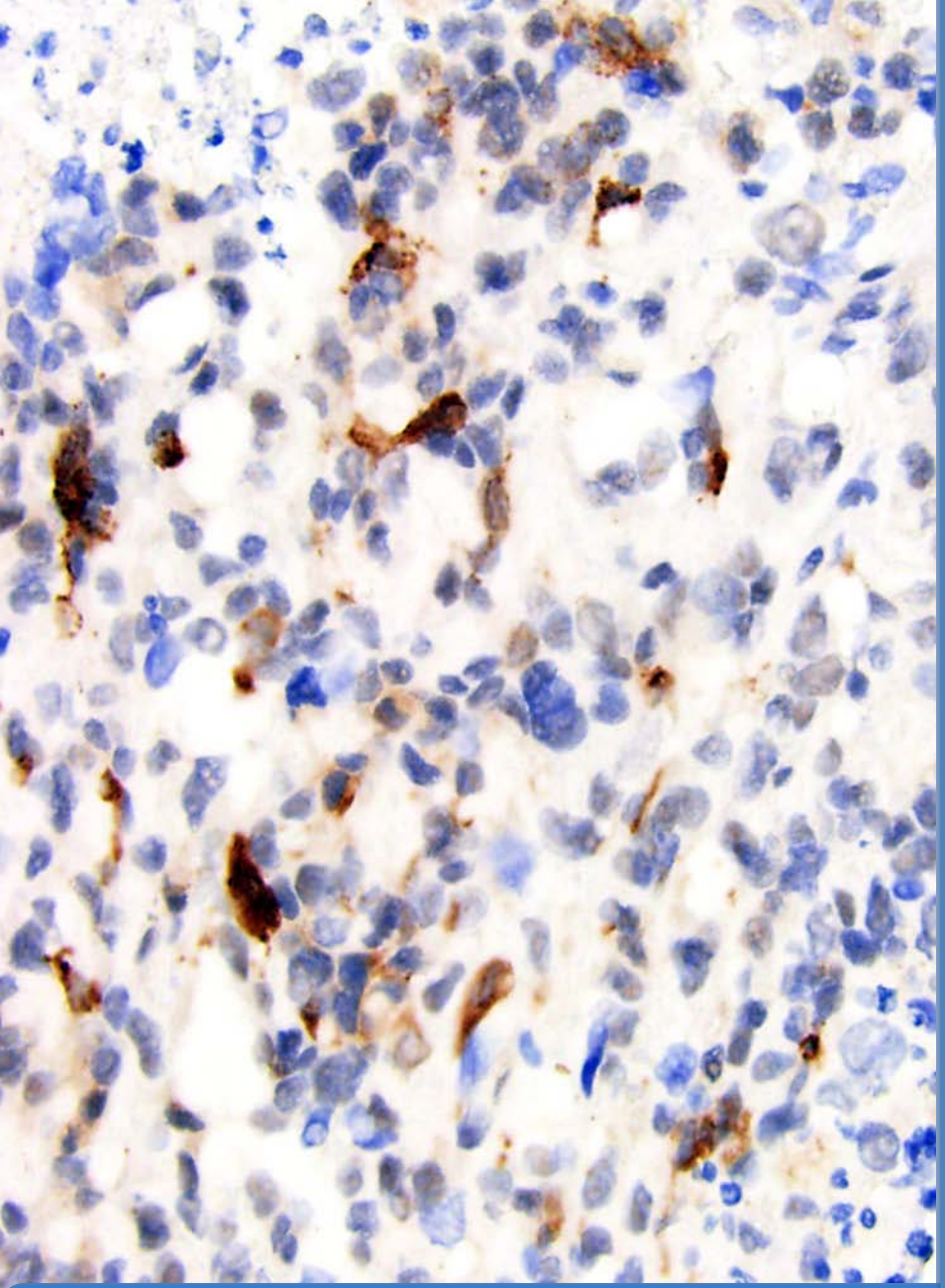
A biopsy was performed.



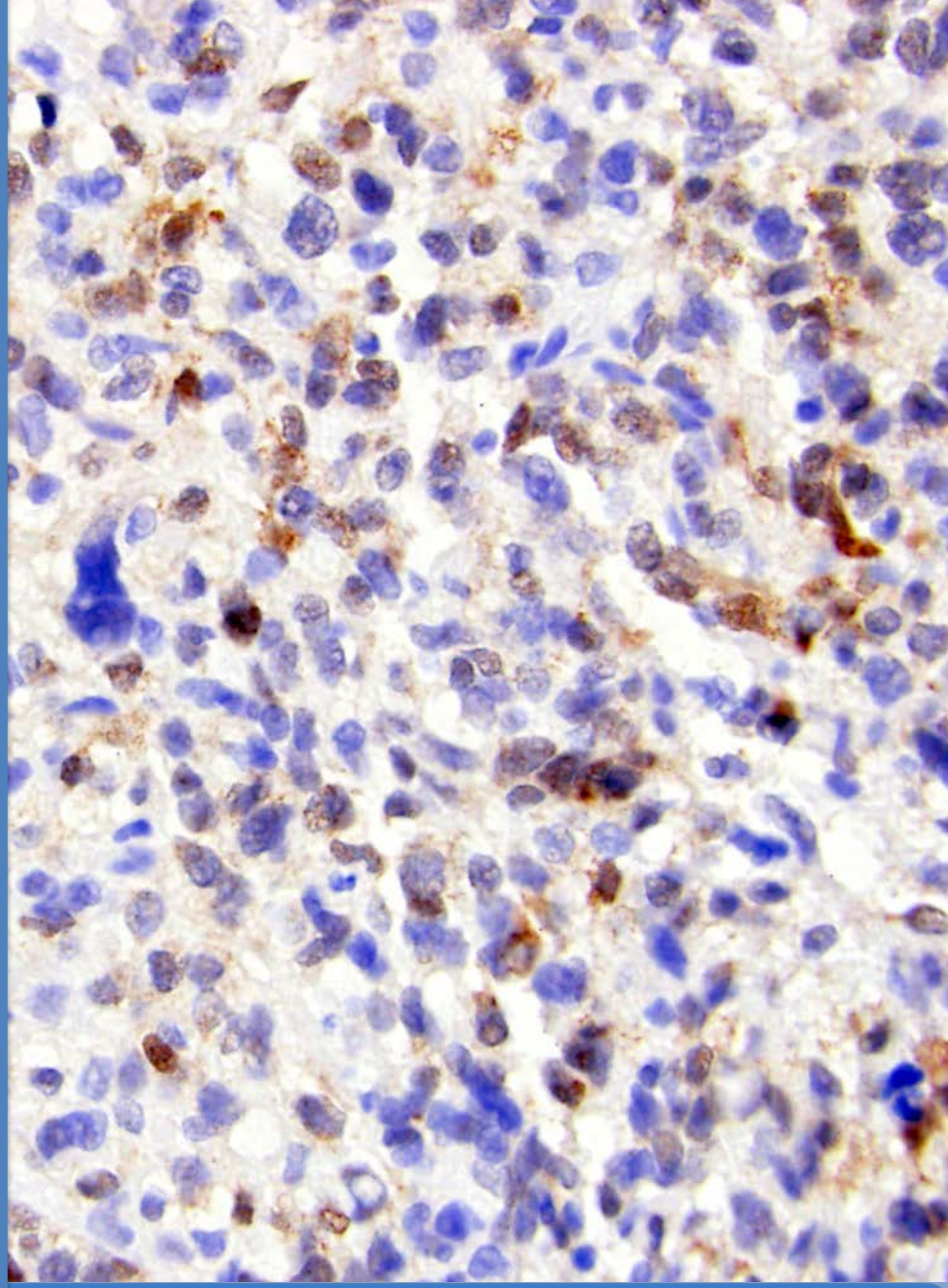








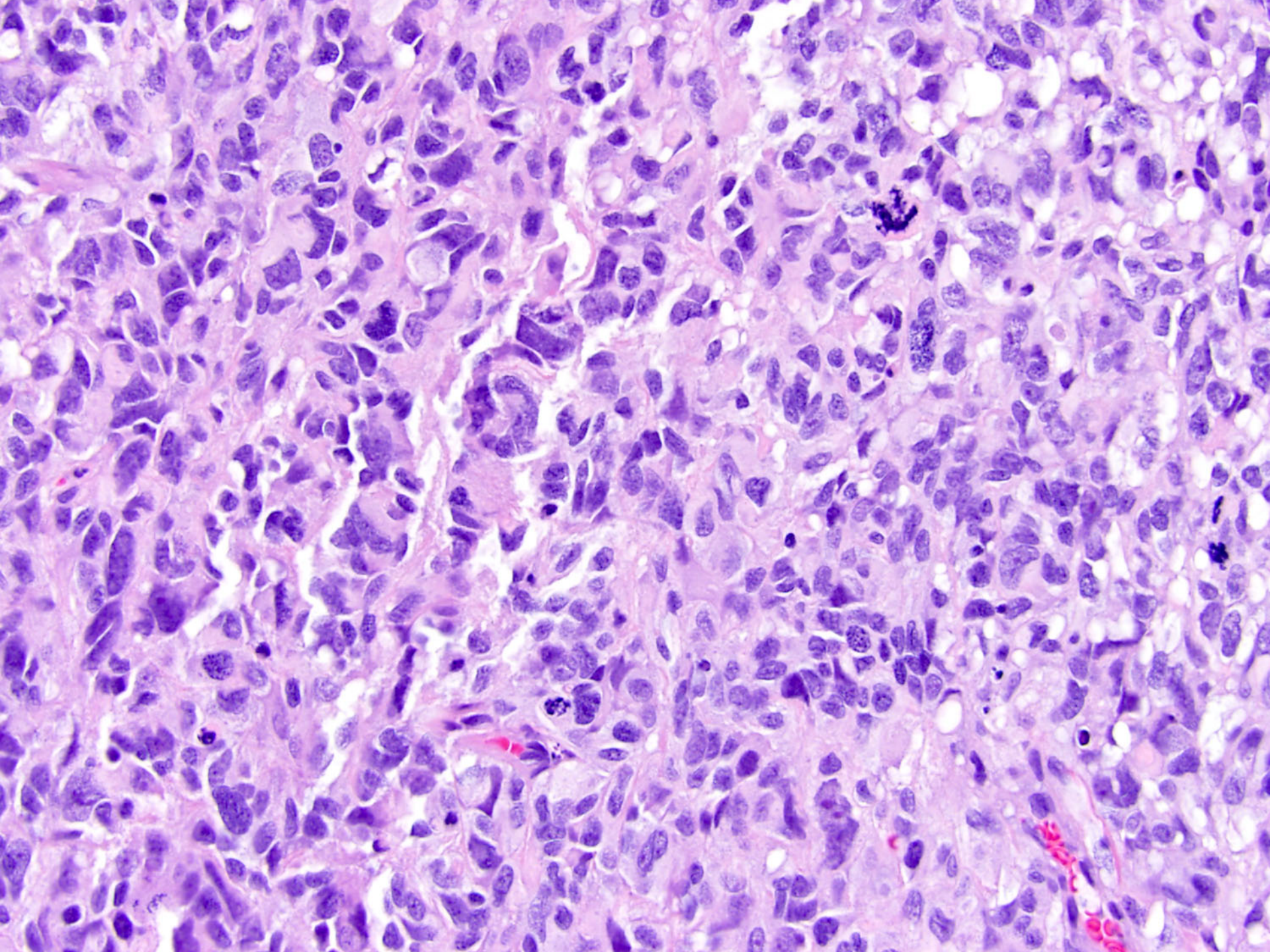
Synaptophysin

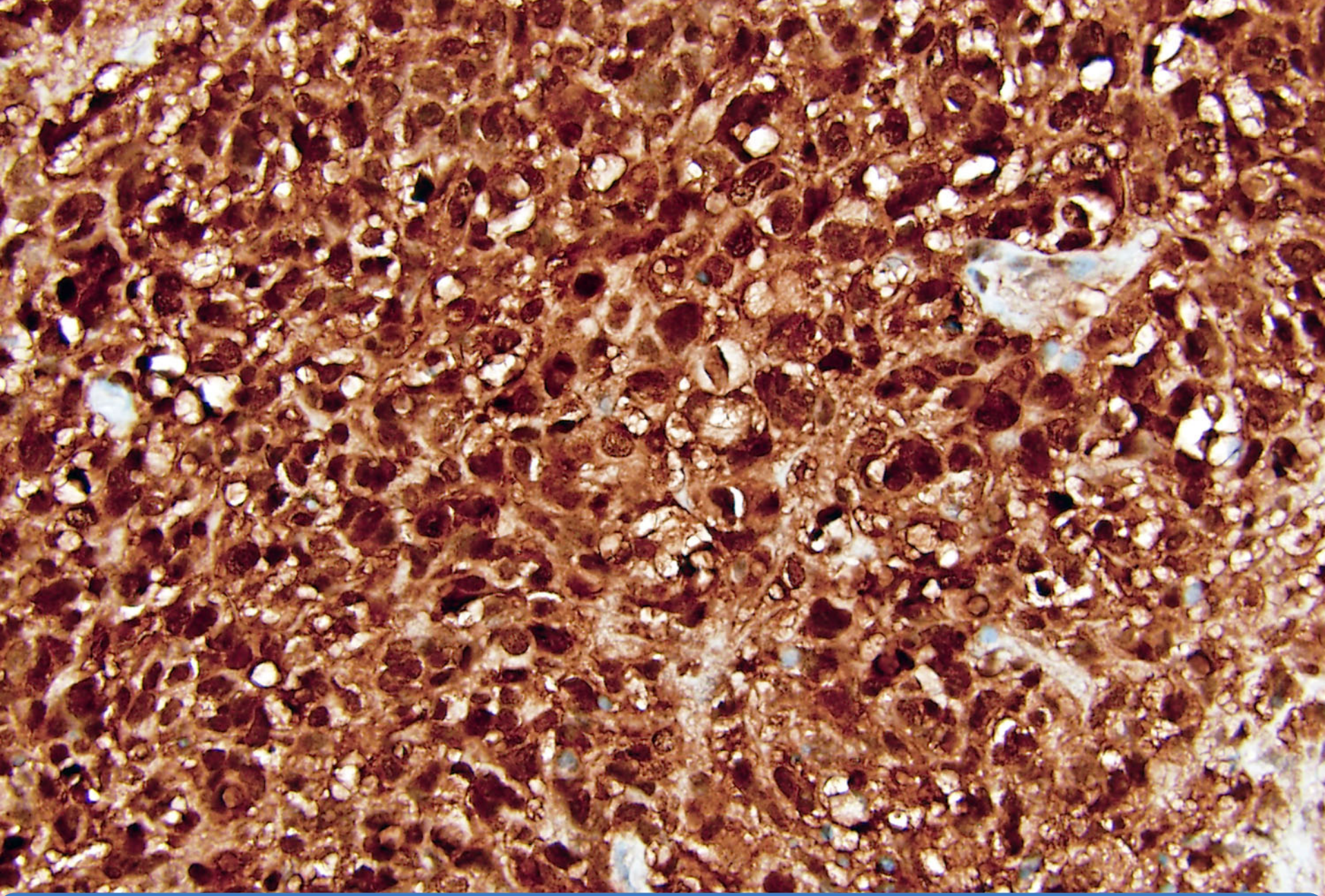


NeuN

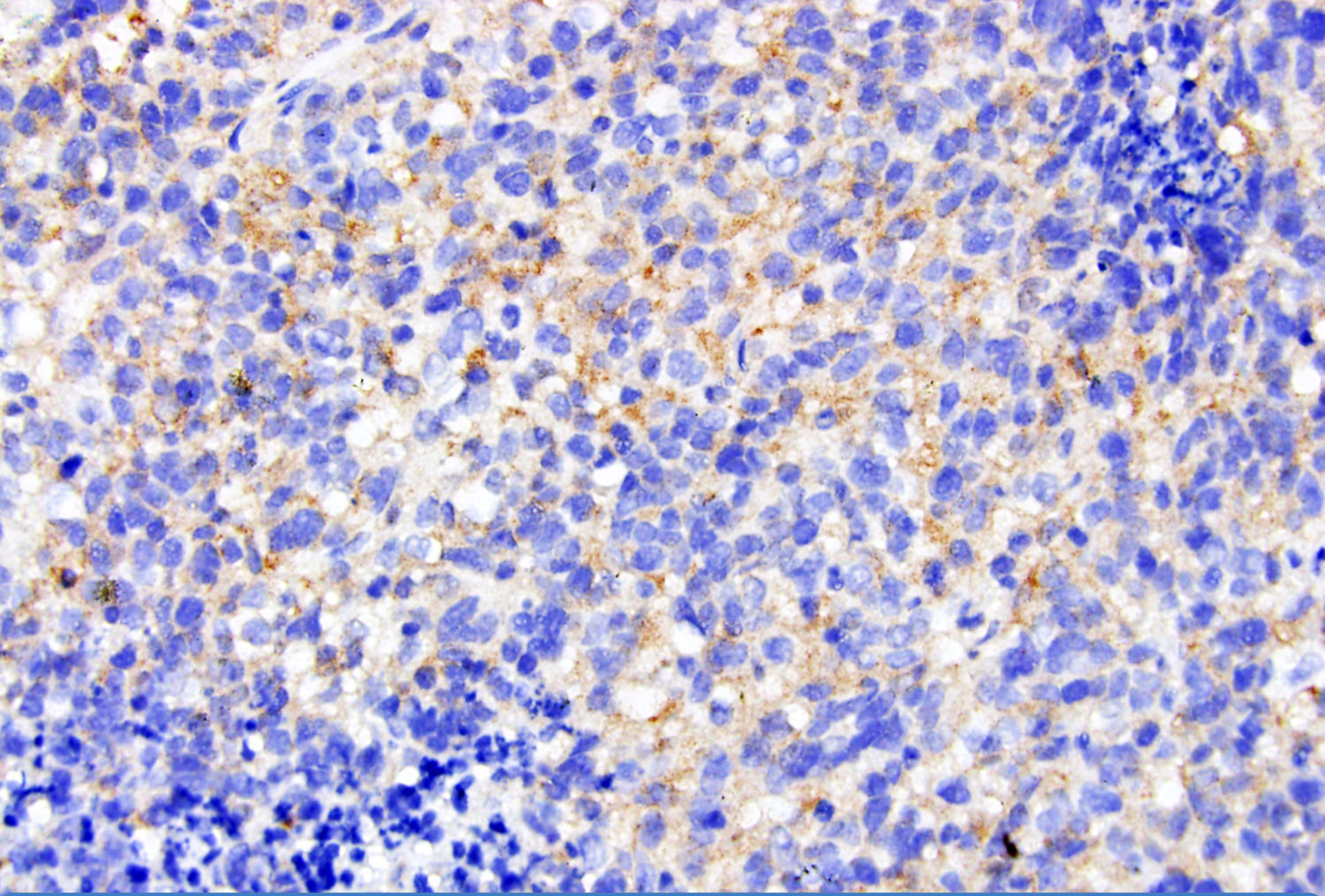
Differential diagnosis?

Additional immunohistochemical or molecular evaluation?

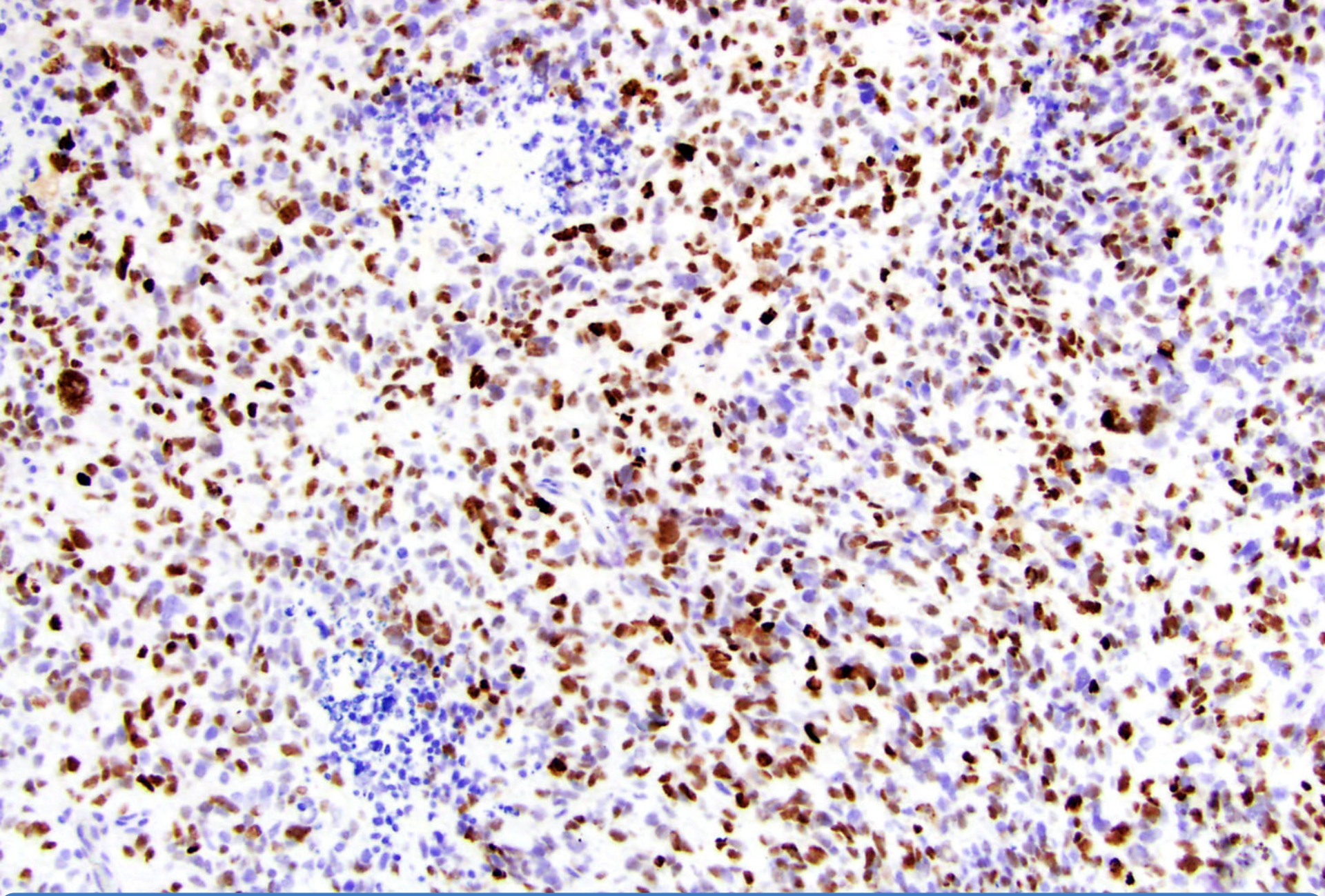




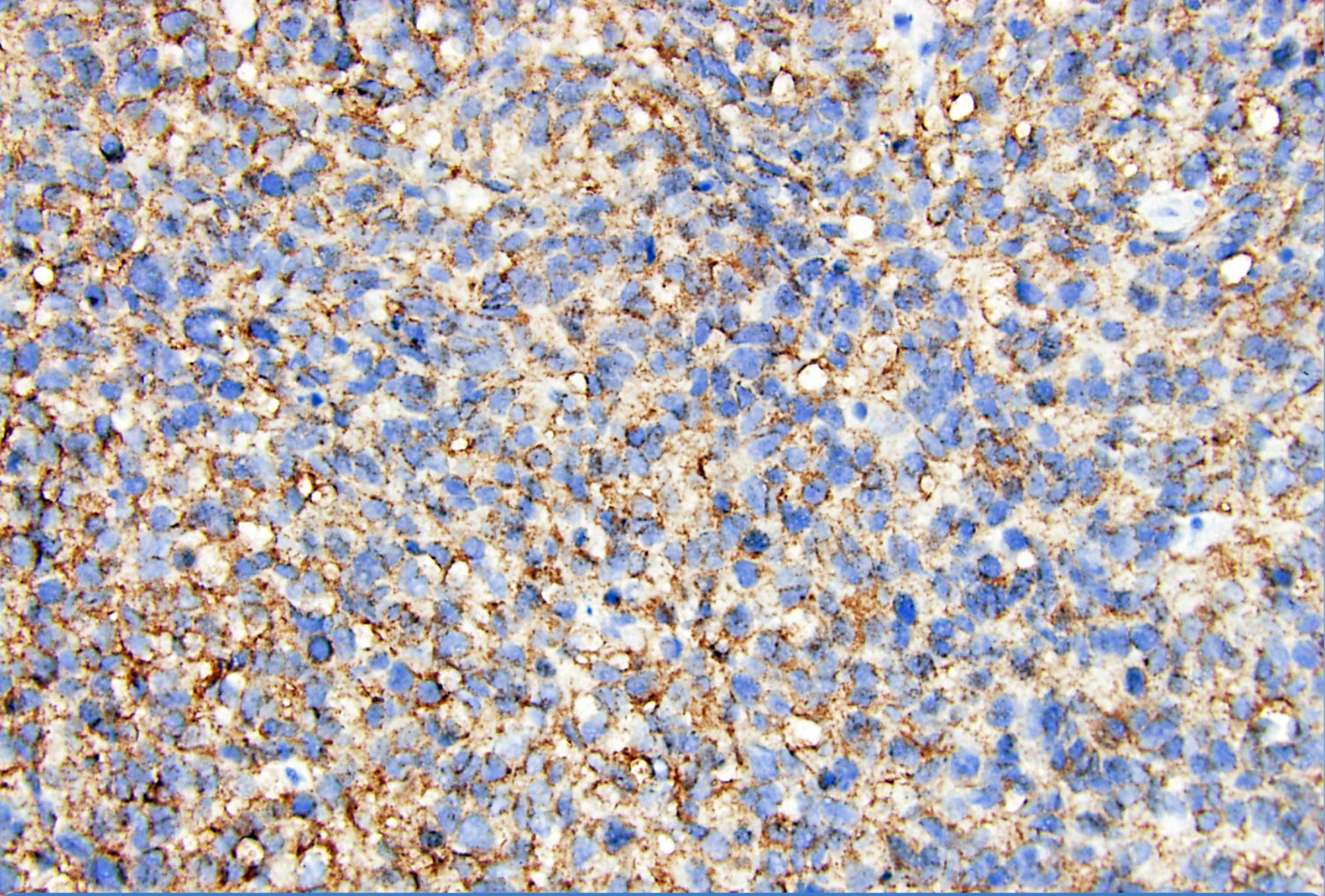
YAP1



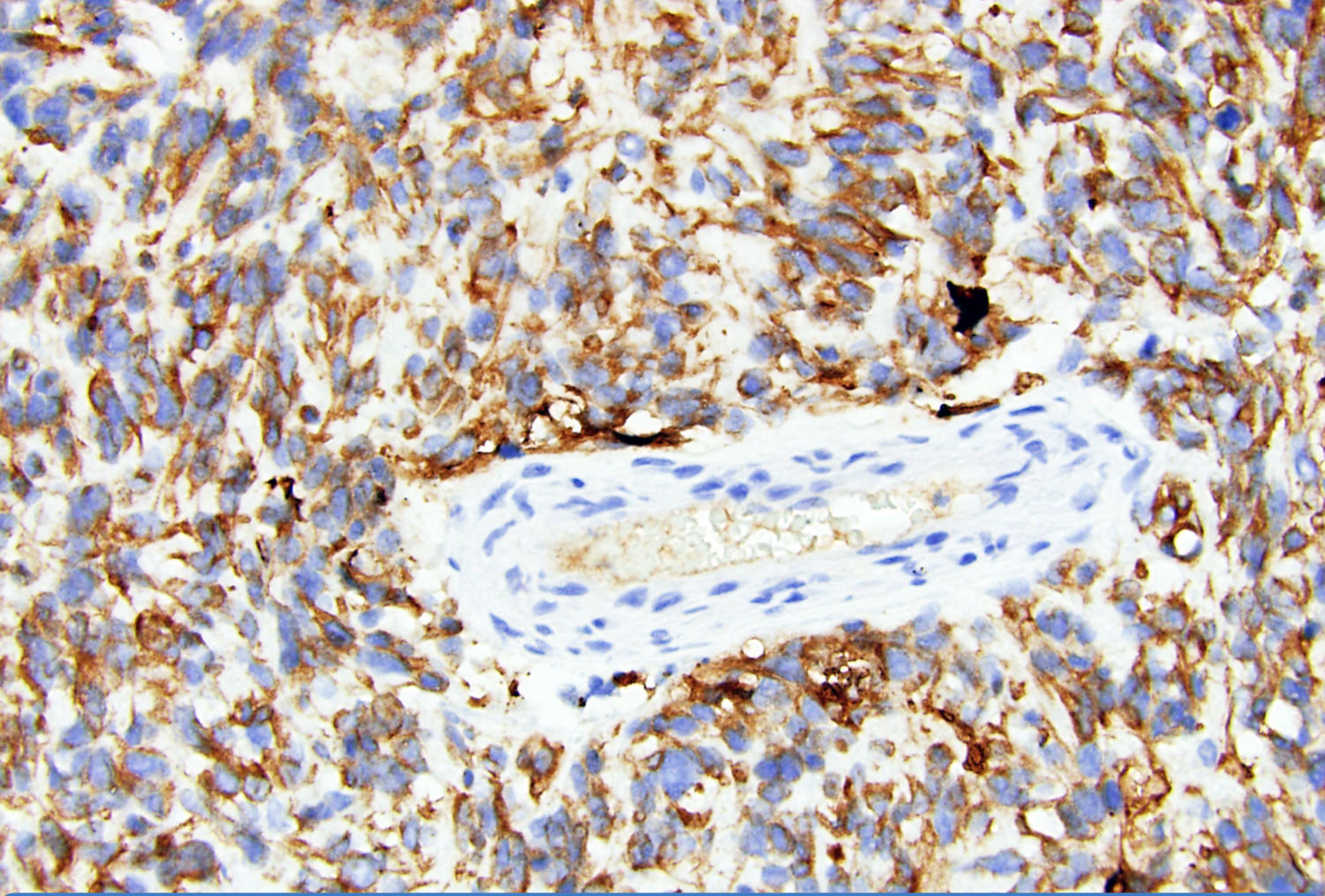
GAB1



p53



EMA

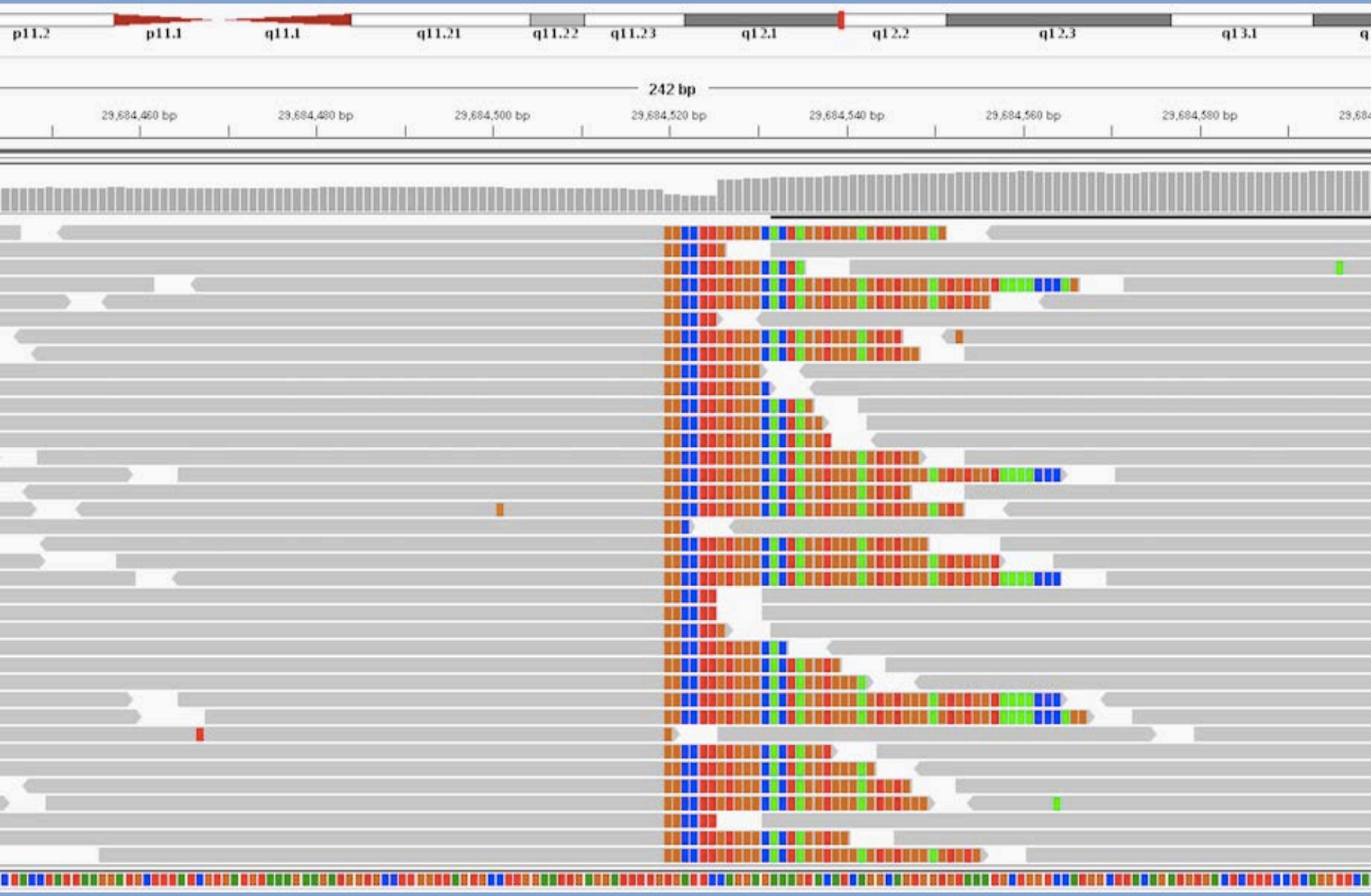


Cytokeratin CAM 5.2

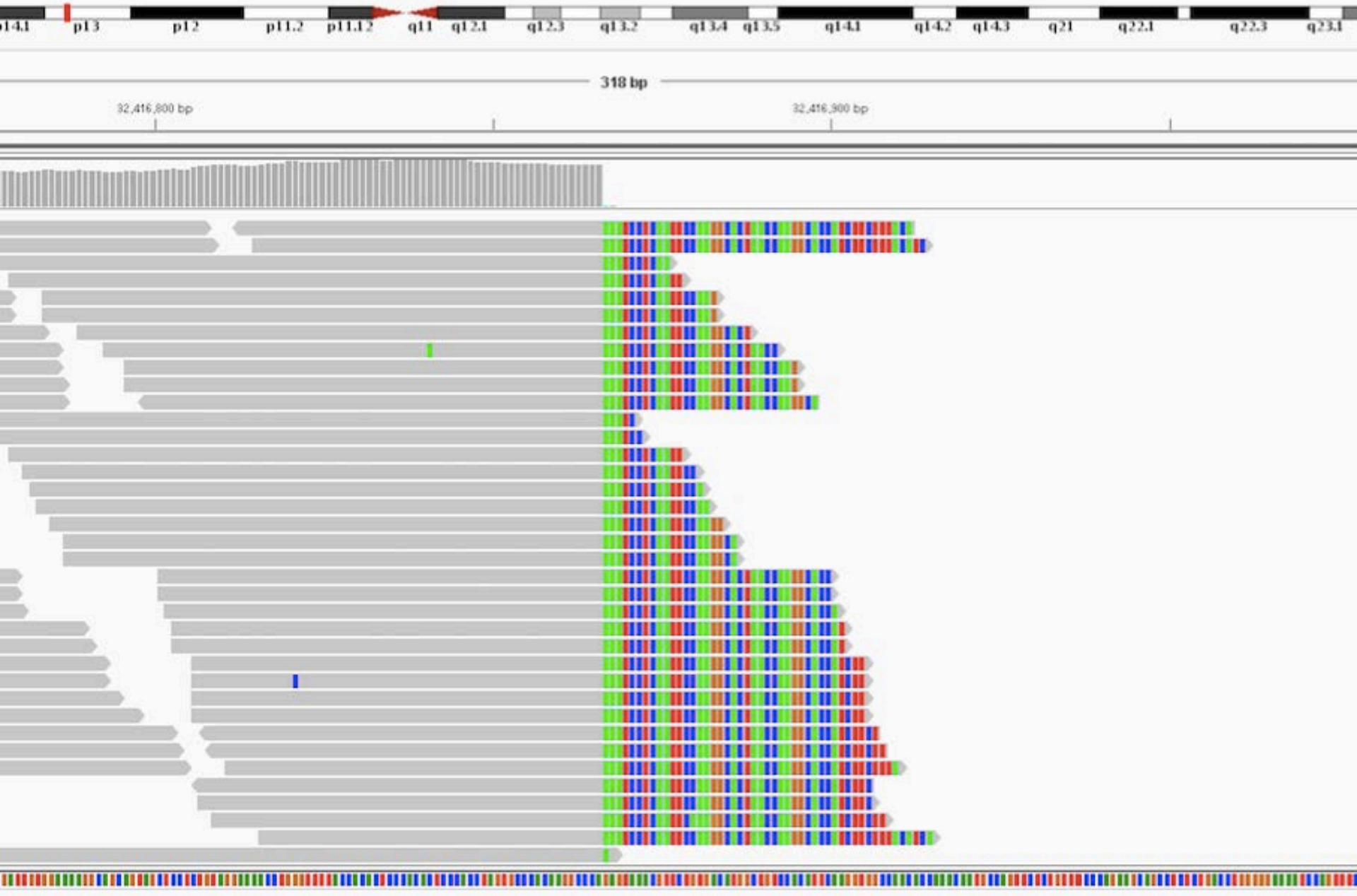
A diagnosis of anaplastic medulloblastoma, SHH-activated and TP53-mutant, WHO grade IV was favored.

The case was evaluated by the UCSF500 NGS panel.

Chromosome 22q12, EWSR1



Chromosome 11p13, WT1



Desmoplastic small round cell tumor (DSRCT)
EWSR1-WT1 fusion t(11;22)(p13;q12)

PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
EWSR1-WT1 gene fusion	NM_013986, NM_024426	Pathogenic	191 over fusion junction	N/A
TERT c.-124C>T	NM_198253	Pathogenic	796	28%

'Reads' indicate the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal.

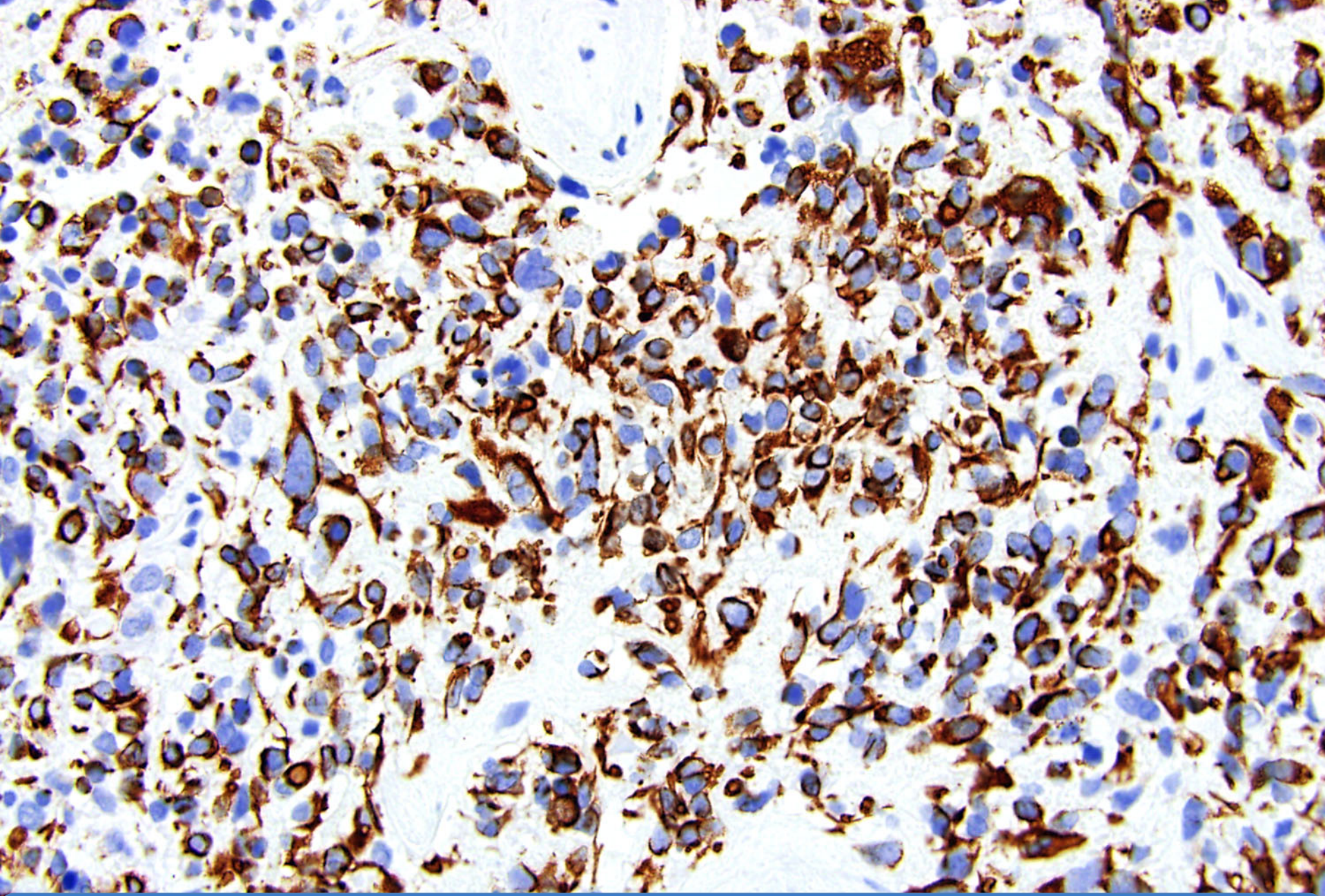
INTERPRETATION

Tumor-only sequencing of this primitive small round blue cell tumor centered in the posterior fossa demonstrates a hotspot mutation in the promoter region of the TERT gene and an EWSR1-WT1 gene fusion. The fusion junction is between intron 8-9 of the EWSR1 gene on chromosome 22q12 and intron 7-8 of the WT1 gene on chromosome 11p13 and is predicted to result in an in-frame fusion protein where the N-terminal portion is composed of exons 1-8 of EWSR1 and the C-terminal portion is composed of exons 8-10 of WT1. Chromosomal copy number analysis demonstrates gains of proximal 1p, 1q, 2, 5, 7, proximal 11p, 11q, 15, 18, 19, 20, 21, and distal 22q, as well as losses of distal 1p, 16, and 17.

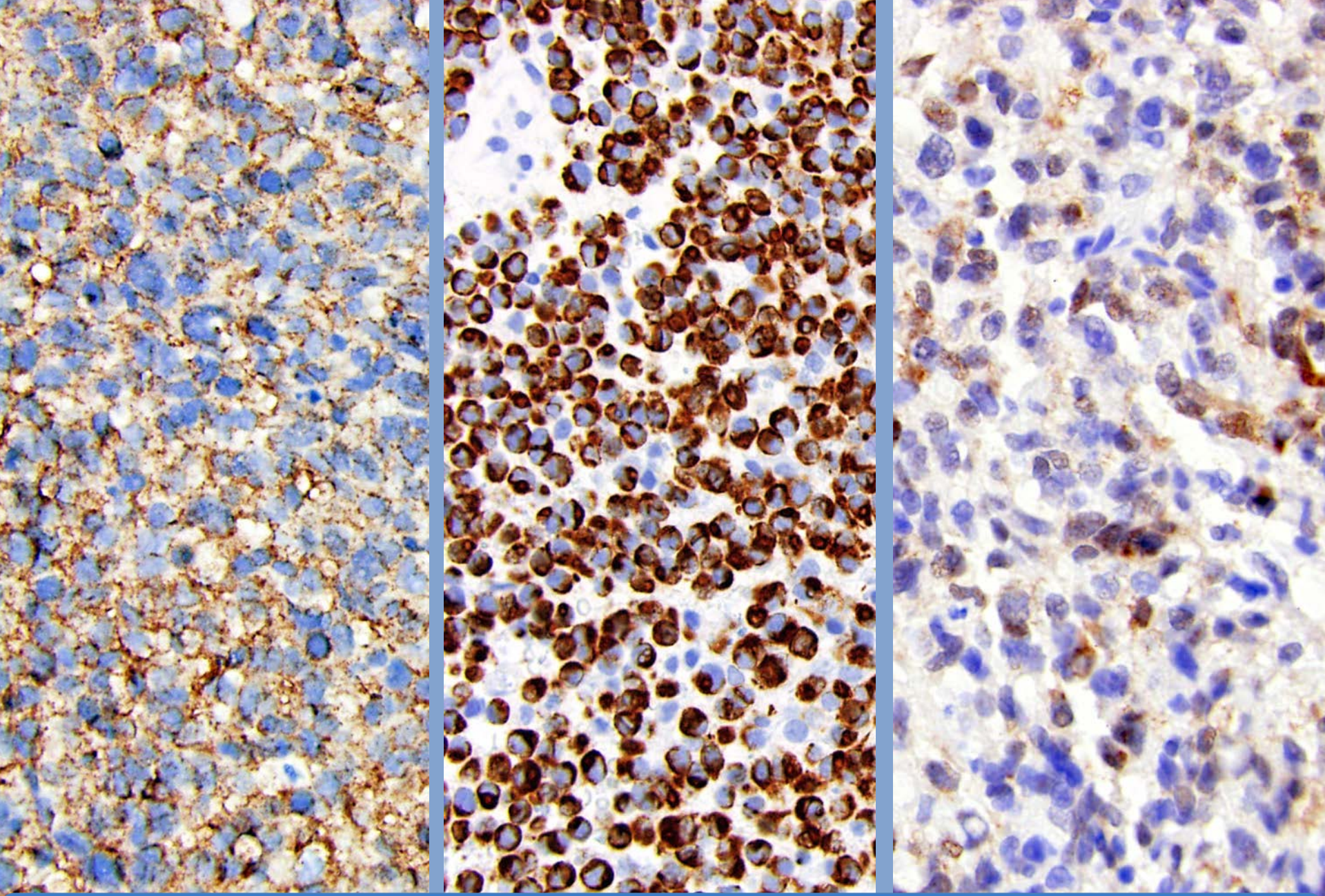
The genetic profile supports a diagnosis of desmoplastic small round cell tumor, a malignant mesenchymal tumor entity defined by EWSR1-WT1 gene fusion [refs. 1-2]. EWSR1-WT1 fusion is not known to be present in other tumor entities, including medulloblastoma or other primary CNS tumors. Additionally, there are not genetic alterations identified that characterize medulloblastoma (e.g. MYC, MYCN, CDK6, SNCAIP, CTNNB1, SMO, PTCH1, SUFU, GLI2), glioblastoma (H3F3A, HIST1H3B, IDH1, EGFR, PTEN, NF1, CDKN2A), or other primary CNS tumor entities. Correlation with the radiographic and histologic features is recommended to achieve the best integrated diagnosis for this tumor, especially given that desmoplastic small round cell tumor usually arises in the abdominal cavity and only a few rare intracranial examples have been reported previously.

References:
1. Ladanyi M, Gerald W. Fusion of the EWS and WT1 genes in the desmoplastic small round cell tumor. Cancer Research 54: 2837-2840, 1994.
2. Gerald WL, Rosai J, Ladanyi M. Characterization of the genomic breakpoint and chimeric transcripts in the EWS-WT1 gene fusion of desmoplastic small round cell tumor. Proc Natl Acad Sci USA 92: 1028-1032, 1995.

DSRCT: malignant neoplasm with polyphenotypic differentiation (epithelial, mesenchymal, and neuronal)



Desmin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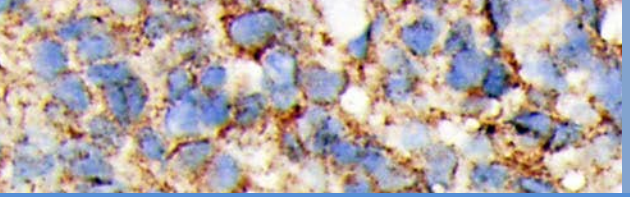
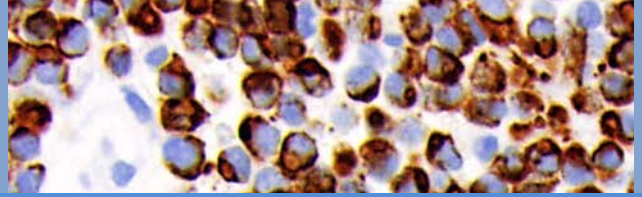
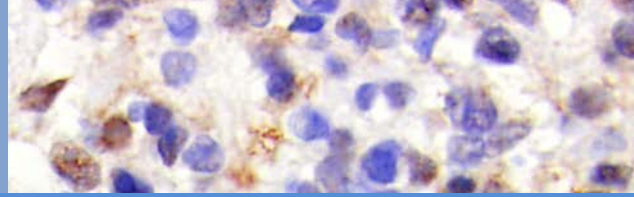
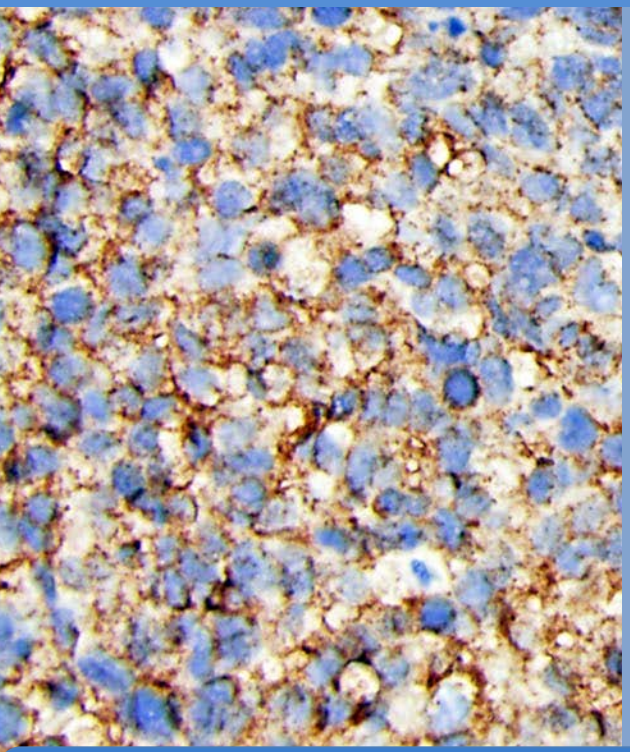
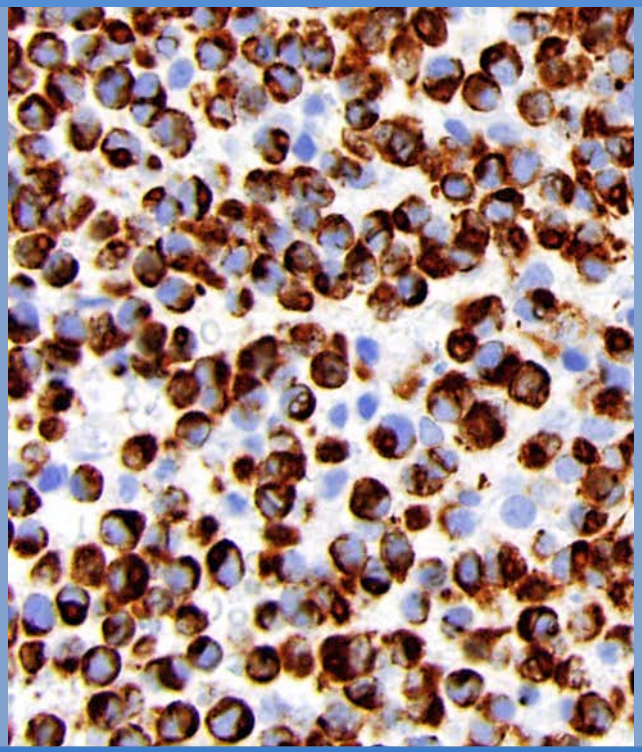
DSRCTs show Polyphenotypic differentiation

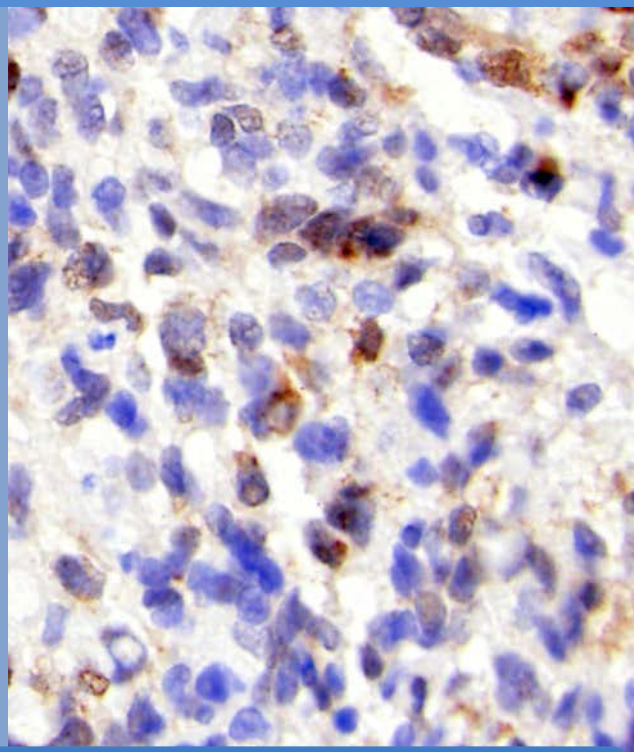












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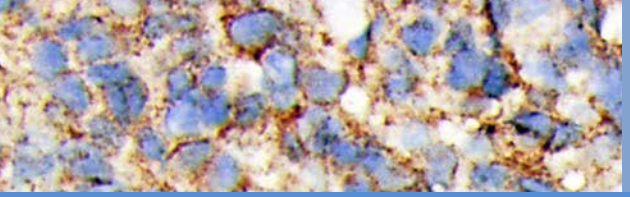
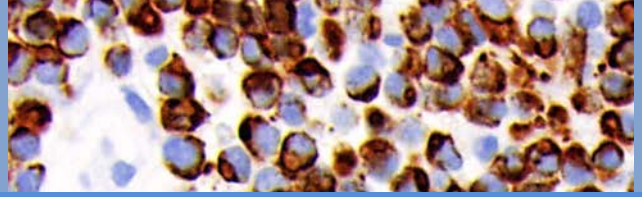
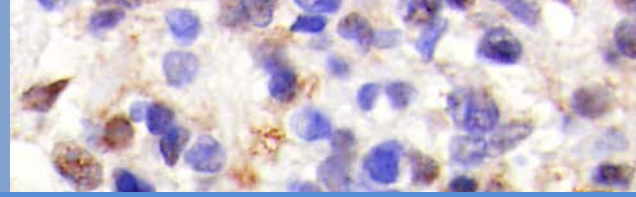
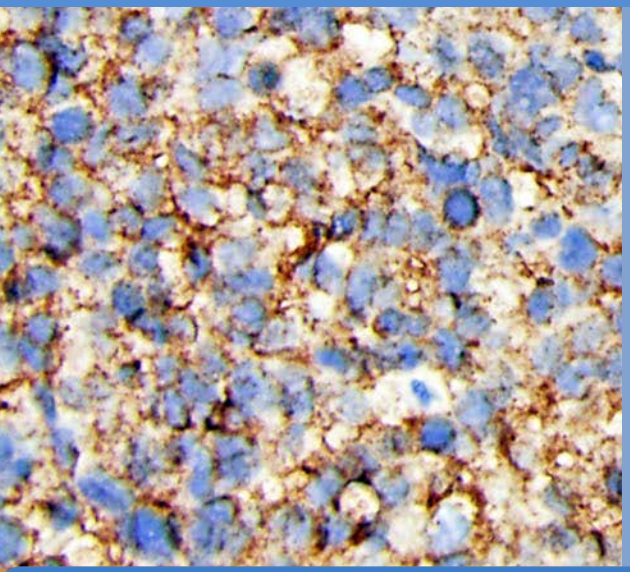
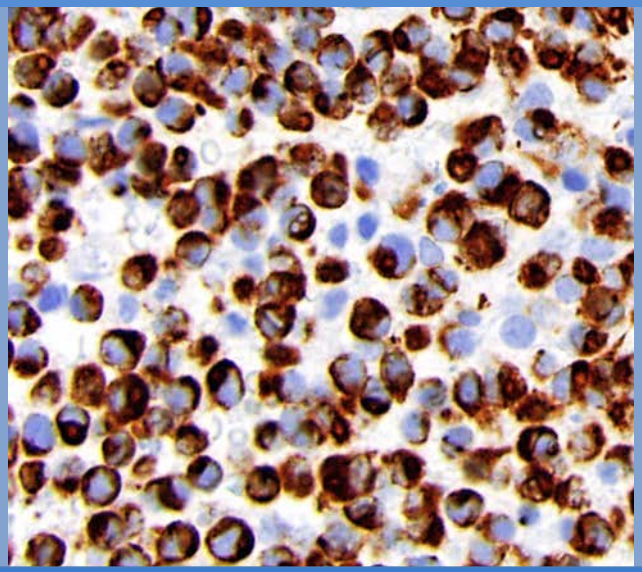
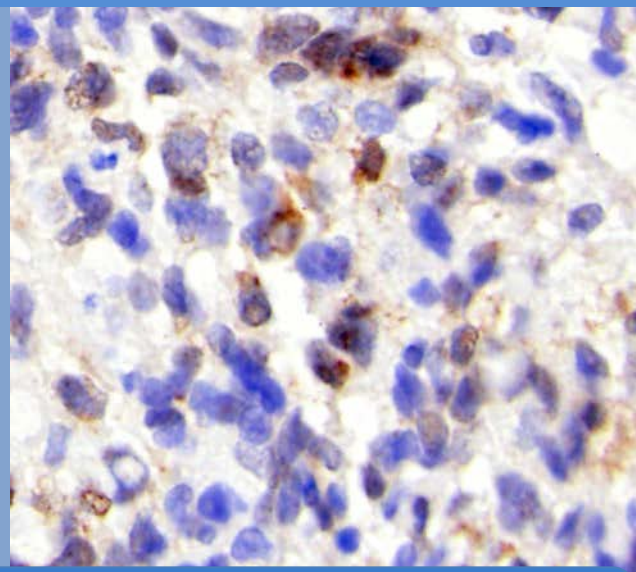




Small cell tumor with divergent differentiation

Polyphenotypic small round cell tumor

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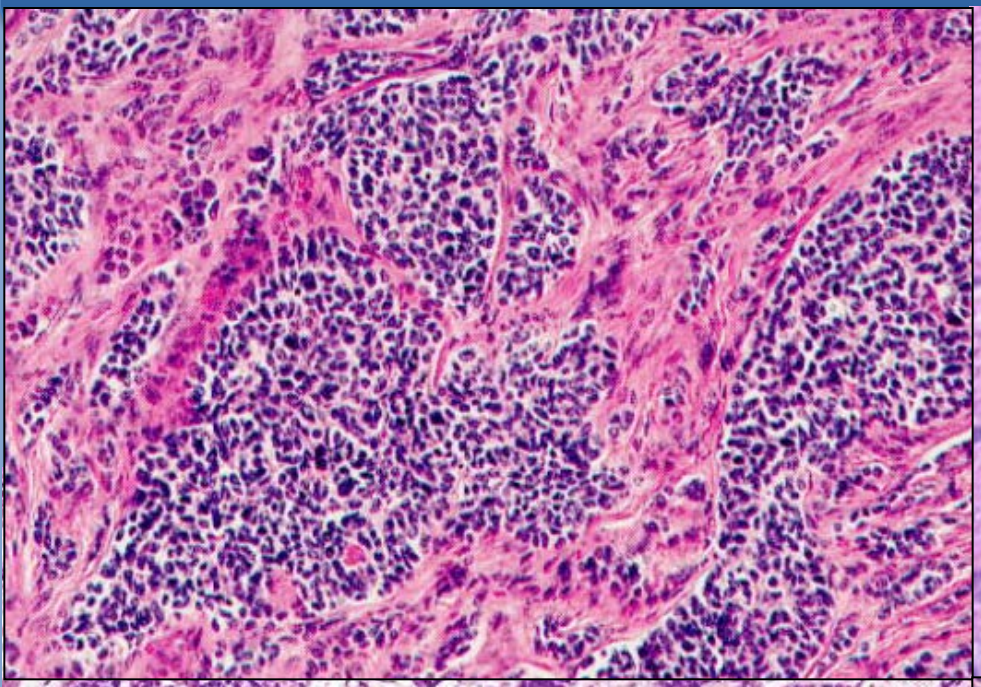
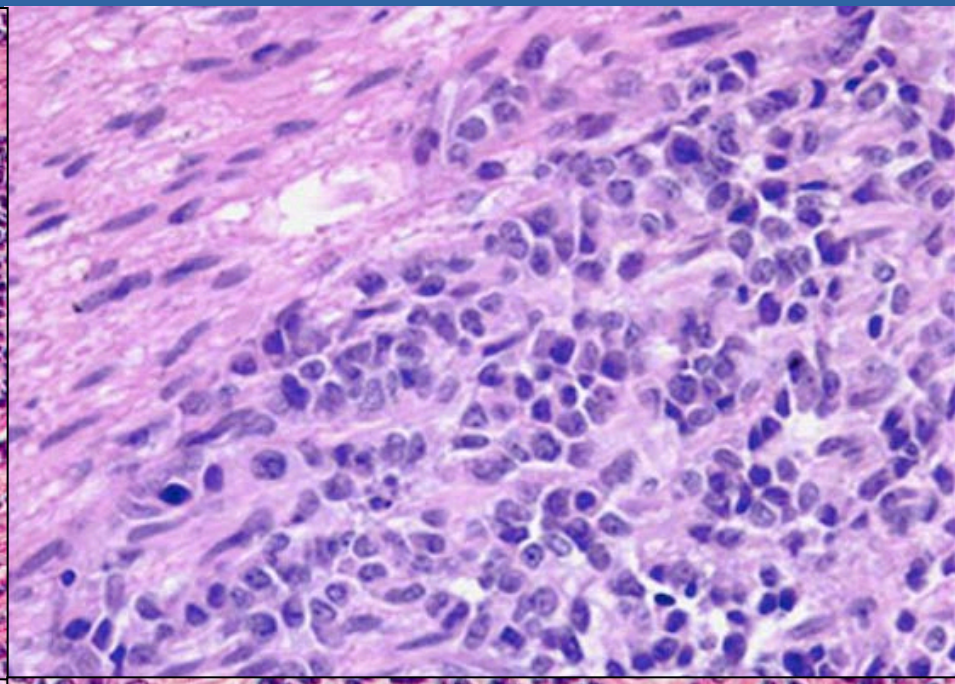
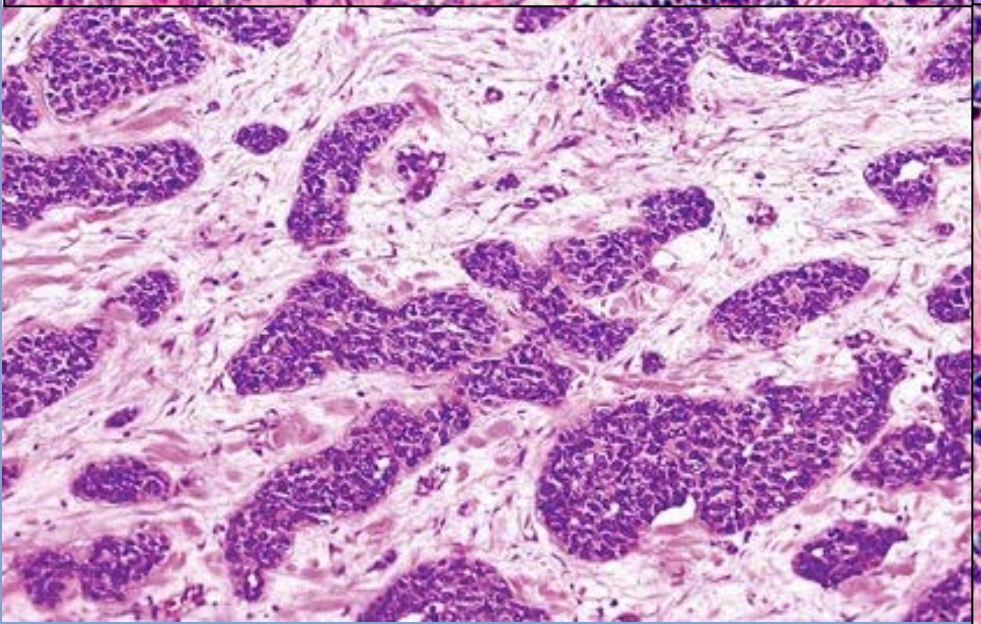
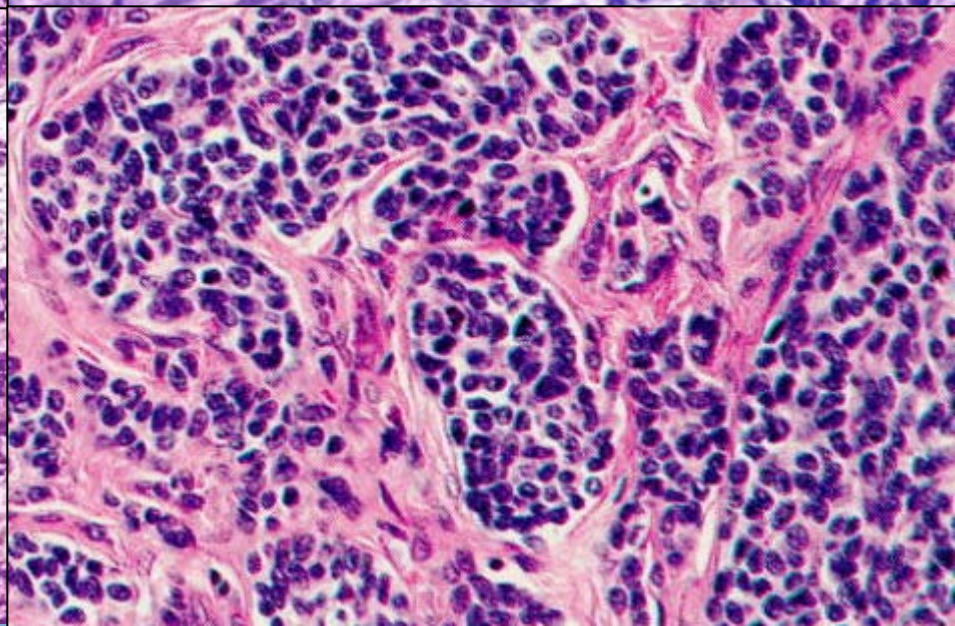
Desmoplastic Small Round Cell Tumor

Usually associated with prominent stromal desmoplasia

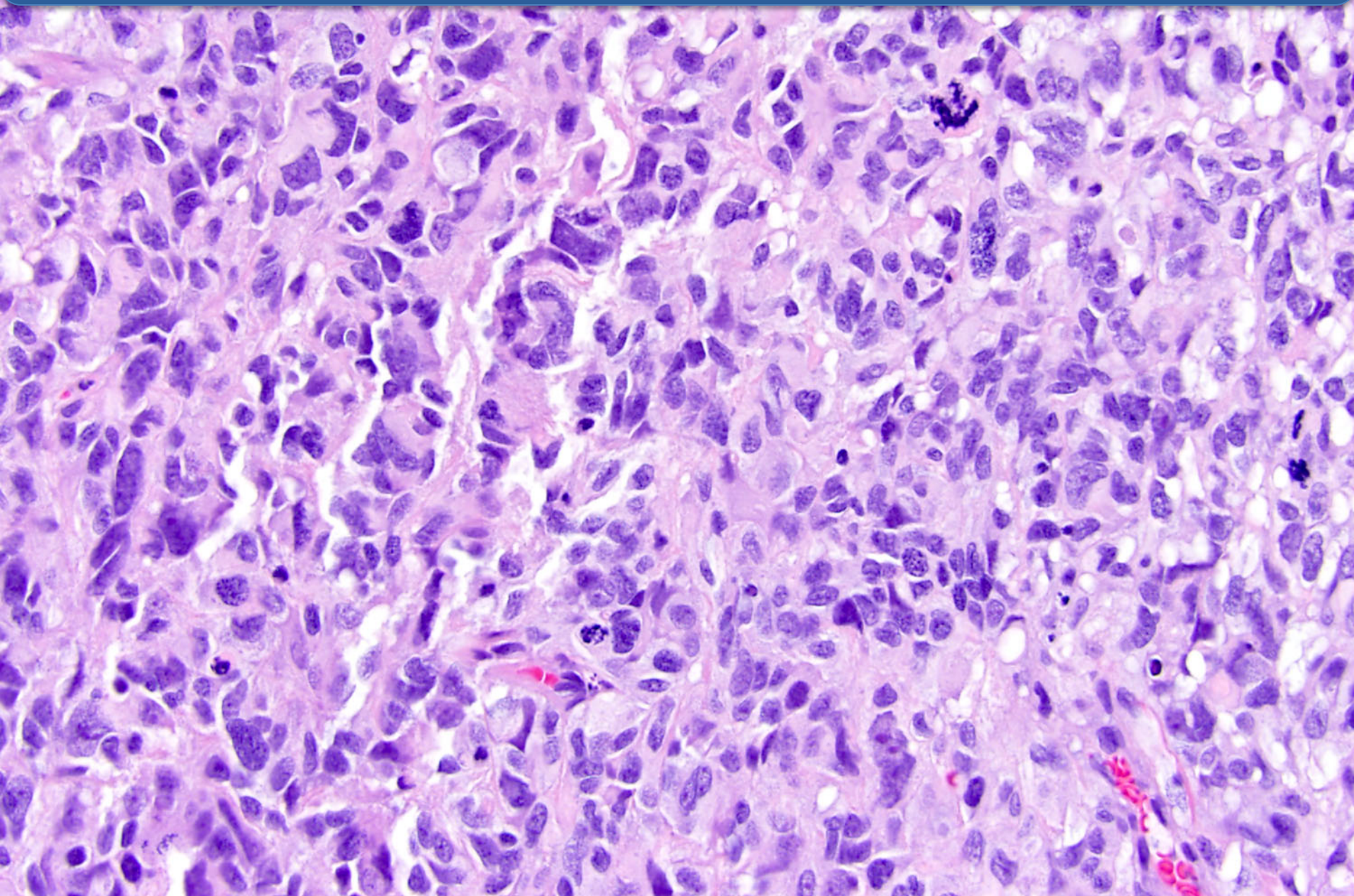








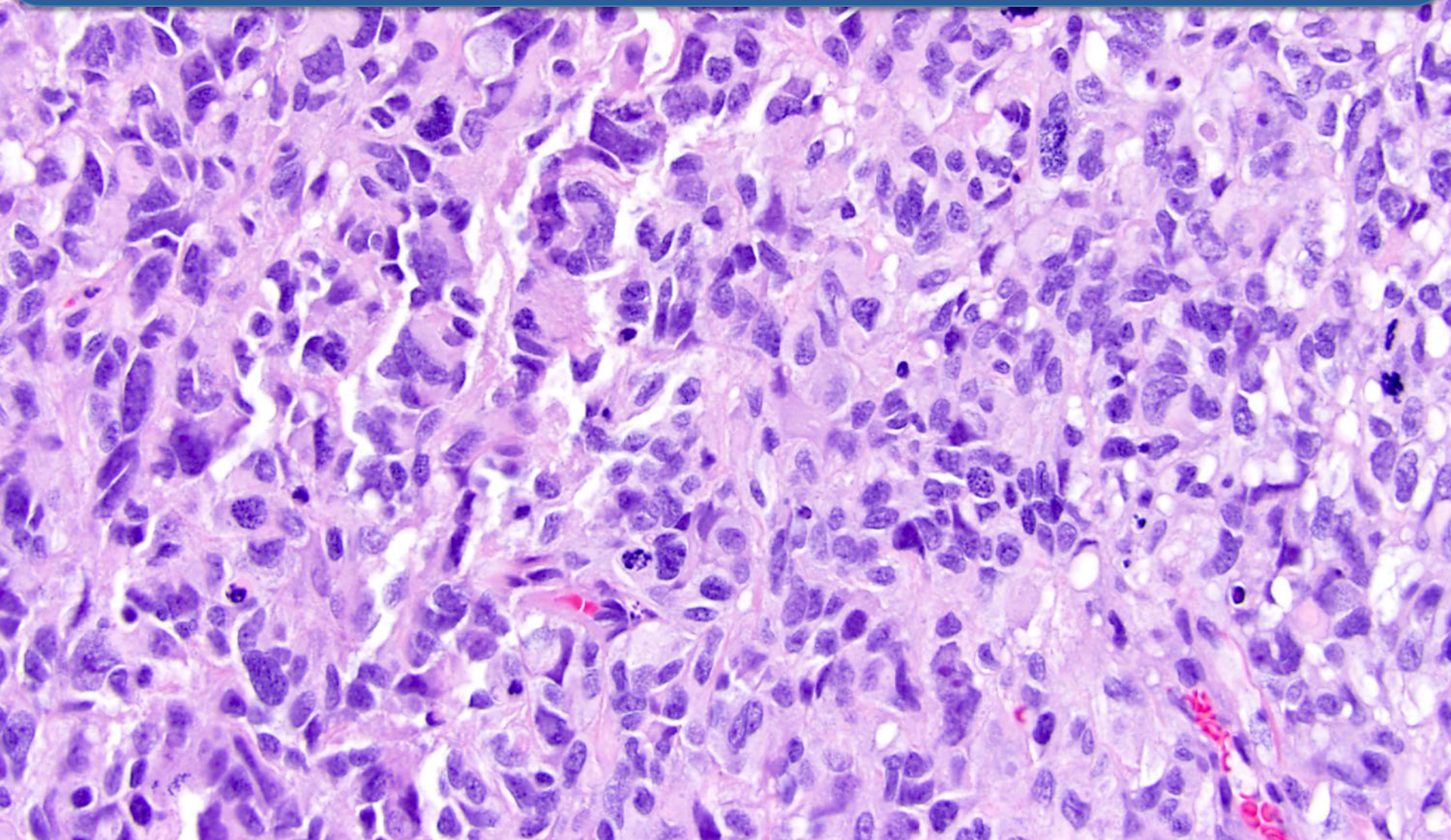
This particular case was a “non-desmoplastic variant” of the Desmoplastic Small Round Cell Tumor



Desmoplastic Small Round Cell Tumor

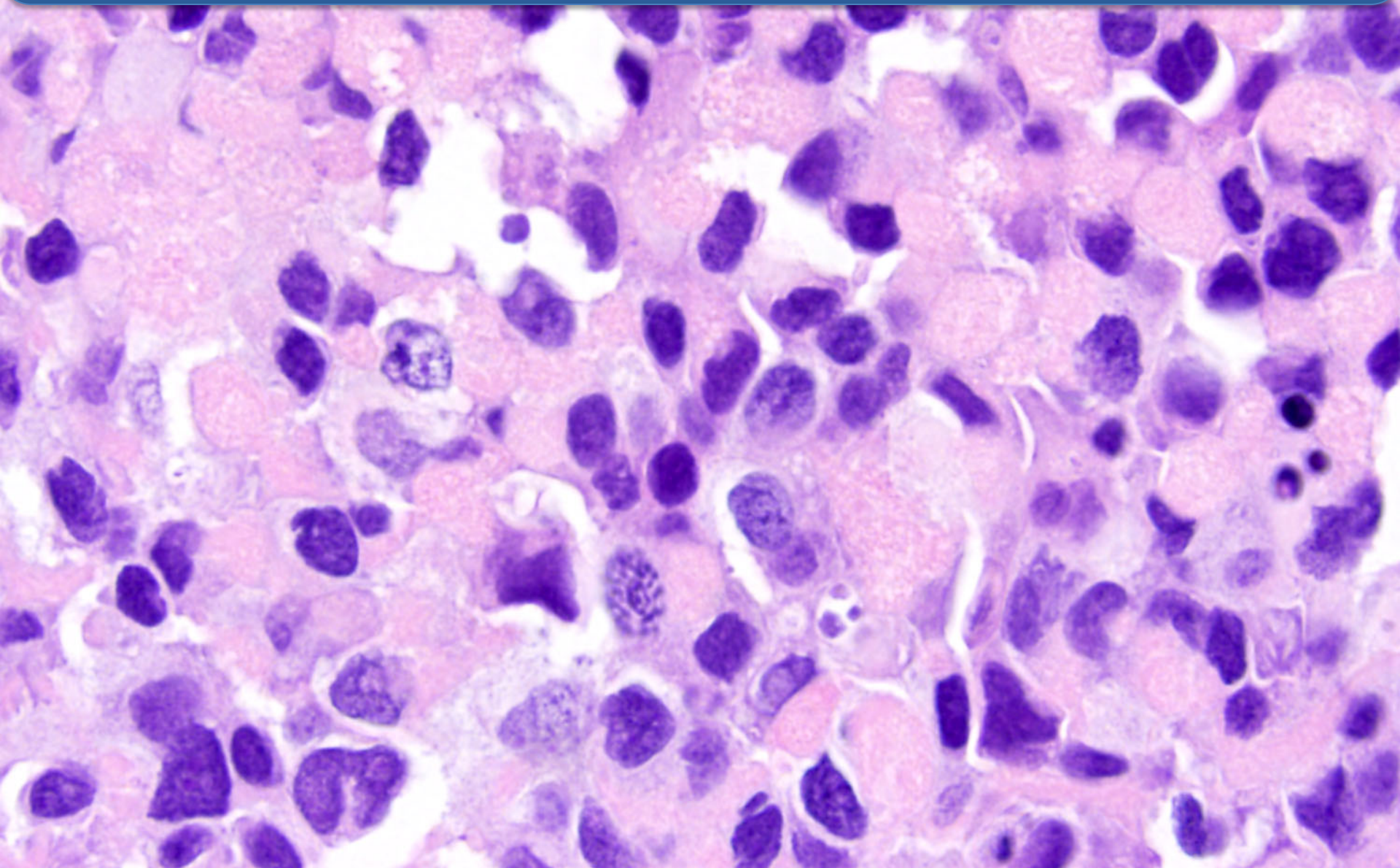
CAUTION: There can be significant histologic overlap with Medulloblastoma

DSRCTs can have Homer Wright-like rosettes



There is a wide range of morphologic features in ~1/3 of cases

There are often rhabdoid-like foci



Anatomic Distribution of 109 Cases of Desmoplastic Small Round Cell Tumor

LOCATION	NO. OF PATIENTS	PERCENTAGE (%)
Abdominal cavity	103	94
Thoracic region	4	4
Posterior cranial fossa	1	1
Hand	1	1
Total	109	100

From Gerald WL, Ladanyi M, de Alava E, et al. Clinical, pathologic, and molecular spectrum of tumors associated with t(11;22)(p13;q12): desmoplastic small round-cell tumor and its variants. *J Clin Oncol* 1998; 16:3028–3036.

DSRCT are most frequently located within the abdominal cavity

Median age diagnosis: 22; Male predominance 4:1

Primary CNS DSRCT is a rare entity, must exclude metastatic disease

TABLE 1. Literature review of reported cases of intracranial DSRCTs

Authors & Year	Age, Sex	Clinical Features on Initial Presentation	MRI Findings	Histology, Immunocytochemistry, & Cytogenetics	Site of Metastasis	Treatment	Outcome
Yachnis et al., 1992	9 mos, F	Projectile vomiting & increased head circumference	Enhancing rt cerebellar mass compressing & displacing brainstem Marked obstructive hydrocephalus	Demarcated nests of tumor cells separated by mesenchymal stroma Nest cell positive for GFAP, cytokeratin, & vimentin Negative for desmin immunoreactivity	None at time of publication	Ventriculoperitoneal shunt Chemo w/ cisplatin, cyclophosphamide, vincristine, & high-dose methotrexate Second craniotomy for debulking surgery 1.5 yrs after original presentation	Alive at time of publication
Tison et al., 1996	24 yrs, M	Headache, vomiting, vertigo, & impaired hearing	Posterior cranial fossa tumor (3 × 4 × 3.5 cm) adherent to tentorium & petrous part of temporal bone, displacing lt cerebellar hemisphere	Nests of small uniform round & oval tumor cells separated by desmoplastic stroma Strong immunoreactivity for keratin, vimentin, desmin, & EMA Southern blot for genomic DNA extraction, PCR analysis of EWS-WT1 fusion gene	None at time of publication	Partial excision of tumor Three cycles of chemo consisting of PCNU cisplatin & V16; intracranial methotrexate every 40 days; radiotherapy	Alive & no clinical signs of relapse at time of publication
Bouchireb et al., 2008	6 yrs, F	3-wk history of headaches, complex partial seizures, & dysphasia	Well-demarcated heterogeneously enhancing mass in rt temporal lobe	Small malignant cells w/ hyperchromatic nuclei & eosinophilic cytoplasm embedded in fibromyxoid stroma Positive staining for vimentin, desmin, & synaptophysin EWS-WT1 translocation by FISH	None at time of publication	Complete excision of tumor Seven courses of chemo w/ P6 protocol (cyclophosphamide, doxorubicin, vincristine, ifosfamide, & etoposide); focal conformal radiotherapy to tumor bed at 54 Gy	Alive & disease free after 18 mos of follow-up
Neder et al., 2009	37 yrs, M	5-mo history of lt-side hearing loss & tinnitus	Heterogeneously enhancing mass in lt CPA w/ mild mass effect	Intracranial & spinal biopsies: round to oval hyperchromatic nuclei w/ inconspicuous nucleoli in addition to desmoplastic stroma Positive staining for EMA, CAM 5.2, desmin, & nuclear INI-1 EWS-WT1 translocation by RT-PCR & FISH	Spinal leptomeninges 6 mos after diagnosis	Initial subtotal resection of CPA mass & stereotactic radiation to tumor bed Debulking of intradural spinal nodules & spinal radiation (4500 rad); radiosurgery to CPA (100 rad) & whole brain (3600 rad) Chemo (carboplatin temozolomide)	Died 2 yrs after diagnosis w/ progressive disease
	39 yrs, M	4-mo history of gait imbalance & bilat lower limb weakness; later developed urinary & fecal incontinence	Multiple enhancing lesions in lt cerebellar hemisphere & metastasis in spinal leptomeningeal space	Laminectomy samples: tumor cells w/ oval to irregular nuclei w/ coarse chromatin & scanty cytoplasm; positive staining for EMA, CAM 5.2, desmin, & nuclear INI-1; EWS-WT1 translocation by RT-PCR	Metastasis to spinal leptomeningeal space at presentation	Decompression of spinal cord & conus medullaris followed by radiotherapy Laminectomy of T12–L5 showed cauda equina nerve roots studded w/ gray tumor nodules Three courses of chemo (cisplatin, etoposide, & Holoxan)	Increase in posterior fossa tumor; further spread in spinal axis after 27 mos of follow-up

chemo = chemotherapy; CPA = cerebellopontine angle.

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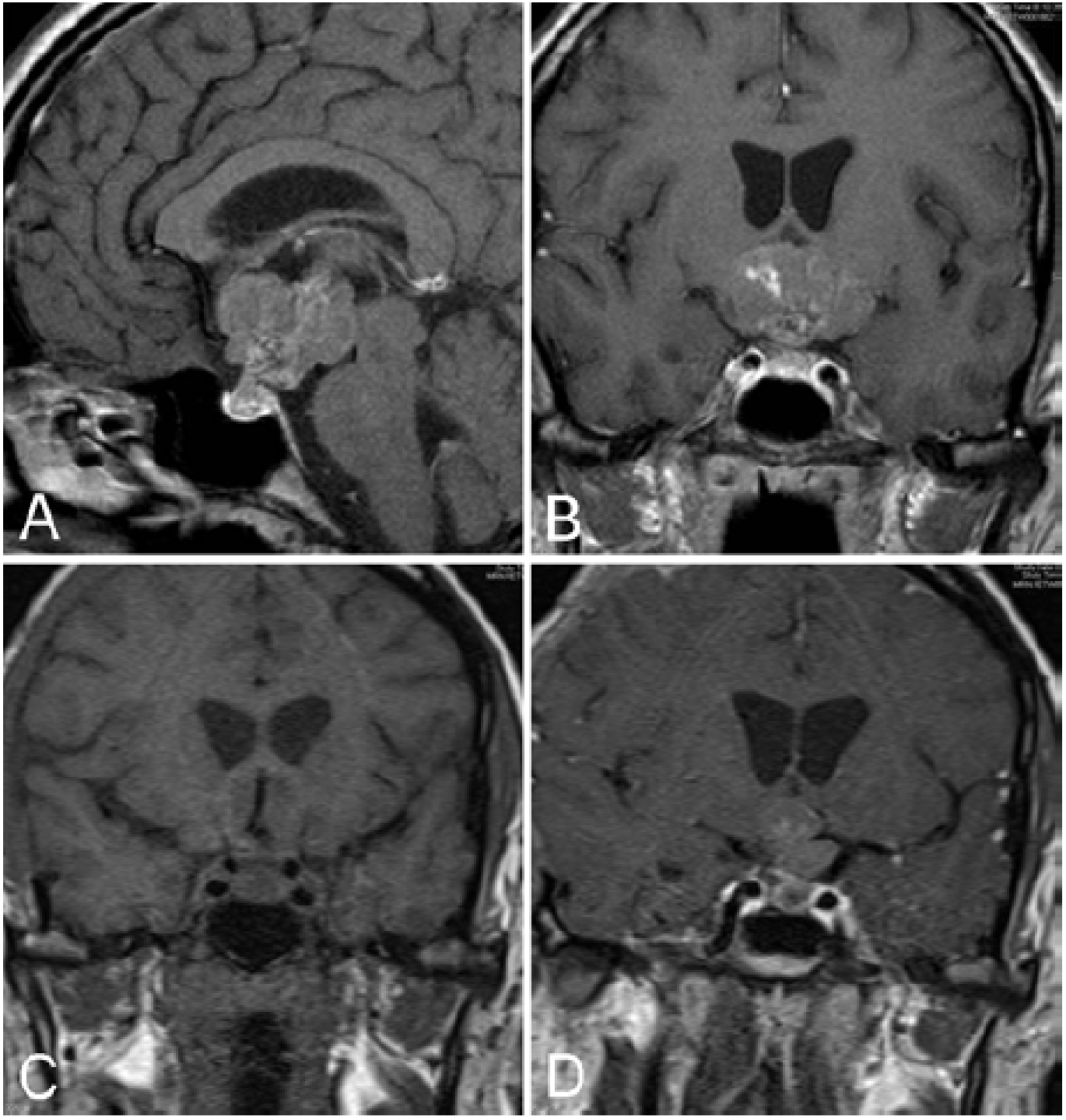
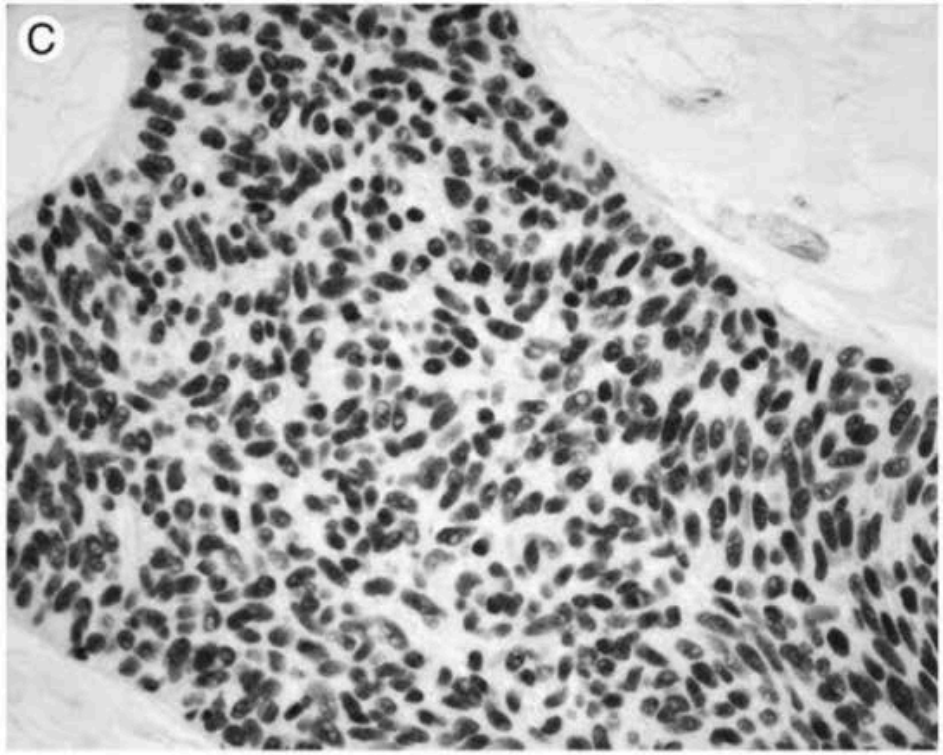
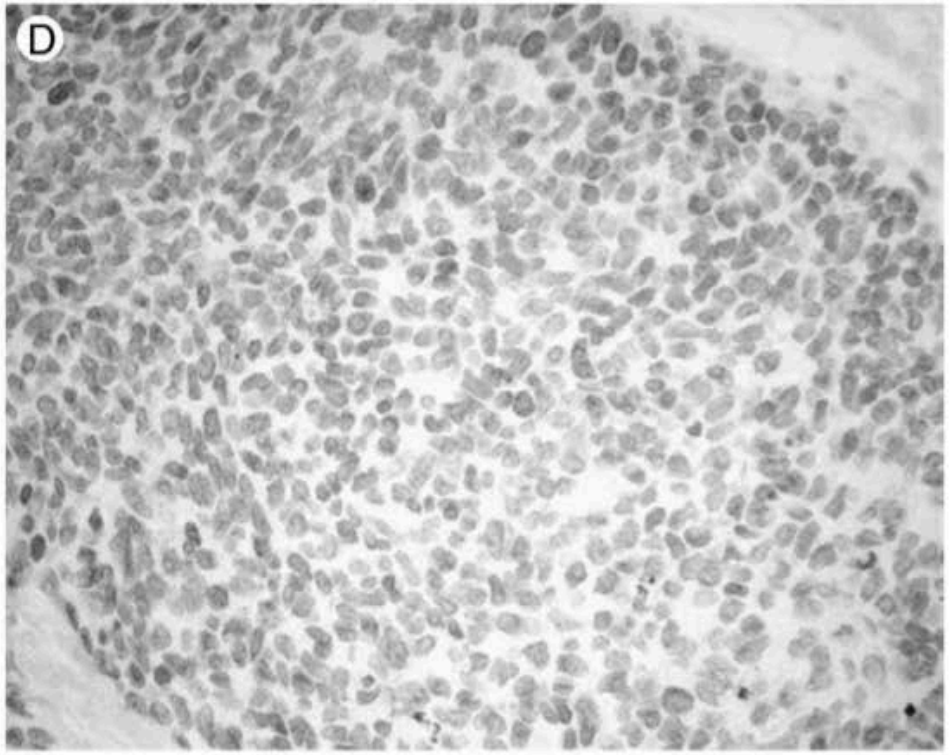


(Thondam et al., 2015)

Nuclear expression of WT1 in DSRCT is detectable by IHC When using an antibody to the WT1 C-terminus But NOT by antibodies to the WT1 N-terminus





Nuclear WT1
detected by IHC
Using antibody to WT1
C-terminus

***Nuclear* WT1**
***NOT* detected by IHC**
Using antibody to WT1
N-terminus

PMID: 18703217

Desmoplastic small round cell tumor of the central nervous system: report of two cases and review of the literature

Luciano Neder · Bernd W. Scheithauer · Keki E. Turel · Mark A. Arnesen · Rhett P. Ketterling · Long Jin · Timothy J. Moynihan · Caterina Giannini · Fredric B. Meyer

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Abstract Desmoplastic small round cell tumor (DSRCT) is a malignant tumor often involving the abdominal and/or pelvic peritoneum. Only one fully documented example has arisen in the central nervous system (CNS). Herein, we describe two additional examples, fulfilling the morphologic, immunohistochemical, and molecular criteria (EWS/WT1 translocation) of DSRCT. Both arose in the cerebellopontine angle (CPA) and underwent spinal dissemination. Patient 1, a 37-year-old male, underwent a subtotal resection, and 2 years later died of recurrent disease with spinal dissemination. Patient 2, a 39-year-old man, presented with cerebellar and CPA lesions as well as spinal leptomeningeal deposits. After 27 months of adjuvant therapy, he is alive with progressive disease. In conclusion, CNS DSRCT follows a similar aggressive course as do peritoneal examples. Although rare, DSRCT warrants consideration in the differential diagnosis of "malignant small blue cell tumors" of the CNS.

Keywords Central nervous system · Meninges · Desmoplastic small round cell tumor · EWS/WT1 translocation

Take Home Points

Desmoplastic small round cell tumor

- should be considered in the differential of a small round cell neoplasm in the CNS
- can display morphologic overlap with medulloblastoma

- *EWSR1-WT1* gene fusion
- polyphenotypic differentiation
- expression of epithelial, mesenchymal, and neuronal markers such as **EMA, desmin, and NeuN**

YAP1, GAB1, beta-catenin, and p53 IHC can be misleading if a diagnosis of medulloblastoma is not yet established

References

1. Ladanyi M, Gerald W. Fusion of the EWS and WT1 genes in the desmoplastic small round cell tumor. Cancer Res. 1994 Jun 1;54(11):2837-40. PMID: 8187063.

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Desmoplastic small round cell tumor: I: a histopathologic study of 39 cases with emphasis on unusual histological patterns.

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Abstract

The clinical and histological features of 39 cases of desmoplastic small round cell tumor (DSRCT) diagnosed at M.D. Anderson Cancer Center are presented. Thirty-two of the patients were men and seven were women ranging in age from 10 to 41 years (mean, 25 years). Twenty-five of the 35 patients for whom follow-up information was available died of widespread metastases 8 to 50 months (mean, 25.2 months) from the time of their diagnosis and the remaining 10 were alive with disease. With the exception of two cases that occurred in the liver and in the scrotum, respectively, all of the cases originated within the abdominal and/or pelvic peritoneum. Eight tumors also involved the retroperitoneum. Although the characteristic histologic pattern of "small, blue cells" embedded in a dense fibrous stroma was seen in most cases, about one third of the tumors exhibited a wide range of morphologic features. The recognition of these uncommon morphologic variants of DSRCT is of paramount importance to avoid a misdiagnosis because these tumors could potentially be confused with other neoplastic conditions.

Of the 35 patients for whom follow-up information was available, 25 died of widespread metastases 8 to 50 months after diagnosis (mean, 25.2 months)