(Am J Surg Pathol 2019;43:422–431)

Neuroglial Differentiation and Neoplasms in Testicular Germ Cell Tumors Lack Immunohistochemical Evidence of Alterations Characteristic of Their CNS Counterparts

A Study of 13 Cases

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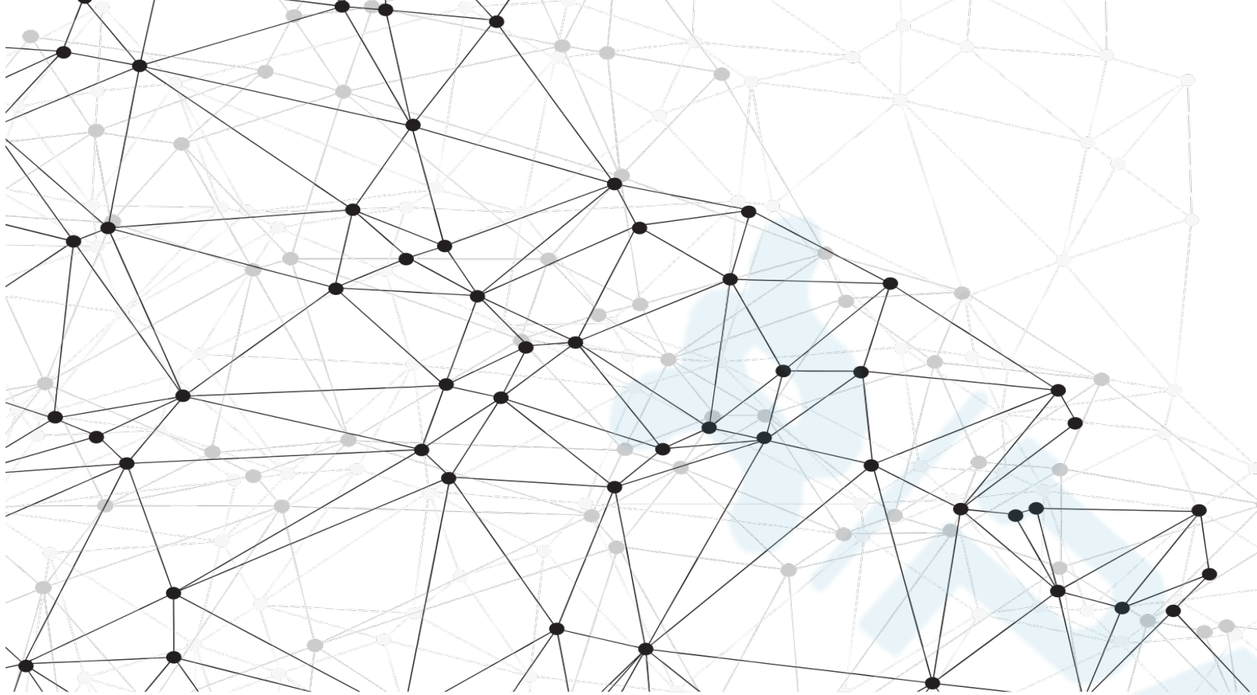


01

背景知识

BACKGROUND KNOWLEDGE

Germ cell tumours derived from germ cell neoplasia in situ (GCNIS)

Non-invasive germ cell neoplasia	
Germ cell neoplasia in situ	9064/2
Specific forms of intratubular germ cell neoplasia	
Tumours of one histological type (pure tumours)	
Seminoma	9061/3
Seminoma with syncytiotrophoblast cells	
Non-seminomatous germ cell tumours	
Embryonal carcinoma	9070/3
Yolk sac tumour, postpubertal-type	9071/3
Trophoblastic tumours	
Choriocarcioma	9100/3
Non-choriocarcinomatous trophoblastic tumours	
Placental site trophoblastic tumour	9104/3
Epitheliod trophoblastic tumour	9105/3
Cystic trophoblastic tumour	
Teratoma, postpubertal-type	9080/3
Teratoma with somatic-type malignancies	9084/3
Non-seminomatous germ cell tumours of more than one histological type	
Mixed germ cell tumours	9085/3
Germ cell tumours of unknown type	
Regressed germ cell tumours	9080/1

Germ cell tumours unrelated to germ cell neoplasia in situ

Spermatocytic tumour	9063/3
Teratoma, prepubertal type	9084/0
Dermoid cyst	
Epidermoid cyst	
Well-differentiated neuroendocrine tumour (monodermal teratoma)	8240/3
Mixed teratoma and yolk sac tumour, prepubertal-type	9085/3
Yolk sac tumour, prepubertal-type	9071/3

睾丸生殖细胞肿瘤前驱病变的名称演变

原位癌（CIS）

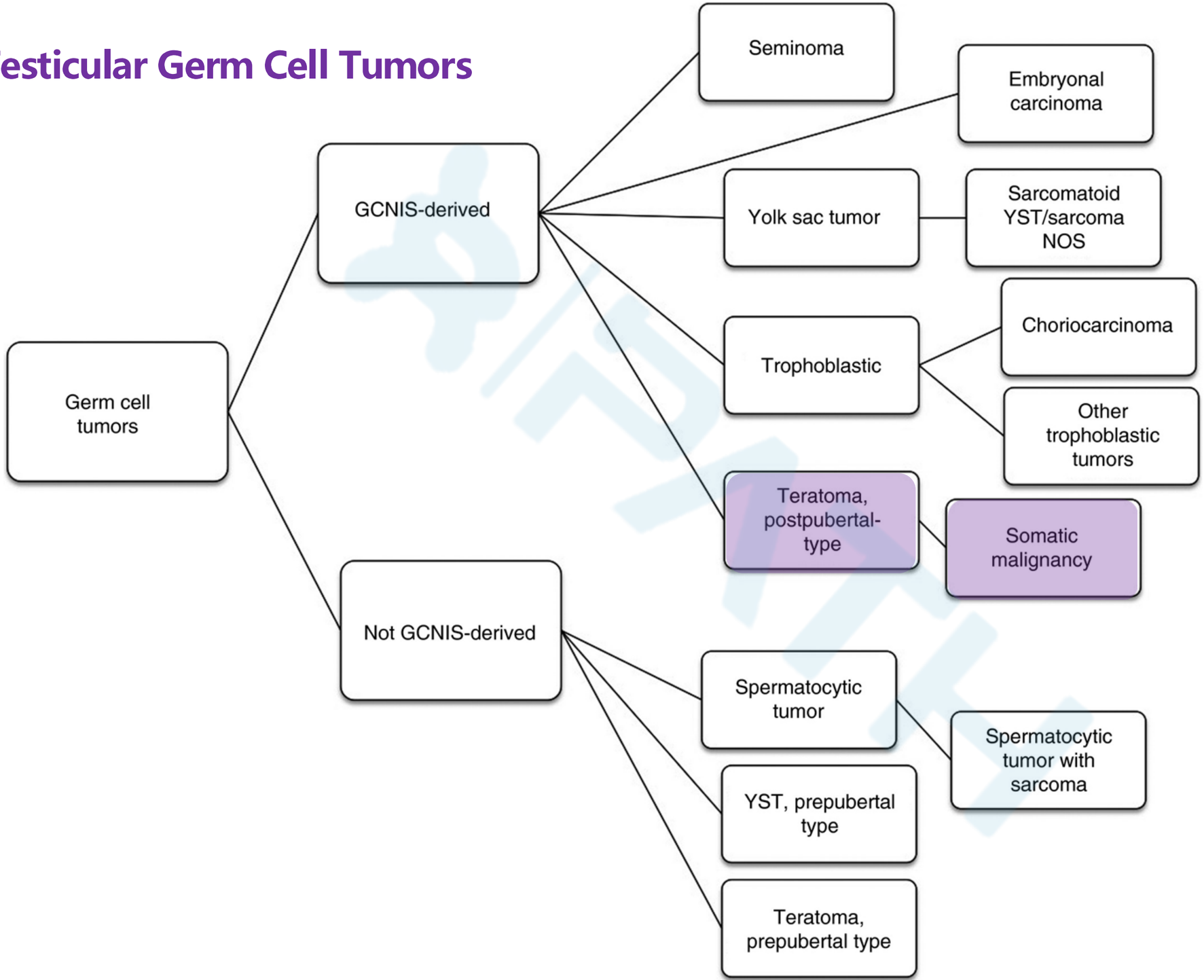
↓

（2004 WHO）
小管内生殖细胞肿瘤，未分类
（IGCNU）

↓

原位生殖细胞肿瘤
（Germ Cell Neoplasia in suit，GCNIS）

Testicular Germ Cell Tumors



Somatic-type malignancy

- 占睾丸生殖细胞肿瘤的3-6%，最常见于青春期后型畸胎瘤，偶见于其他类型的生殖细胞肿瘤。
- 定义：在肿瘤中查见体细胞型恶性成分（癌/肉瘤等）的膨胀性或浸润性生长，占据至少一个低倍视野（×4物镜，直径5毫米）。
- ICD-O 编码： 9084/3
- 临床特征：可发生于睾丸内，更常见于转移的病例，尤其是在化疗后。最常见的部位是腹膜后淋巴结。且从GCTs的诊断到体细胞型恶性肿瘤发病间隔长，中位间隔时长约为108个月。
- 预后：若仅限于睾丸，则预后一般不受影响，但转移的病例预后不好。可切除的情况下，手术切除为首选治疗方法。其余病例在顺铂的基础上进行治疗。
- 组织学特征：肉瘤是最常见的组织学类型，其中超过一半是横纹肌肉瘤；其次相对常见的是PNET。而神经胶质成分过度生长的情况则极为罕见。

02

材料和方法

MATERIALS AND METHODS

MATERIALS AND METHODS

收集1995-2018年13例具有神经胶质细胞分化的生殖细胞肿瘤

2位泌尿外科病理学家（A.M.和J.I.E.）以及1位神经病理学家（F.J.R.）

免疫组化：ATRX、IDH 1、BRAF V600E、GFAP

在约翰霍普金斯实验室进行BRAF突变分析：
＜3%的突变信号→阴性
4-5%的突变信号→不确定
≥5%突变信号或10%肿瘤细胞为杂合子突变)

MATERIALS AND METHODS

TABLE 1. Clinicopathologic Characteristics of Patients

	Age (y)	Specimen With Neuroglial Difference	Prior Chemo	Tumor Size (cm)	Size of Neuroglial Component (cm)	Primary Tumor	Components Other than Neuroglial
1	46	Orchiectomy	No	7	NA	NA	Teratoma
2	19	Orchiectomy	No	1.7	0.9	NA	Teratoma
3	39	RPLND, 38 mo after orchiectomy/RPLND	Yes	NA	NA	Teratoma with metastasis to retroperitoneal LNs	Only glial elements
4	34	Orchiectomy	No	4.6	1.2	NA	Seminoma, teratoma, regressed germ cell tumor, EC
5	49	RPLND	Yes	0.6	0.5	Testis with no residual tumor, orchiectomy performed at the same time of RPLND	Teratoma
6	28	RPLND	Yes	7.5	7.5	Teratoma, YST, EC, PNET; PNET in RPLND at time of orchiectomy, 60 mo prior	Only glial elements
7	54	RPLND	NA	6.5	6.5	Teratoma, seminoma, YST, EC	Only glial elements
8	35	RPLND	No	10	3	Teratoma, YST, EC, PNET	Seminoma
9	32	RPLND	Yes	7	NA	Teratoma, seminoma, EC, PNET	Only glial elements
10	22	RPLND, 6 mo after orchiectomy	Yes	15	NA	Teratoma, YST, EC	Teratoma
11	24	Axillary lymph node metastasis	No	4.5	4.5	NA	Teratoma
12	33	RPLND	NA	1.3	1.3	Seminoma, EC, YST	Teratoma
13	31	Orchiectomy	No	7.3	4.5	NA	Teratoma, seminoma, YST, EC

DOD indicates dead of disease; EC, embryonal carcinoma; NA, not available/not applicable; NED, no evidence of disease; YST, yolk sac tumor.

MATERIALS AND METHODS

13 例

平均年龄34y

（19-54y）

转移9例

（平均肿瘤大小6.4cm（0.6-15），

最大神经胶质成分6.5cm）

腹膜后淋巴结8例

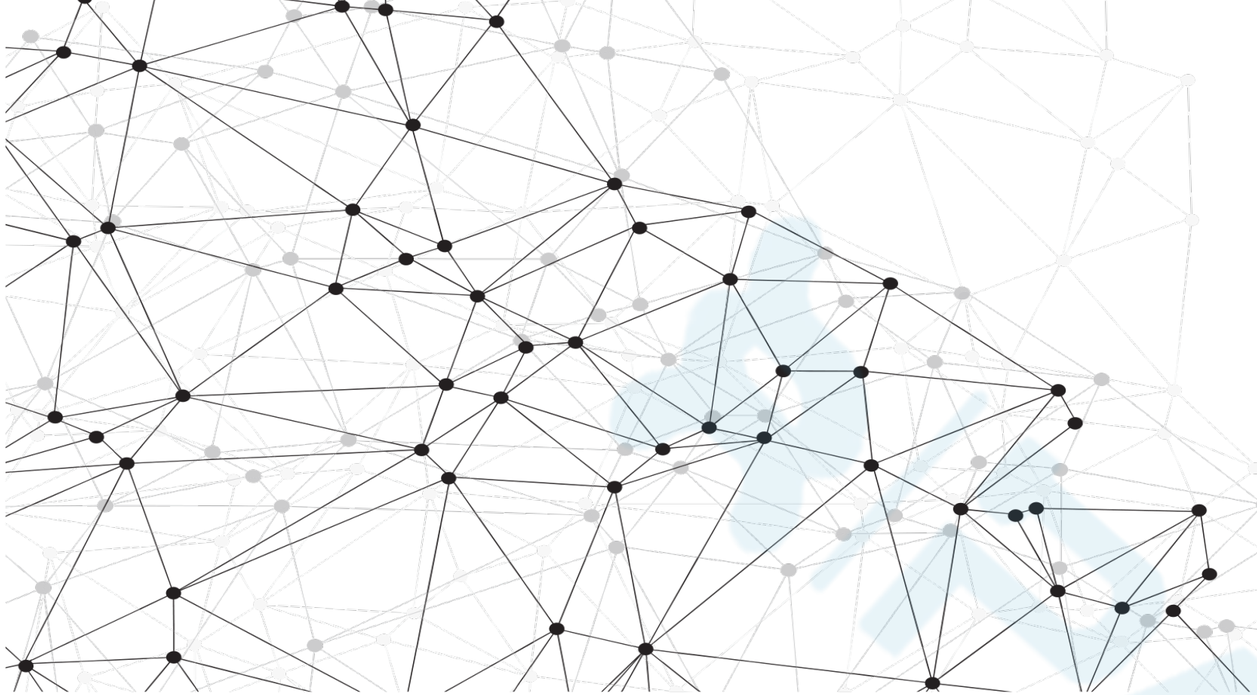
（5例为化疗后）

腋窝淋巴结1例

原发4例

（平均肿瘤大小5.15cm（1.7-7.3），

最大神经胶质成分0.9cm）



03

结果

RESULTS

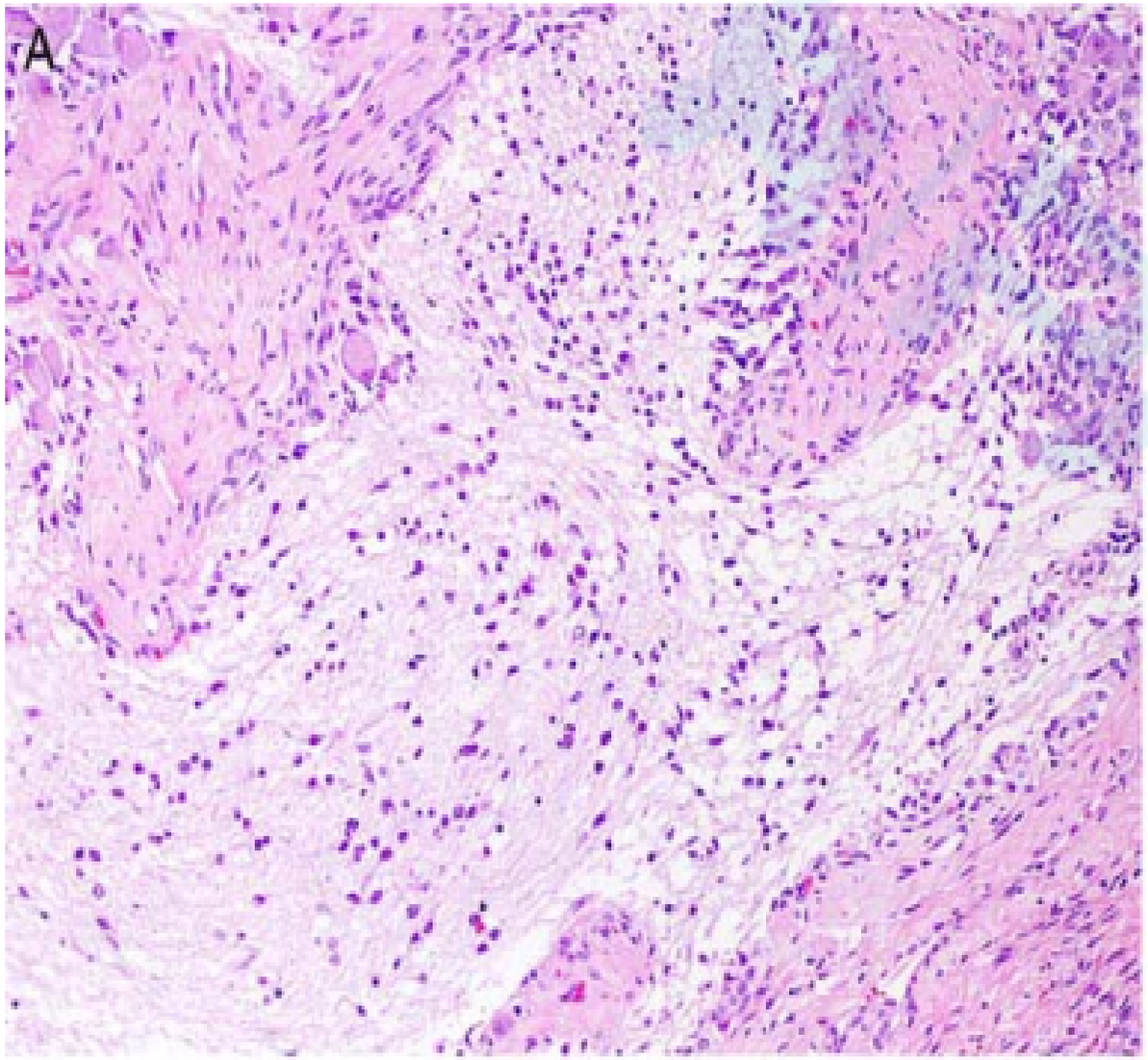
RESULTS

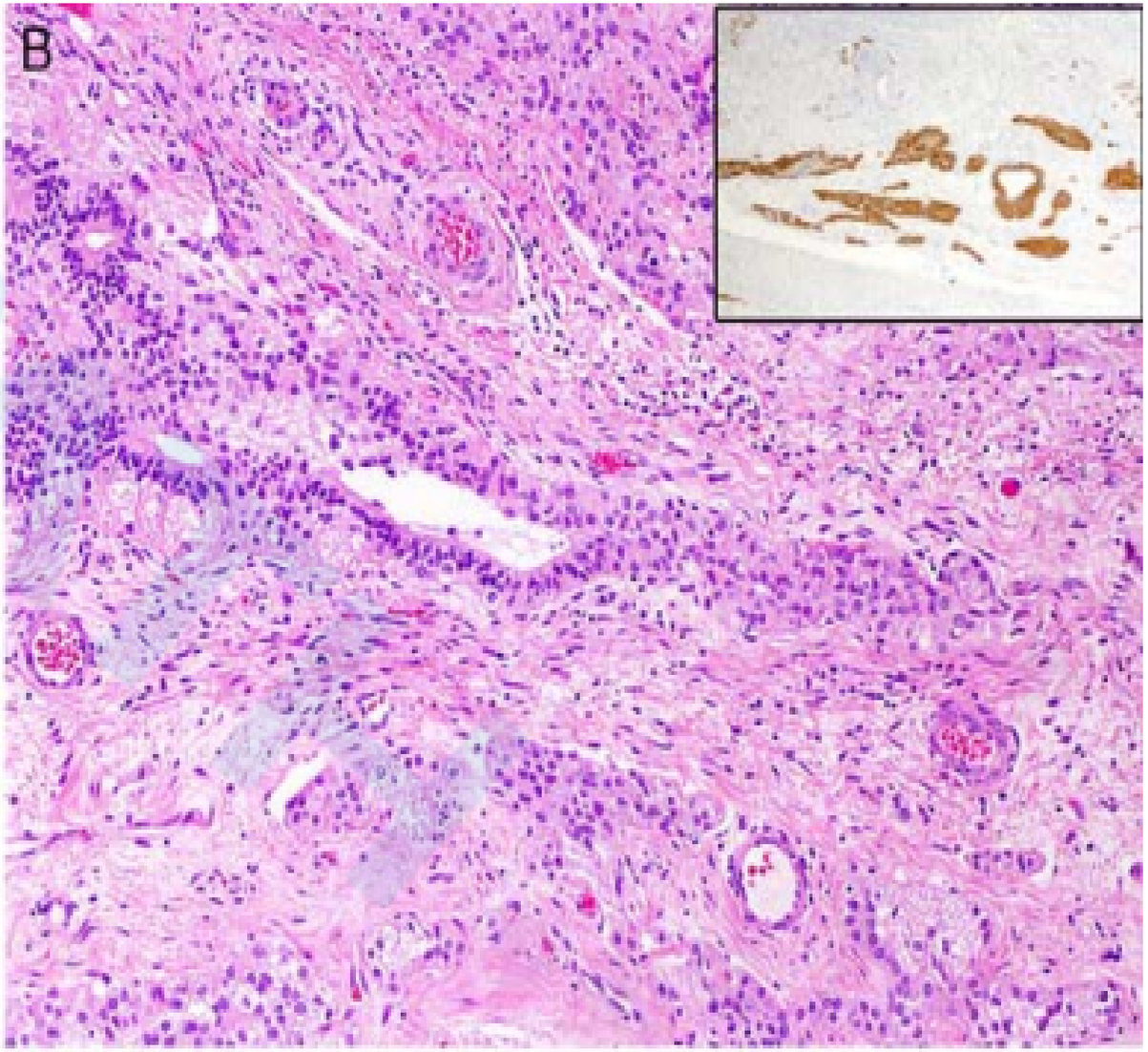
TABLE 1. *(Continued)*

Classification of Neuroglial Component	GFAP IHC	ATRX IHC	Mut IDH1 IHC	Mut BRAF IHC	P53 IHC	Follow-up Status/ Months
Gemistocytic astrocytoma (WHO grade II)	+	NA	NA	NA	NA	NED/6
Gemistocytic astrocytoma (WHO grade II)	+	NA	NA	NA	NA	NED/2
Gliosarcoma (WHO grade IV)	+	Retained	−	+	+ > 50% cells	DOD metastasis in lung/85
Ganglioglioma (WHO grade I)	+	NA	NA	NA	NA	NA
Glioblastoma (WHO grade IV)	+	Retained	−	−	−	NED/16
Low-grade astrocytoma (WHO grade I/II)	+	Retained	−	−	−	NA
Low-grade astrocytoma (WHO grade I/II)	+	Retained	−	−	−	NA
Anaplastic astrocytoma (WHO grade III), with focal gangliocytic differentiation	+	Retained	−	−	+ > 50% cells	NA
Low-grade astrocytoma (WHO grade I/II)	+	Retained	−	−	+ 20% cells	NA
Gemistocytic astrocytoma (WHO grade II), developing CNS	+	Retained	−	−	−	NA
Developing CNS	+	Retained	−	−	−	DOD/83
Anaplastic astrocytoma with giant cells (WHO grade III)	+	Retained	−	−	+ > 50% cells	NA
Glioblastoma (WHO grade IV)	+	Retained	−	−	5%	NED/1

Case 10

GFAP

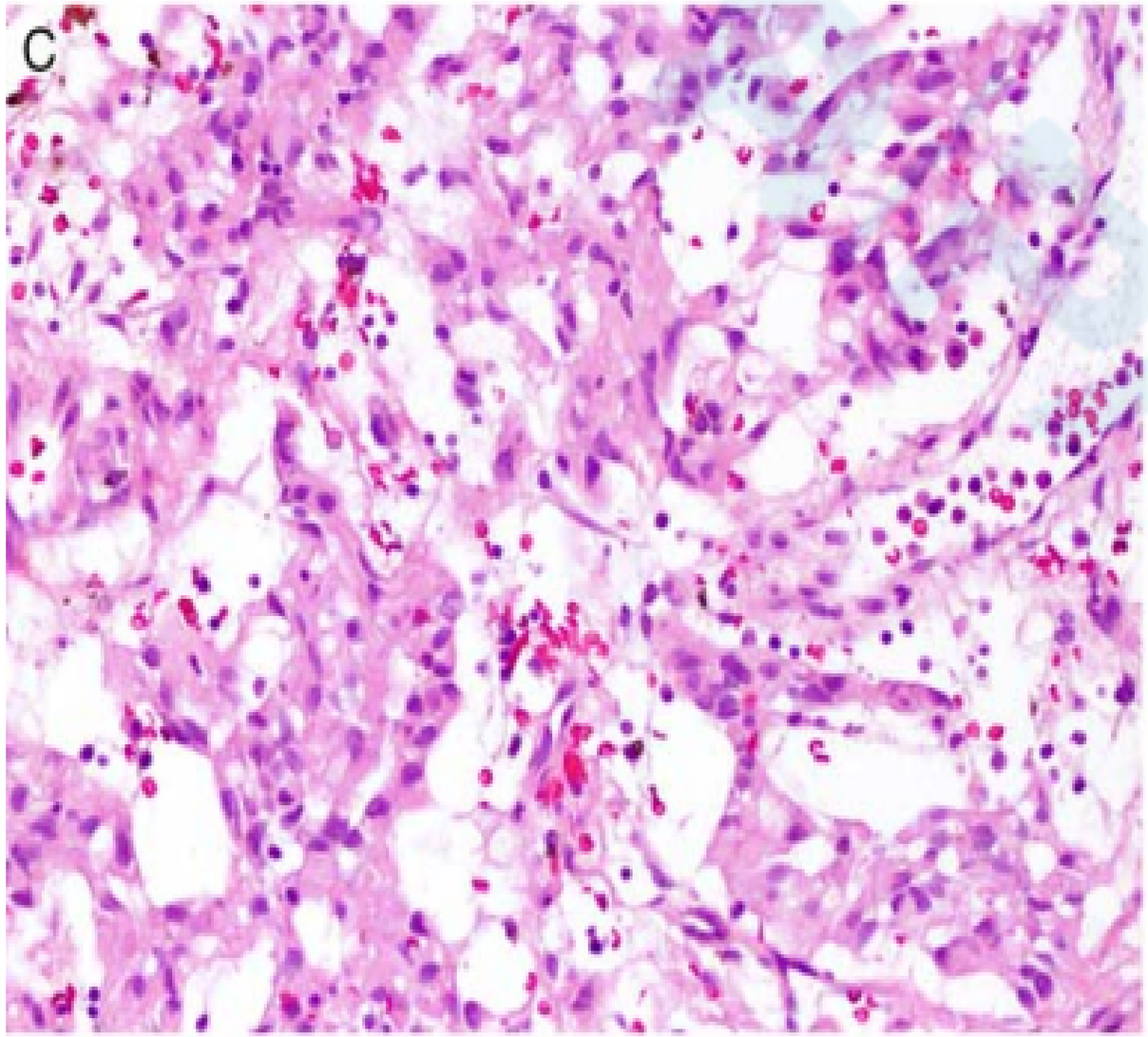


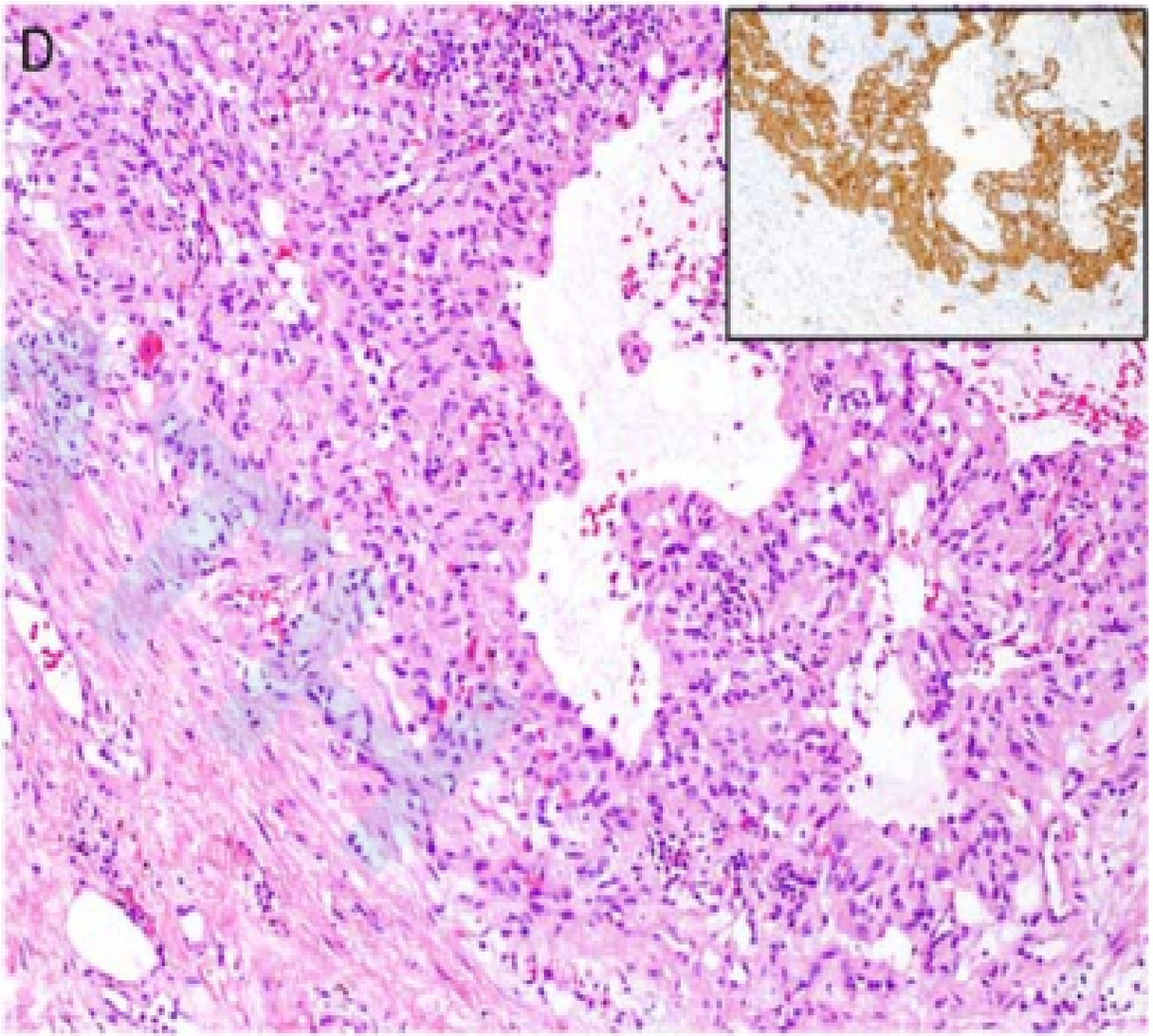


Low Grade Astrocytoma (WHO Grade I/II)

Case 6

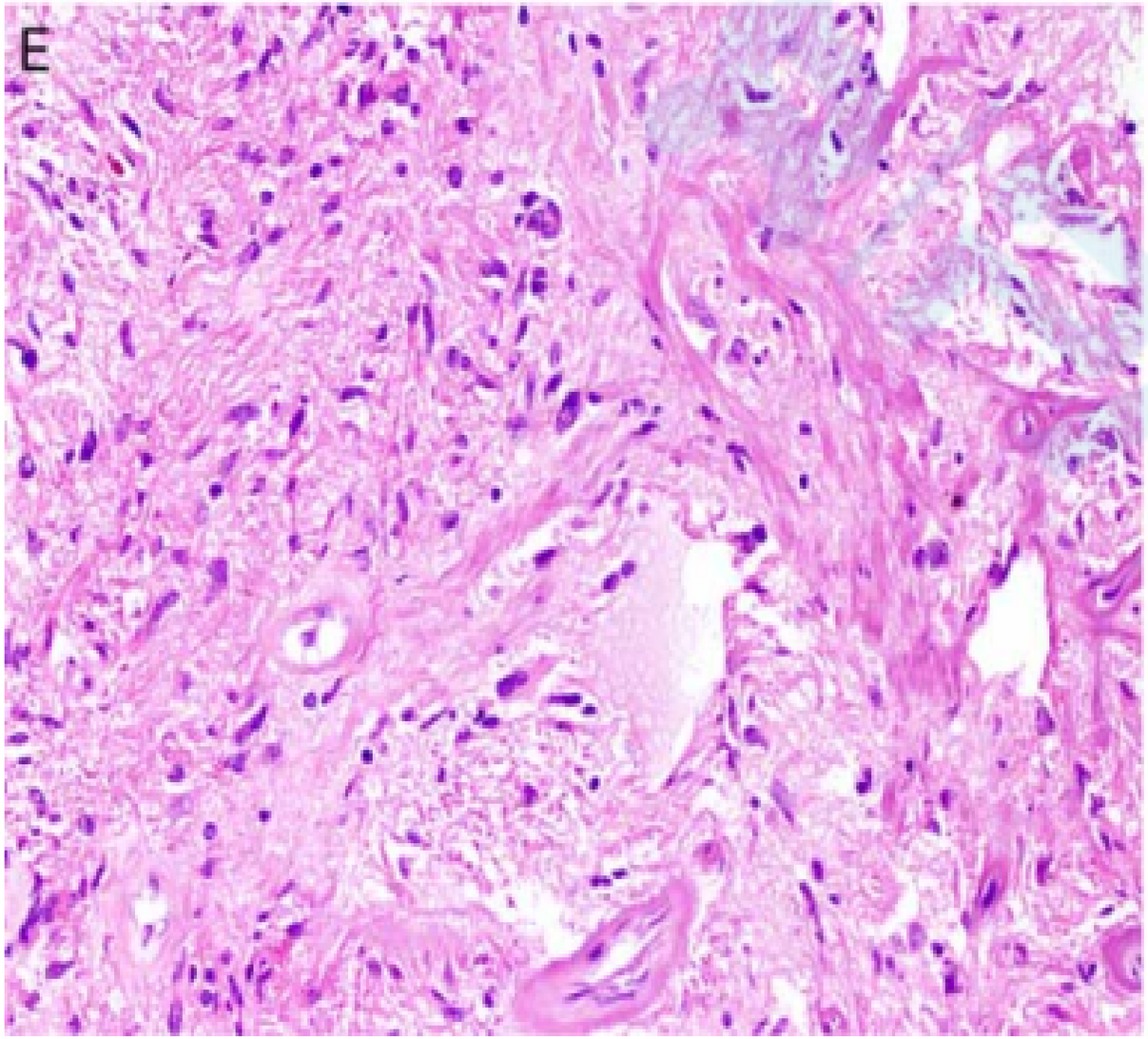
GFAP



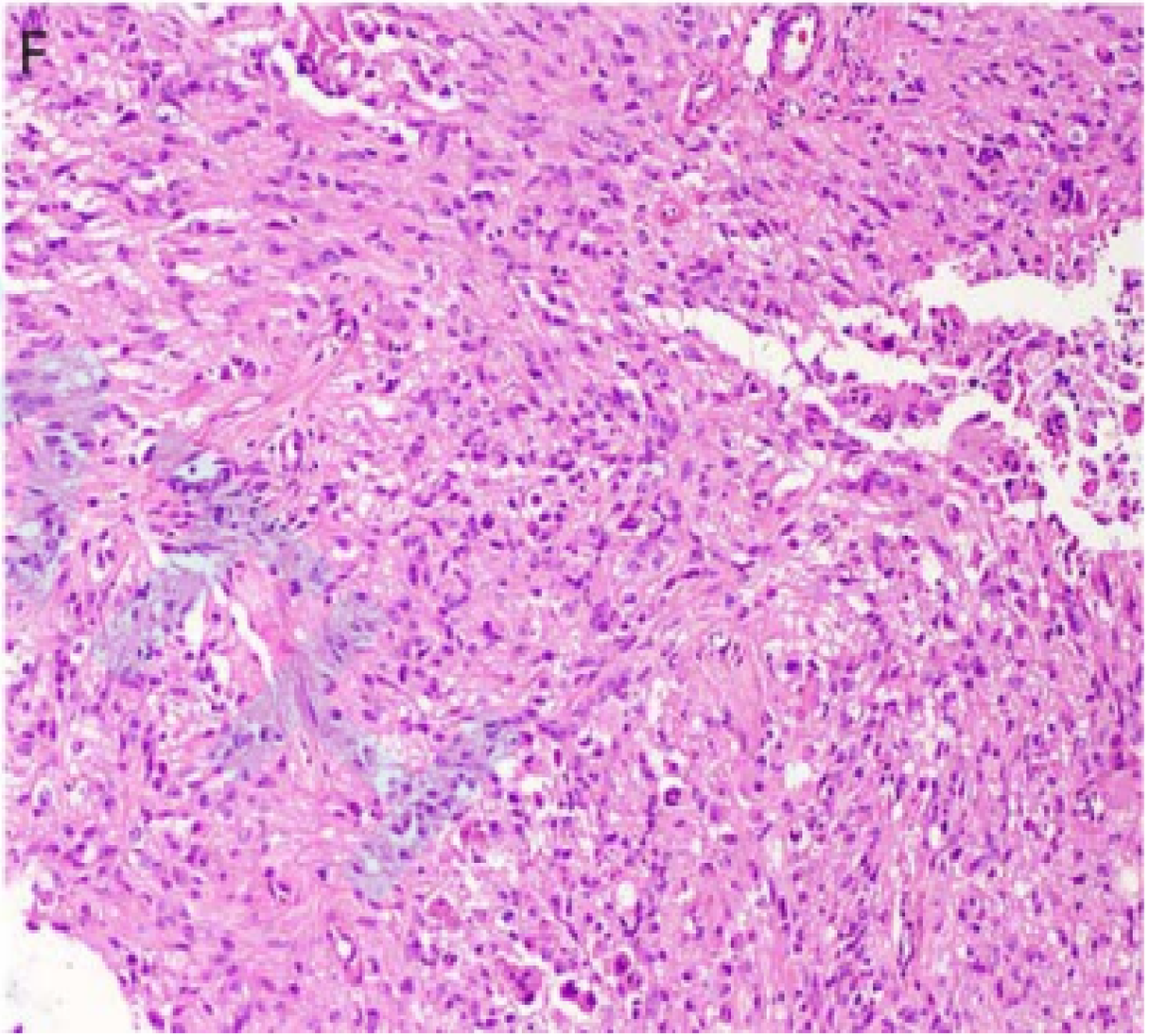


Low Grade Astrocytoma (WHO Grade I/II)

Case 7



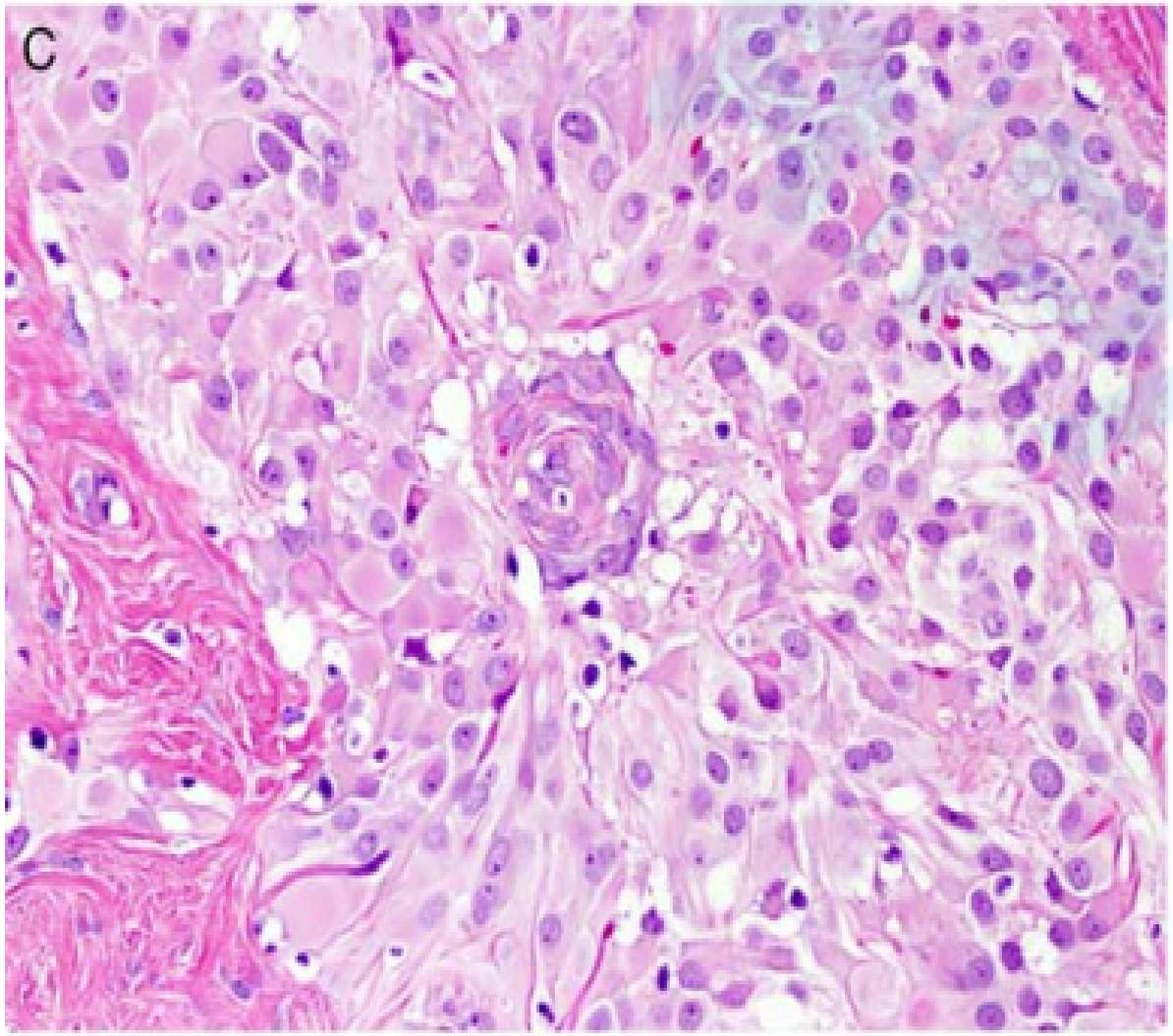
Case 9

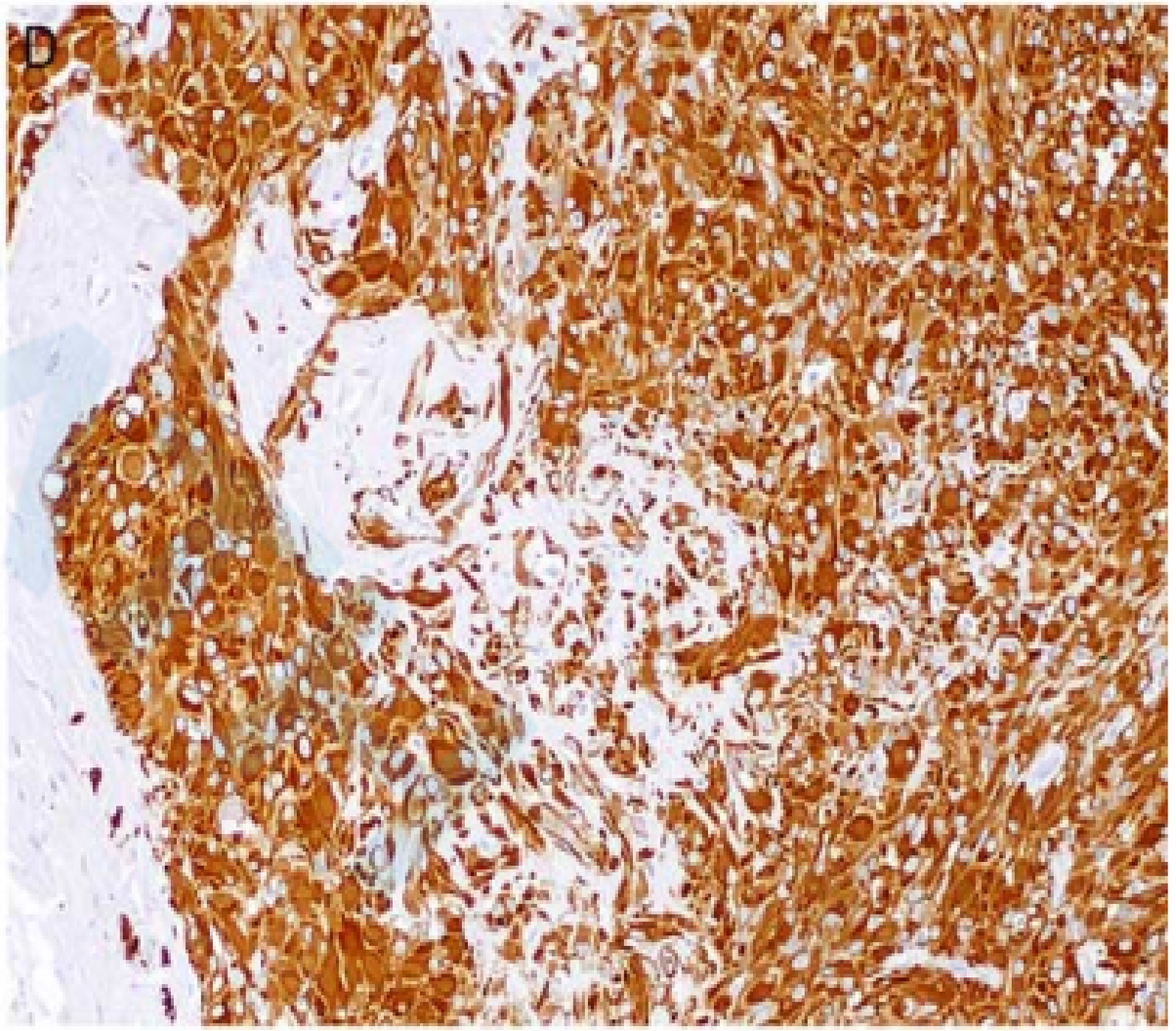


Gemistocytic Astrocytomas (WHO Grade II)

Case 2

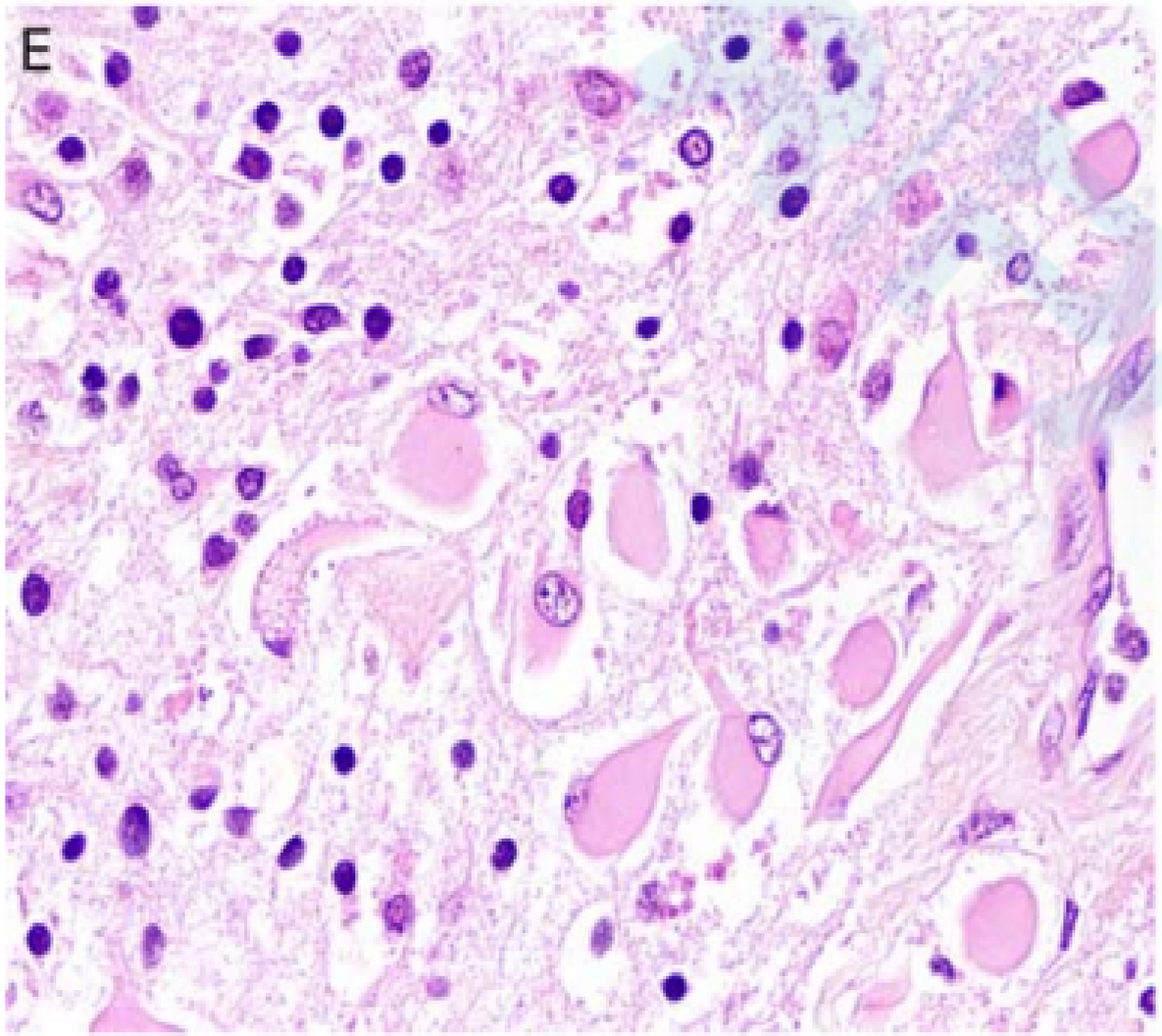
GFAP



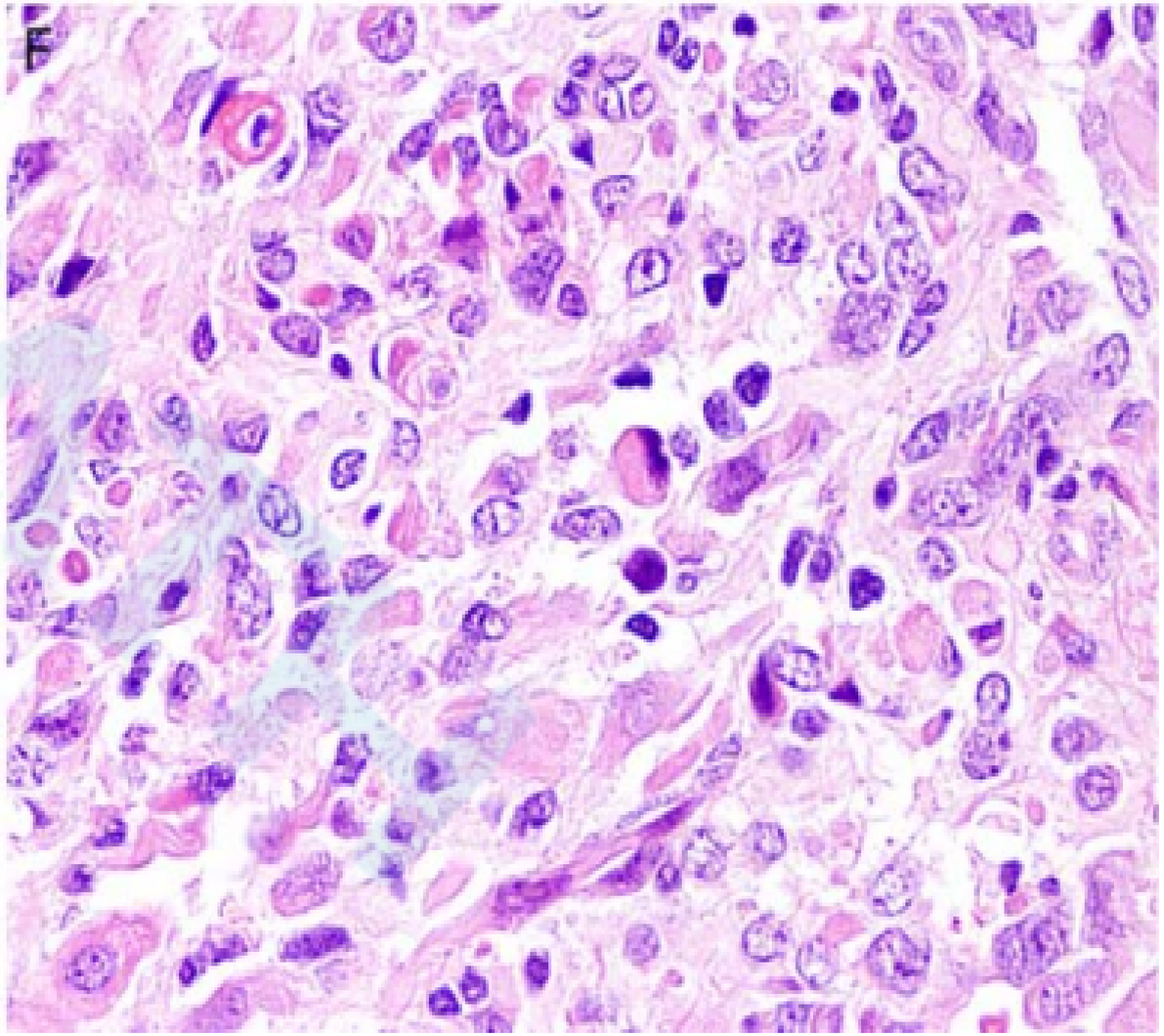


Gemistocytic Astrocytomas (WHO Grade II)

Case 1

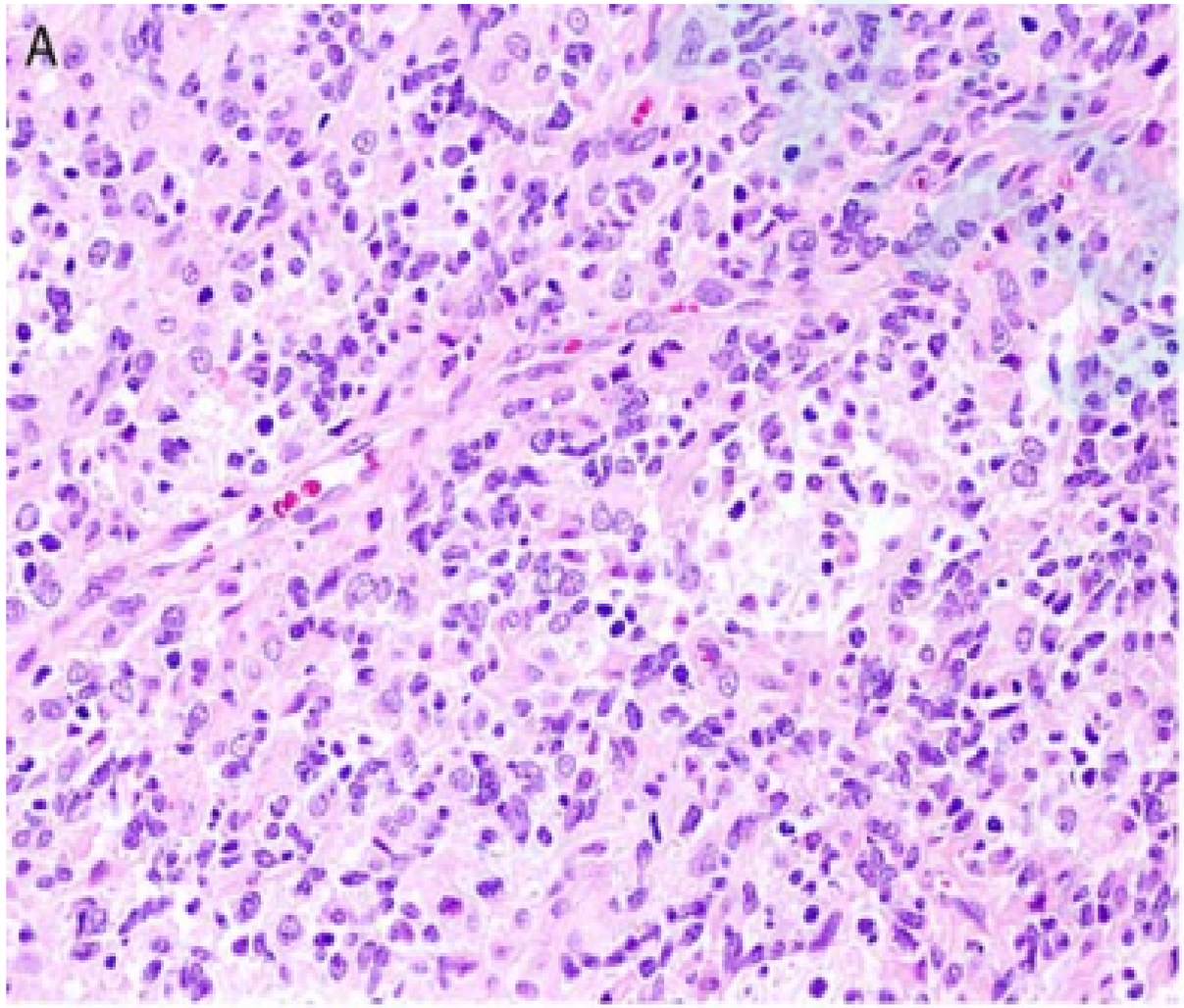


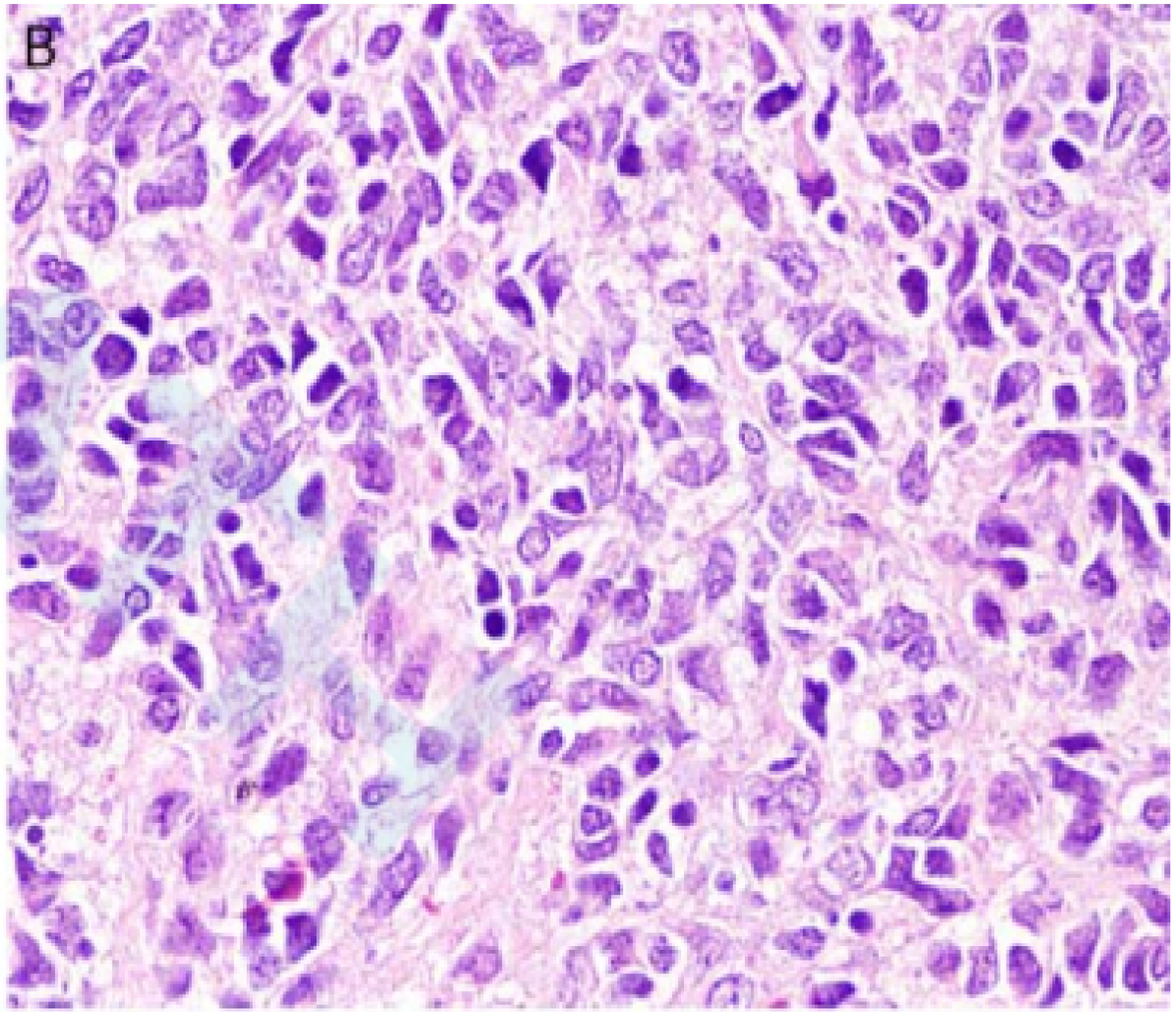
Case 10



Anaplastic Astrocytoma (WHO Grade III)

Case 8

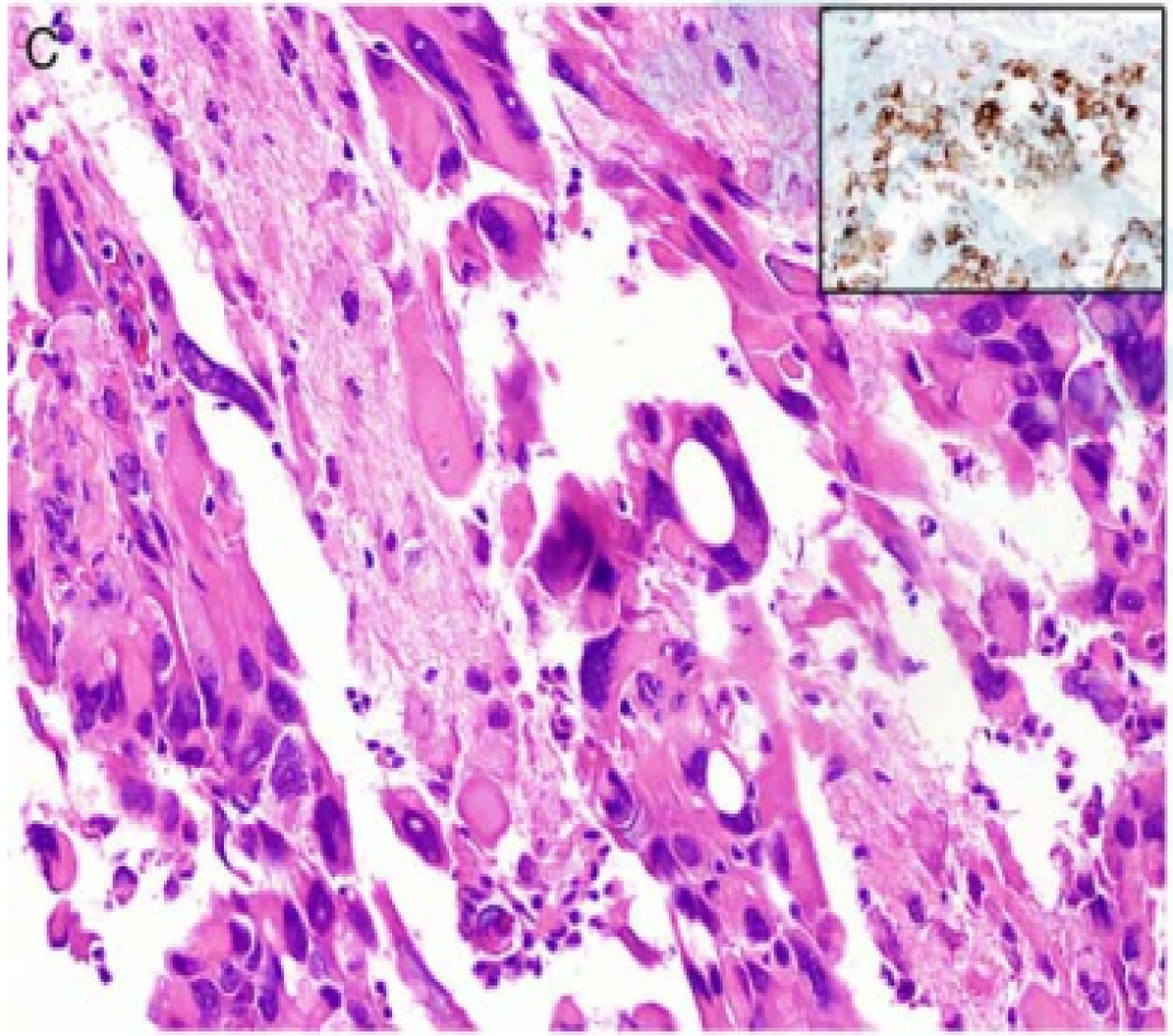




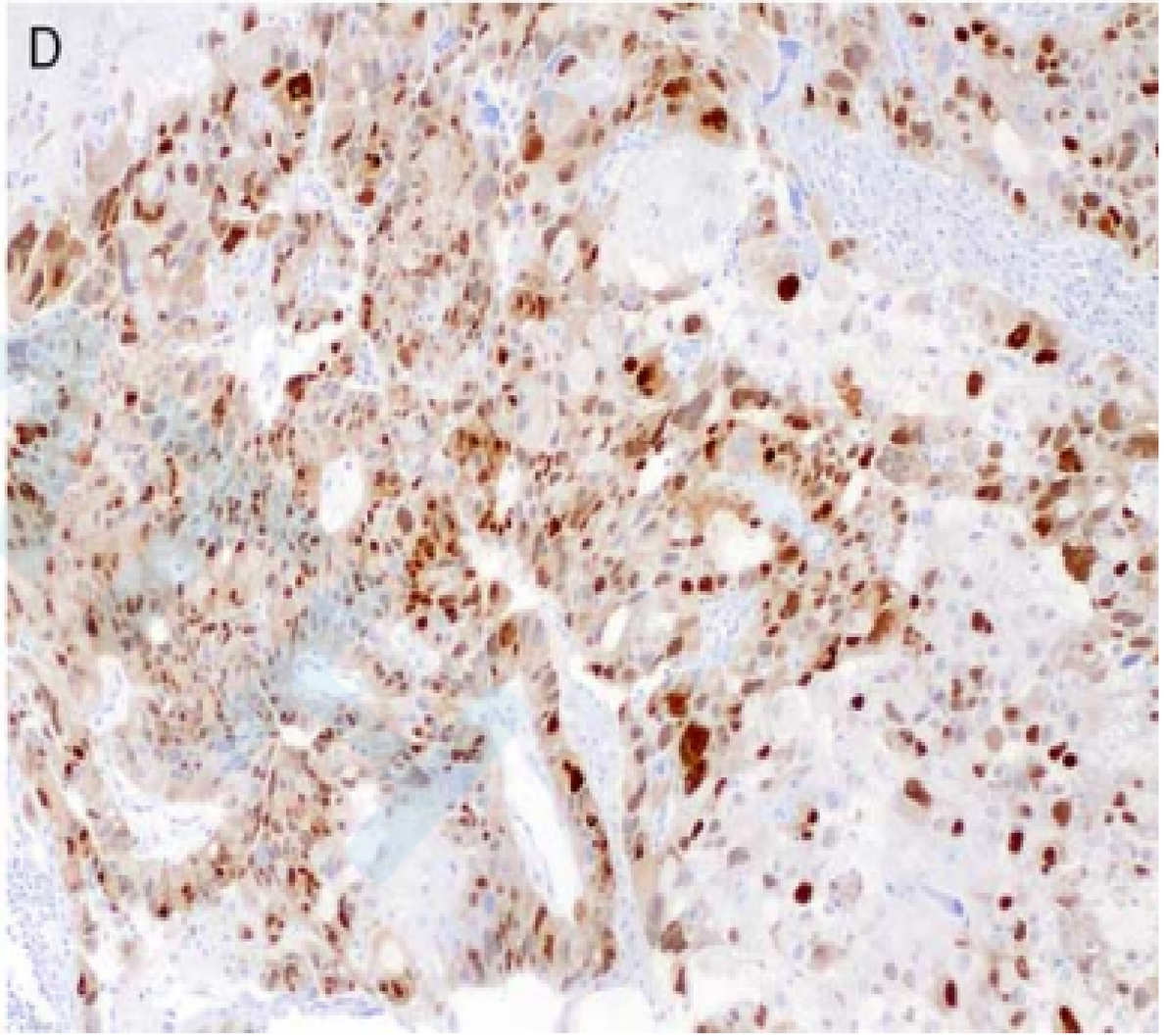
Anaplastic Astrocytoma (WHO Grade III)

Case 12

GFAP

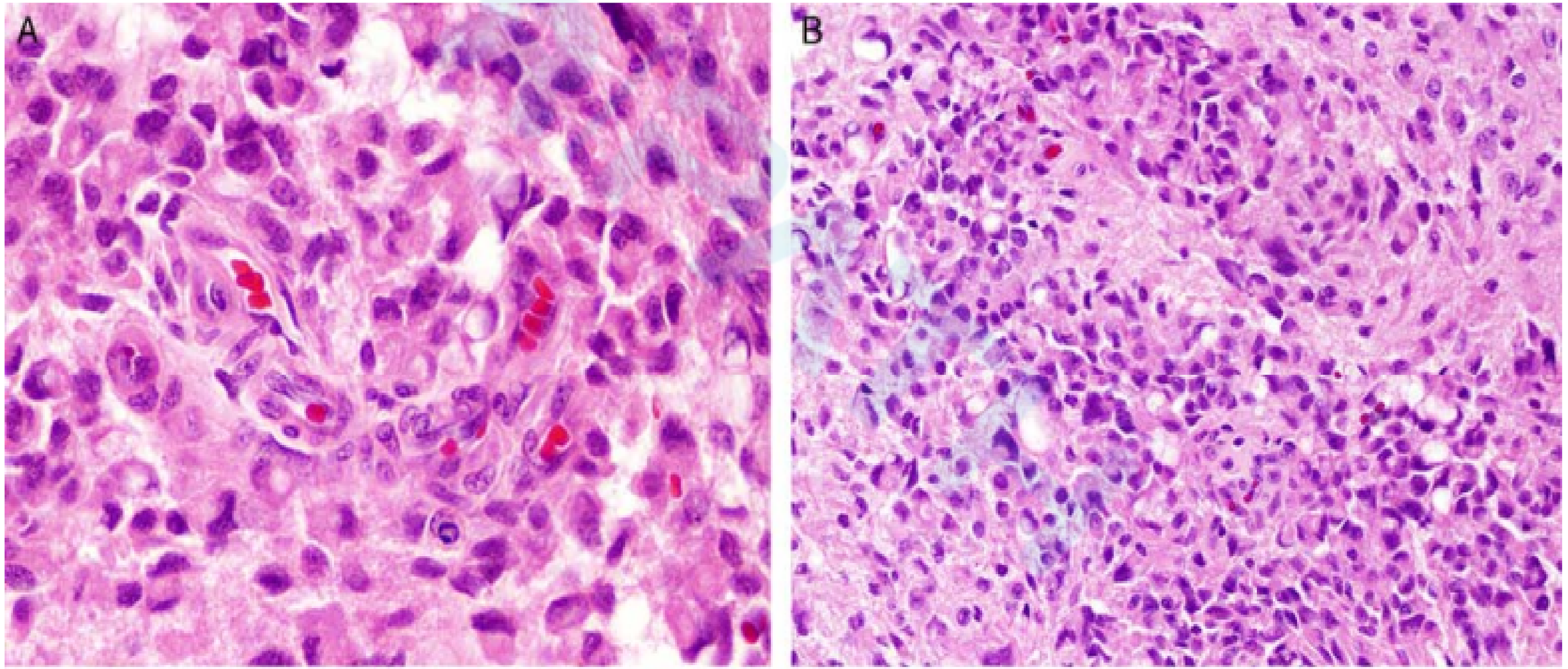


P53



Glioblastoma (WHO Grade IV)

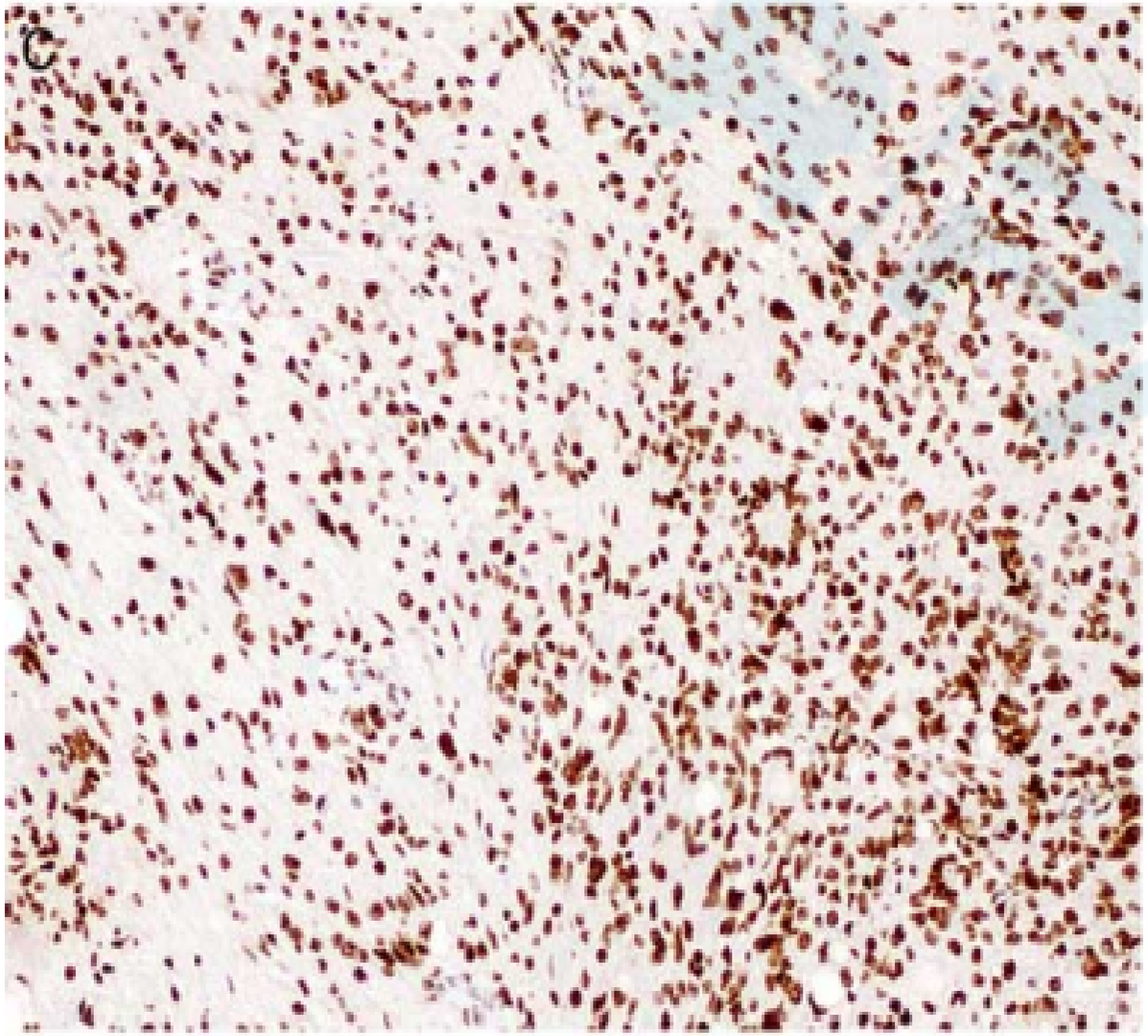
Case 5



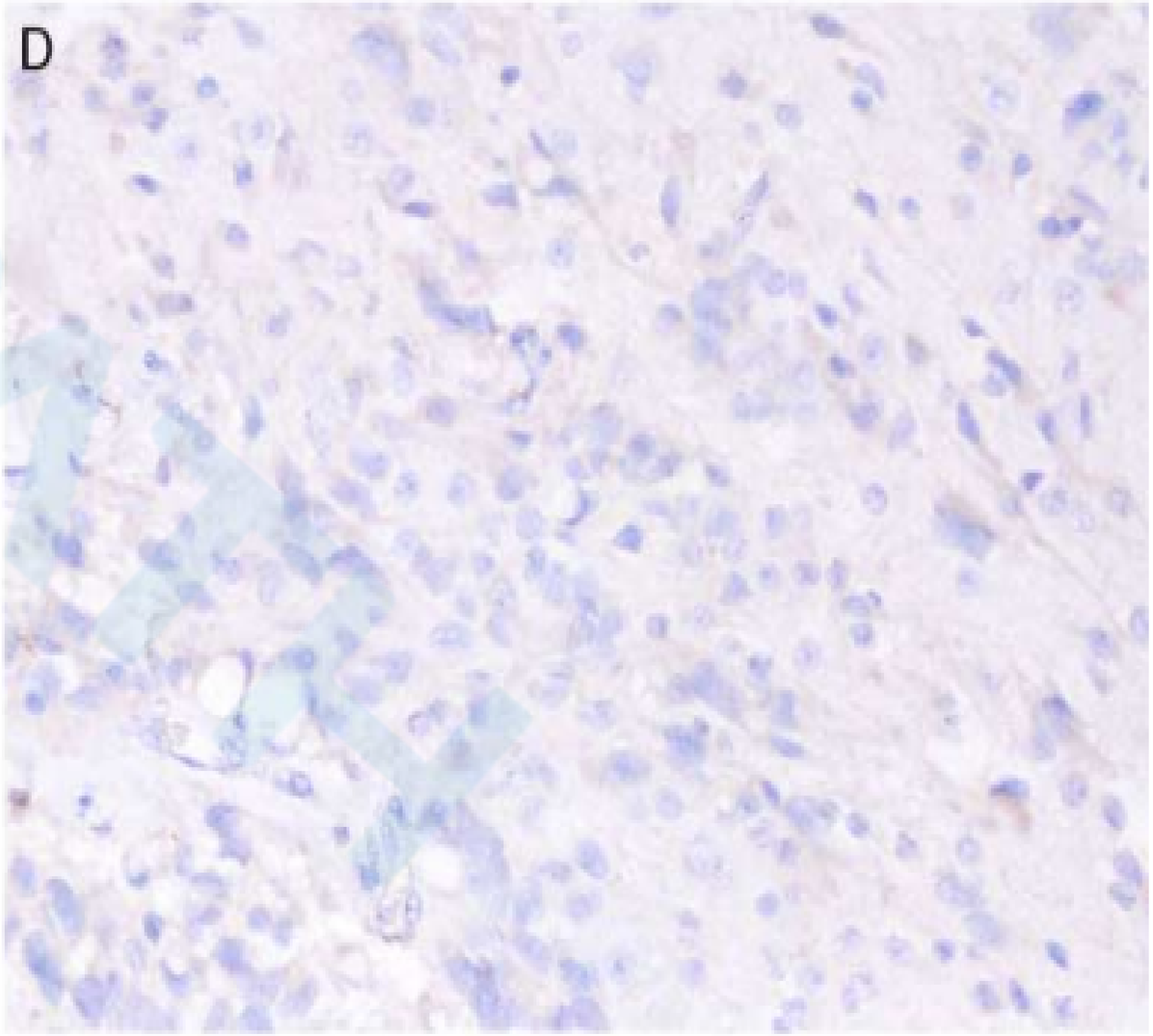
Glioblastoma (WHO Grade Ⅳ)

Case 5

ATRX

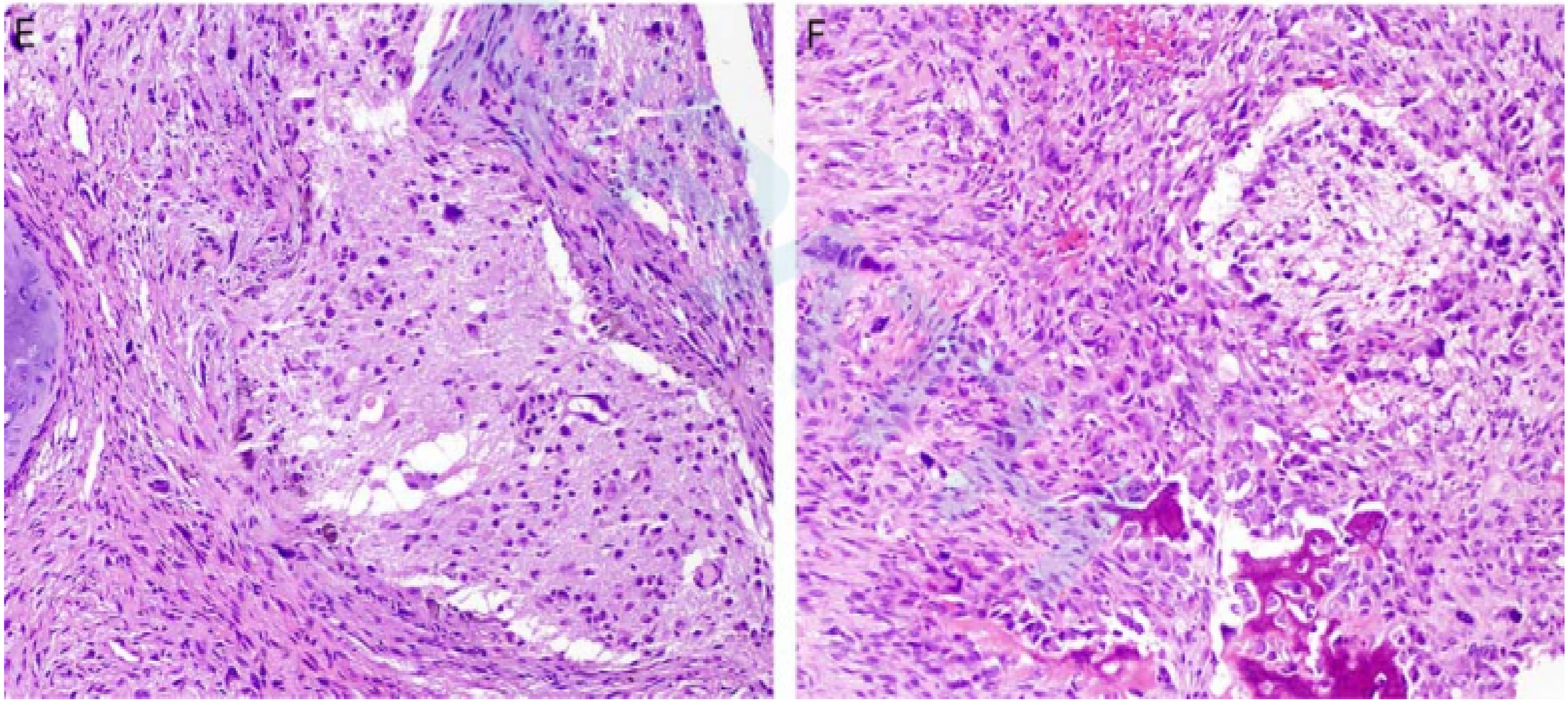


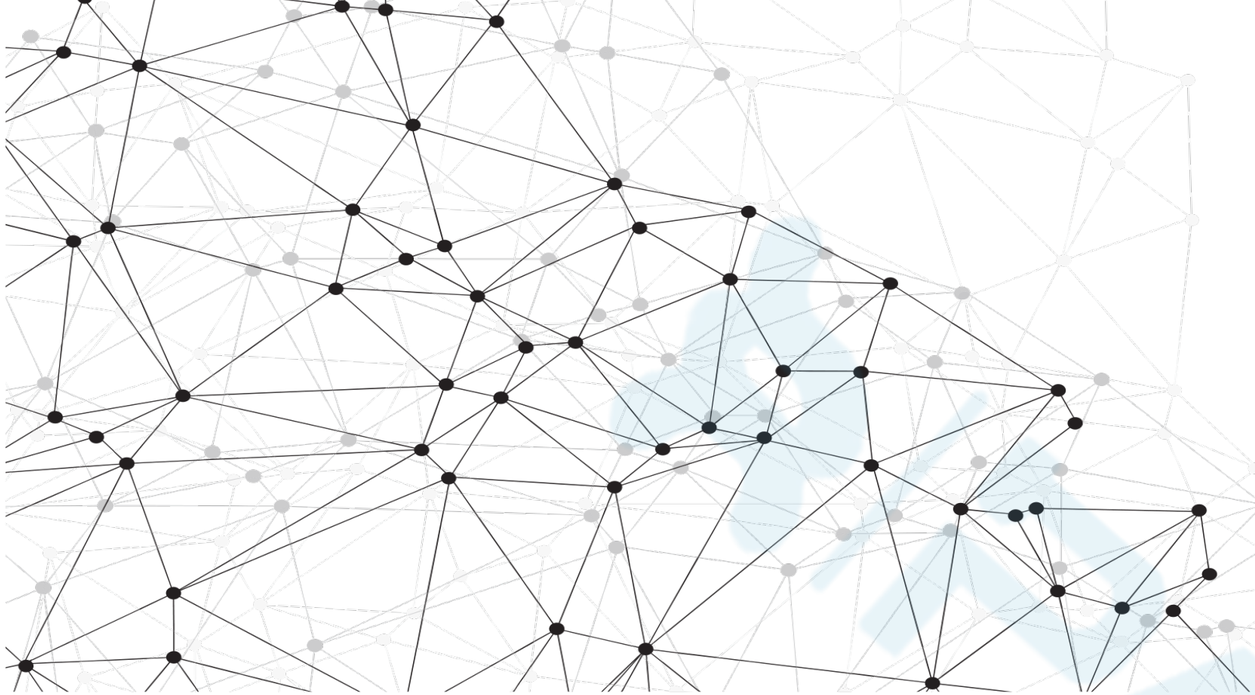
IDH 1



Gliosarcoma (WHO Grade Ⅳ)

Case 3





04

讨 论

DISCUSSION

DISCUSSION

讨论1：睾丸生殖细胞肿瘤中出现的神经胶质肿瘤属于体细胞型恶性肿瘤

WHO对于体细胞型恶性肿瘤的定义标准是在肿瘤中查见体细胞型恶性成分（癌/肉瘤等）并且占据至少一个低倍视野（×4物镜，直径5毫米）。

Developing Central Nervous System → 畸胎瘤的分化成分

Low Grade Astrocytoma (WHO Grade I/II)

Ganglioglioma (WHO Grade I)

Gemistocytic Astrocytomas (WHO Grade II)

Anaplastic Astrocytoma (WHO Grade III)

Glioblastoma and Gliosarcoma (WHO Grade IV)

\+ 所有病例都有并发或者既往畸胎瘤病史

“germ cell tumor with neuroglial neoplasm”（具有神经胶质肿瘤的生殖细胞肿瘤）应列入“teratoma with somatic-type malignancy”范畴

讨论2：免疫组化及分子研究结果表明

- ✓ 睾丸生殖细胞肿瘤中出现的神经胶质肿瘤与CNS发生的神经胶质肿瘤对比，有不同的发生机制。

- ✓ 本次研究没有进行分子研究来证明神经胶质成分在染色体12p上有改变，作者认为在本研究的病例中没有必要证明神经胶质成分起源于生殖细胞肿瘤，因为中枢神经系统原发肿瘤的外转移是非常罕见的，而且所有病例中没有一例有中枢神经系统恶性肿瘤的病史。

讨论3：与临床相关的情况还有待研究

本研究中获得的随访信息有限且病例数量少

✓在所有可随访的病例中，有一例发生胶质肉瘤的患者发生肺转移，形态与腹膜后淋巴结标本中的胶质肉瘤相似。尚不清楚在该系列中观察到的其他胶质肿瘤亚型是否有可能转移。

- ✓ 无法评估根据中枢神经系统肿瘤的分级方法对这些肿瘤进行分级是否与临床相关
- ✓ 对睾丸生殖细胞肿瘤中的神经胶质肿瘤最佳治疗方法尚不清楚。

讨论4：生殖细胞肿瘤中神经胶质肿瘤的诊断要点

- ✓ 关键的诊断特征是具有轻度核多形性、核较深染，胞浆嗜酸的肿瘤细胞的存在。辅助性诊断特征则是细胞间质中的纤维背景，但在细胞密度较高的病例中，纤维间质较少，识别相对困难。

- ✓ 在此类神经胶质细胞分化的病例中，主要的诊断挑战是腹膜后肿块的穿刺活检。在这种情况下，认识纤维背景进行鉴别诊断是至关重要的。同时分化差的神经母细胞瘤虽然在成人中很少见，但应该在鉴别诊断中加以考虑。

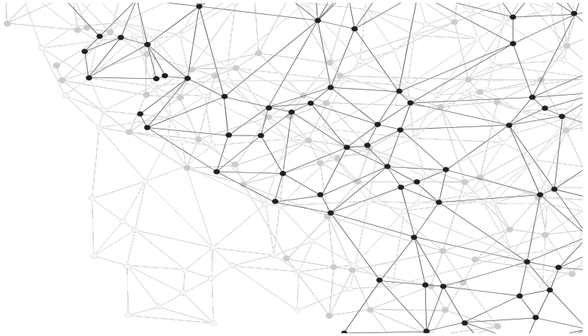
- ✓ IHC对证明神经胶质细胞的分化很有帮助，但需要充分取材才能作出诊断。

综上

1 报道了迄今为止睾丸生殖细胞肿瘤中神经胶质细胞分化的最大系列病例

2 这些病例具有广泛的形态学谱

3 虽然形态学上这些肿瘤都可以根据中枢神经系统肿瘤分类的最新分类进行分类，但其中大部分缺乏中枢神经系统肿瘤中相应的遗传学改变。



Thanks!

感谢聆听