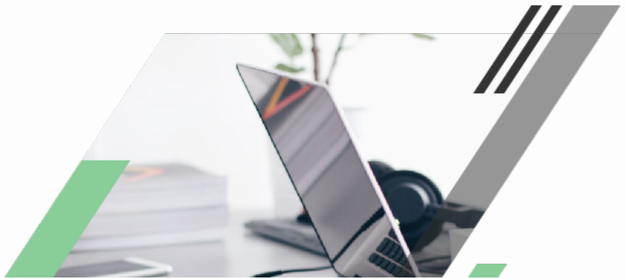
Pericytoma With t(7;12) and *ACTB-GLI1* Fusion

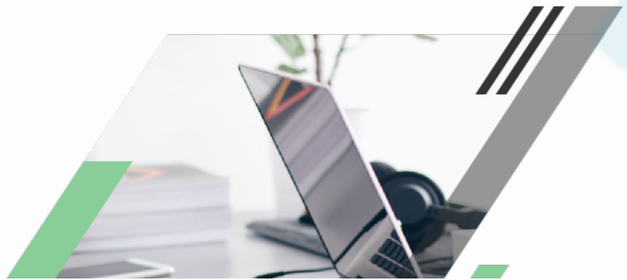
Reevaluation of an Unusual Entity and its Relationship to the Spectrum of GLI1 Fusion–related Neoplasms

汇报人：付欣



背景知识：

Myopericytomas（肌性周细胞瘤/肌周皮细胞瘤）



Myopericytomas（肌性周细胞瘤/肌周皮细胞瘤）

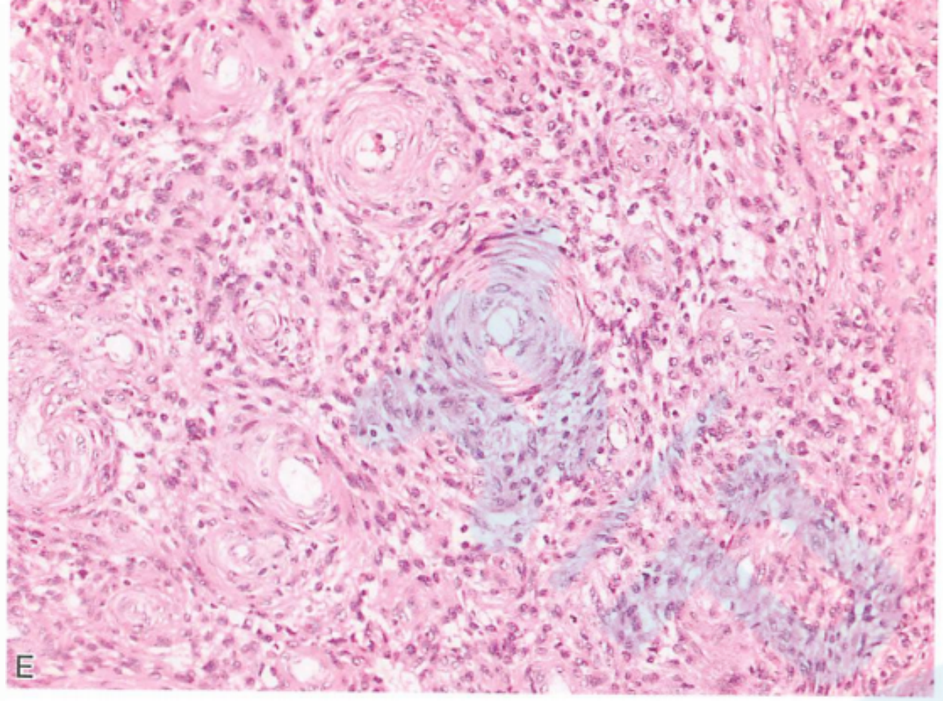
•是一种位于皮下的良性肿瘤，由卵圆形至梭形的肌样细胞组成，在血管周围呈显著的同心圆状排列。与血管平滑肌瘤、肌纤维瘤、血管球瘤、所谓的婴幼儿型血管外皮瘤共同构成一个瘤谱。

•可见于任何年龄，但常见于中年人；

•多发生于皮下，常累及肢体远端，表现为无痛性、缓慢生长的结节；

•大体检查：直径一般＜2cm，界限清楚；

- 组织病理学：
  - 无包膜，但大多数有明显局限性；
  - 病变由相对较一致的卵圆形至梭形肌样细胞构成，多层排列在血管周围，呈明显同心圆状生长，胞质嗜酸性，核分裂少见，小于1个/10HPF；
  - 病变可以是实性细胞结节，也可伴显著粘液样变，而细胞成分少；
  - 病变内含大量大小不一的血管， 有时有大量薄壁分支状或不连续的血管；
  - 常见血管壁内皮下肿瘤细胞增生，有时也可表现为血管球细胞的特征（立方形，细胞界清，胞质透明，核居中）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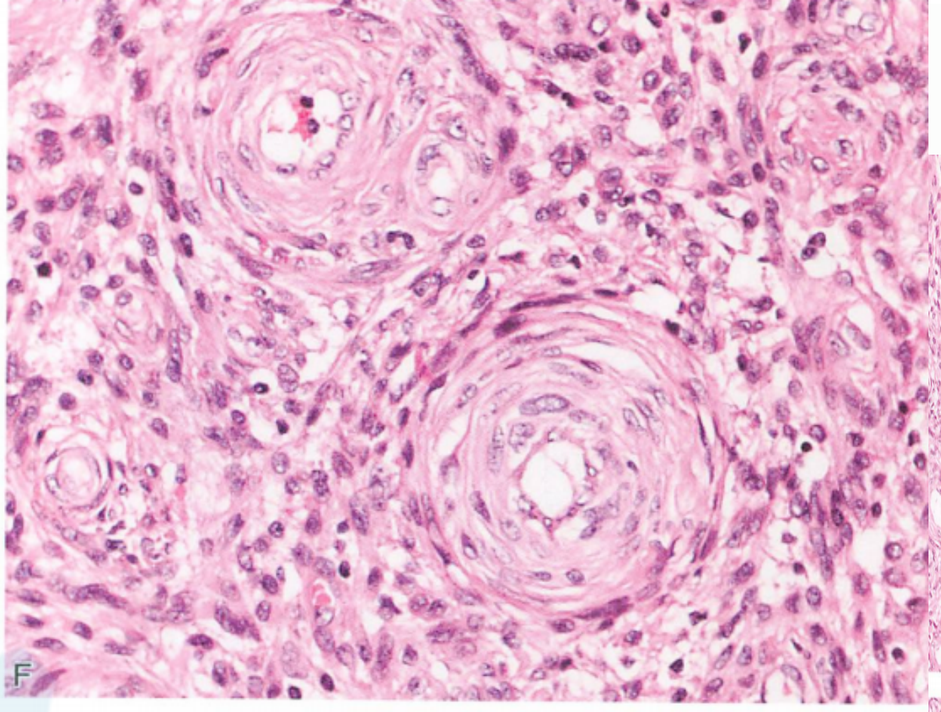
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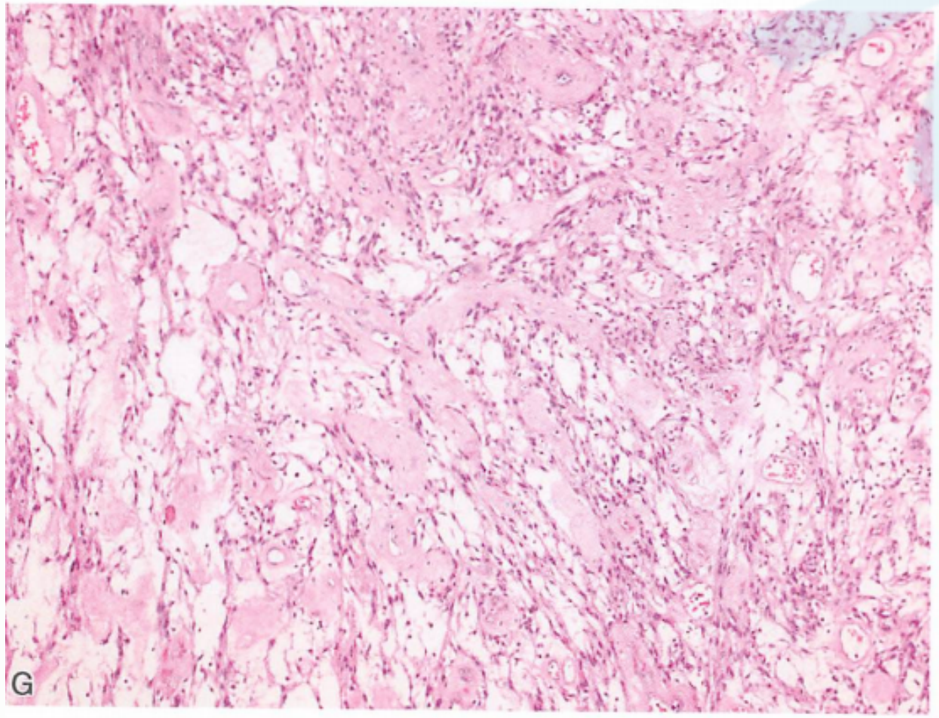
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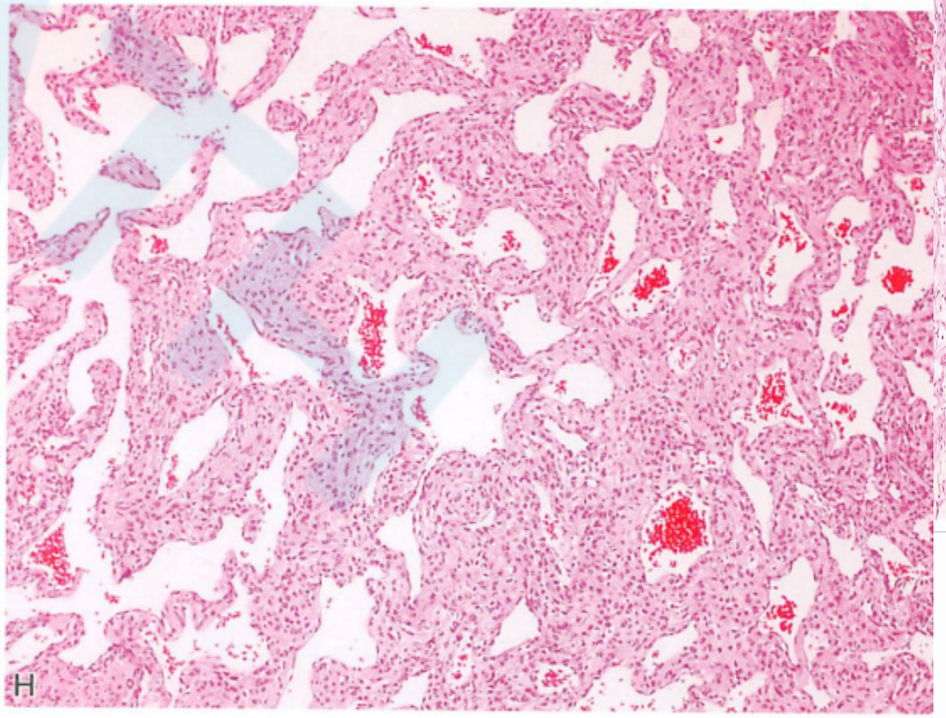
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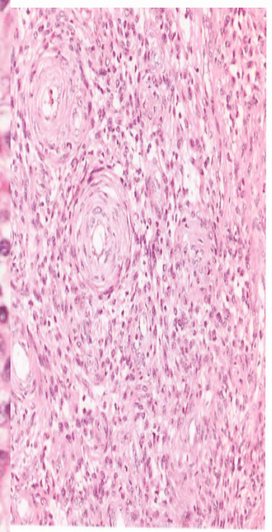
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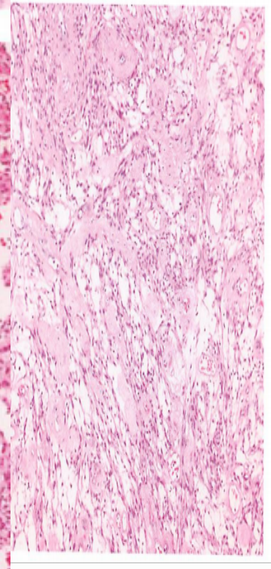
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- 免疫组化常表达SMA、 h-caldesmon，少数病例可灶性表达desmin和CD34,但不表达S-100和CK。

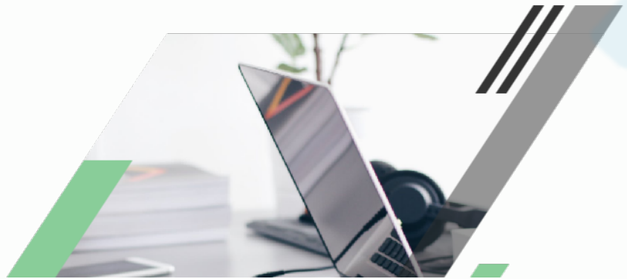
- **伴有 t(7;12）周细胞瘤**暂时被认为是肌性周细胞瘤的一个特殊类型（但尚存争议），特征在于其独特的细胞遗传学特征： t(7;12)(p22;q13)，导致位于7p22上的ACTB基因与位于12q13上的GLI基因的融合。

TABLE 3. Clinicopathologic Features of Tumors With *ACTB-GLI1* Gene Fusions, Including Previously and Currently Reported Cases

Case # (y)	References	Sex	Age (y)	Tumor Site	Size (cm)	Clinical Presentation	Histology and Assessment of Biological Potential	IHC Features	Treatment	Follow-Up (mo)
1-5 (2004)	Dahlén et al[1]	Male	61	Calf	2.0	NA	Spindle-to-ovoid; homogenous, arranged around thin-walled blood vessels; infiltrative/lobular growth; 3/5 focal myxoid stroma; 2/5 subendothelial protrusion into vascular lumina. Benign	+SMA, EMA (f) −Desmin, S100, CK	Resection	Died of unrelated causes, NED (60)*
	Dahlén et al[1]	Female	27	Tongue	0.8	NA		+SMA −Desmin, S100, CK, EMA	Neoadjuvant chemo+resection	NED (60)
	Dahlén et al[1]	Male	11	Tongue	5.0	NA		+SMA (f) −Desmin, S100, CK, EMA	Neoadjuvant chemo+resection	NED (22)
	Dahlén et al[1]	Female	65	Stomach	5.5	NA		+SMA (f) −Desmin, S100, CK, EMA	Resection	NED (24)
	Dahlén et al[1] (previously reported)[10]	Female	12	Tongue	2.4	Growing tongue mass		+SMA (f) −Desmin, S100, CK	Resection	NED (120)
6 (2012)	Bridge et al[2]	Male	67	Bone (talus)	2.7	Pain in right foot and ankle	Spindle-to-ovoid; cellular, prominent lesional vasculature; focal myxoid stroma; invasive growth. Low-grade malignant on biopsy, benign on the excision	+SMA (f), EMA (f) −Desmin, S100, CK	Amputation	NED (204)*
7 (2016)	Castro et al[3]	Female	9	Stomach	6.9	Abdominal pain and vomiting	Ovoid-to-spindle; plexiform vasculature, cystic, circumscribed with the lymphoid capsule, ischemic necrosis. Biological potential not specified	+EMA (f) −Desmsin, SMA, CK, S100	Partial gastrectomy	NED (6)
8-11 (2018)	Antonescu et al[4]	Male	20	Thigh	NA	NA	Round to epithelioid; arranged in nests, cords, and reticular patterns; mostly solid, occasional myxoid stroma. Biological potential malignant based on clinical	+S100 −SMA, CK, EMA	NA	NA
	Antonescu et al[4]	Female	30	Foot	1.5	NA		+S100 −SMA, CK, EMA	NA	AWD, LN met (21)
	Antonescu et al[4]	Female	79	Retroperitoneum	NA	NA		−S100, SMA, CK, EMA	NA	AWD, LN met (interval NA)
	Antonescu et al[4]	Female	38	Chest wall (muscle)	NA	NA		+CK (f) −S100, SMA, EMA	NA	NA
12 (2018)	Koh et al[9]	Female	11	Ovary	15.0	Abdominal pain and distension	"Round to spindle"; alternating hypocellular and hypercellular, cystic, pushing border; necrosis; "rare" mitoses; +subendothelial tumor proliferation. Biological potential not specified	+S100 −Desmin, SMA, CK, EMA	Left salpingoophorectomy	NED (24)*
13-15	Current cases	Female	57	Bone (tibia)	9.8	Painless mass	Round-to-ovoid; richly vascularized stroma; myxoid stroma in 1 case. Low to intermediate grade malignant	+SMA (f), EMA (f) −S100, CK, desmin	Neoadjuvant chemo+resection	AWD, bone met (27)
		Male	62	Bone (scapula)	7.5	Palpable mass		+SMA (+/f) −S100, EMA, CK, desmin	Resection +adjuvant radiotherapy	AWD, lung met (84) and soft tissue/bone met (180)
		Female	41	Ovary	7.0	Incidental ovarian cyst	Ovoid; alternating hypocellular and hypercellular, solid/cystic; necrosis. Biological potential not clear	+SMA (f), S100 (f), EMA, CK −Desmin	Total abdominal hysterectomy with bilateral salpingoophorectomy	NED (14)

*Per personal communication with the prior author(s).
AWD indicates alive with disease; IHC, immunohistochemistry; LN, lymph node; met, metastasis; NA: not available; NED, no evidence of disease; S100, S100 protein; chemo, chemotherapy.

三个病例临床病理特征



- 女,57y,

- MRI显示

  组织内-

  周围软

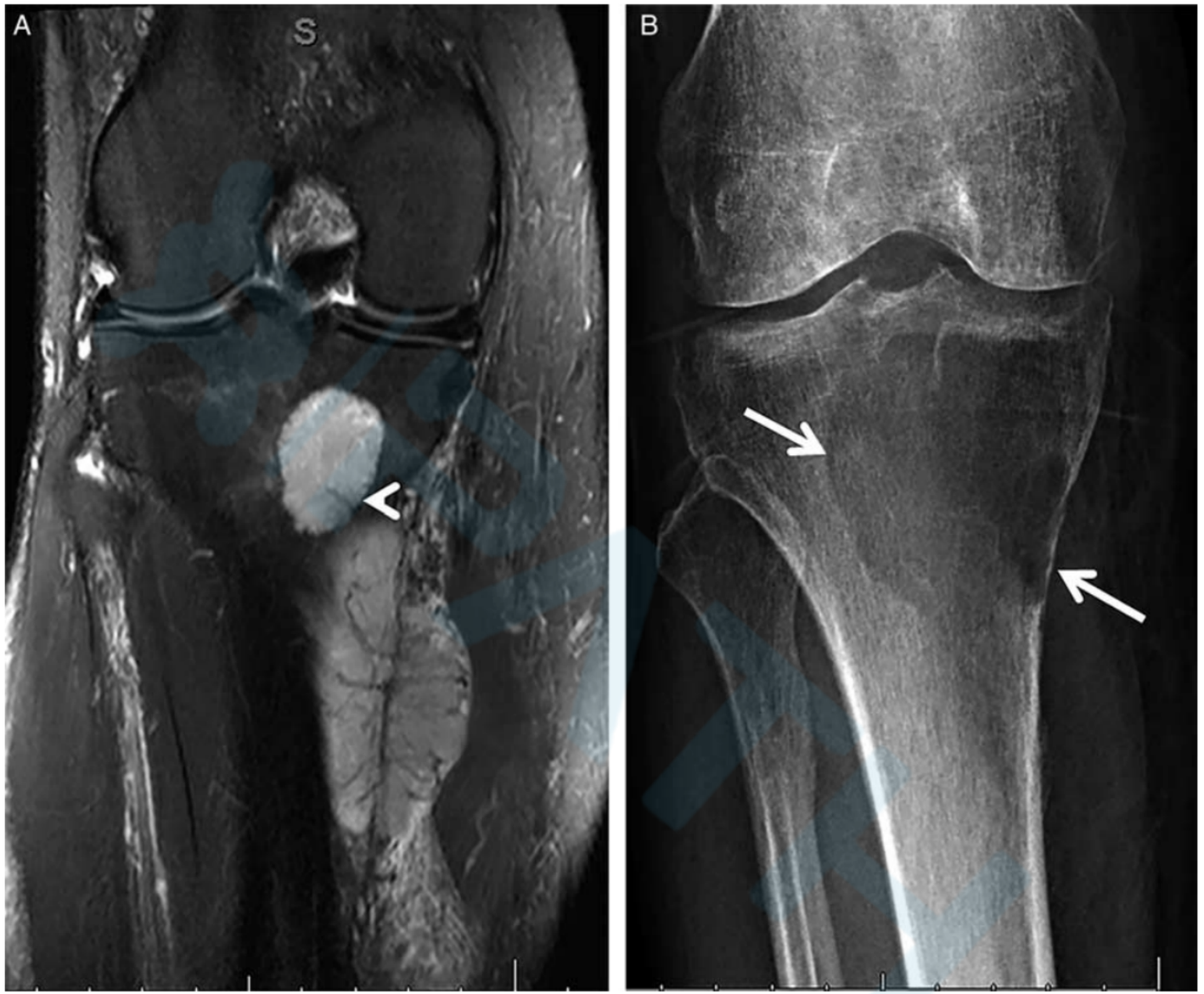


FIGURE 1. Case 1, Radiologic findings, preoperative and postneoadjuvant therapy. A, Preoperative coronal fat-saturated T2-weighted MRI demonstrates heterogeneous hyperintensity in both intraosseous and extraosseous components with a small perforating vessel at the posterior medial margin of the tibia (arrowhead) that may have allowed spread of the tumor between intraosseous and extraosseous components. The tumor vasculature in the soft tissue component is arborizing and hypointense. B, Radiograph of the tumor after neoadjuvant therapy shows a lytic lesion in the subarticular region of the proximal tibia, with sharp but nonsclerotic margins laterally (upper left arrow), and a more poorly defined inferior margin. High-grade endosteal scalloping of the proximal tibia is present medially (lower right arrow).

大体所见：

- 包块位于胫骨骨骺和干骺端，大小约5.5×4.0×3.0cm；
- 红白相间，以囊性骨内肿瘤为主，可见出血；其邻近的软组织内可见一个粉红色的实性包块；

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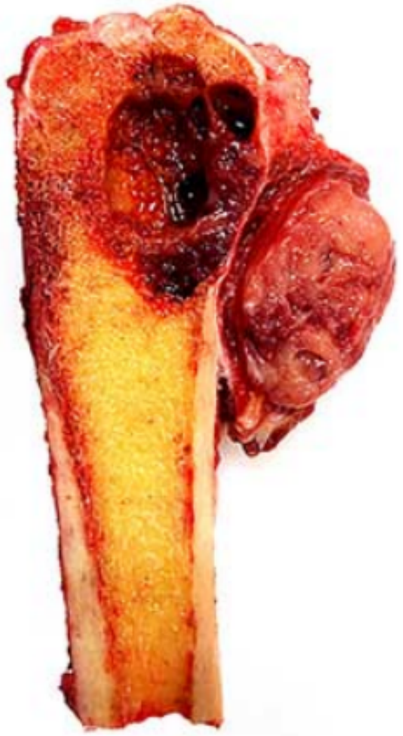
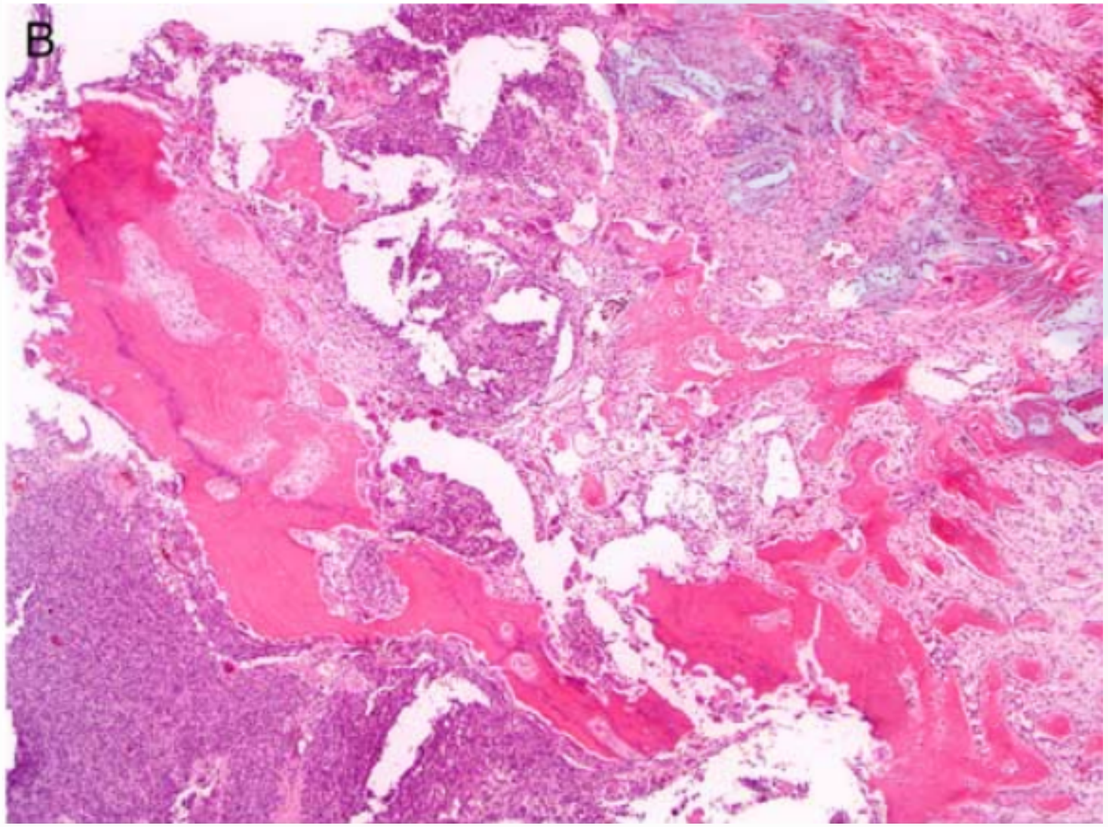


显微镜下所见：

- 低倍镜：
  - 显示肿瘤存在于髓腔内，浸润骨皮质，并延伸到邻近的骨膜，且浸润邻近的软组织；
- 高倍镜：
  - 显示肿瘤表现为多结节和局灶性血管周围生长，有明显的“血管外皮细胞瘤”样血管；
  - 肿瘤细胞较小，呈圆形到卵圆形，核为卵圆形或不规则形，可见小核仁，胞质嗜酸性；
  - 核分裂像约5/10HPF；大约40%的肿瘤坏死（主要为骨内囊性变成分），手术切缘阴性。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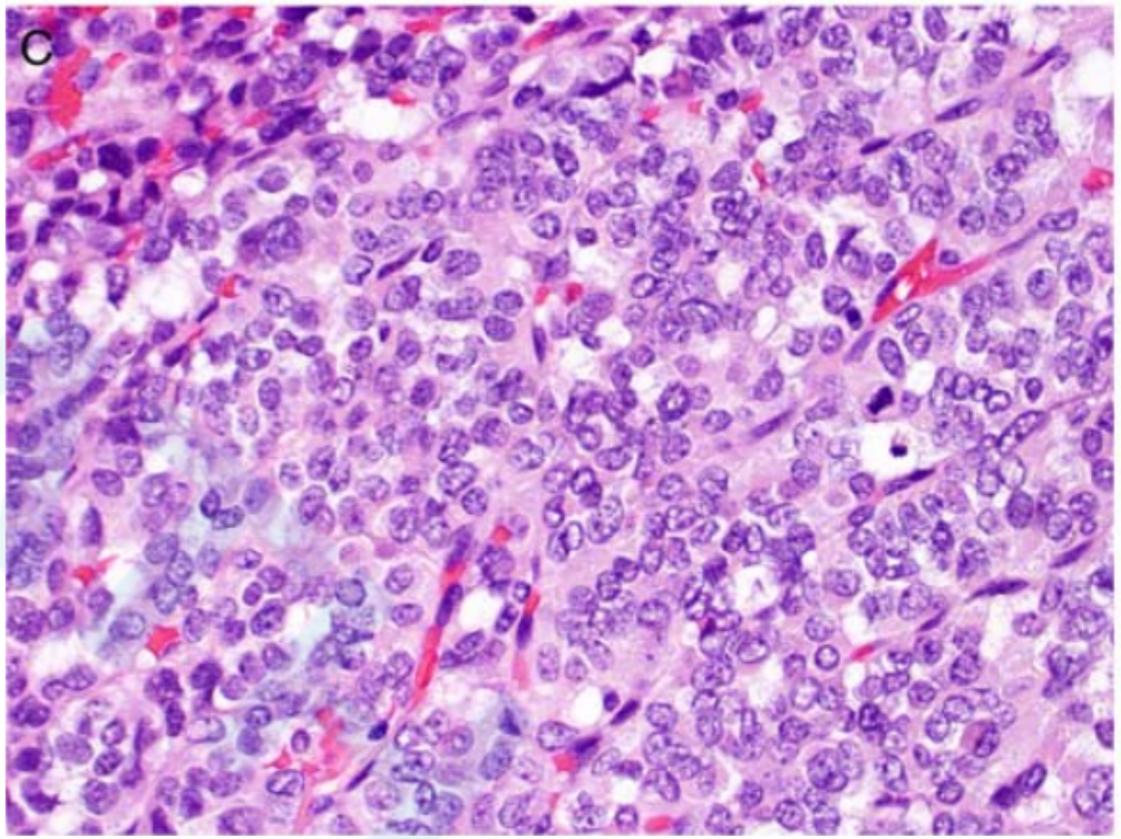
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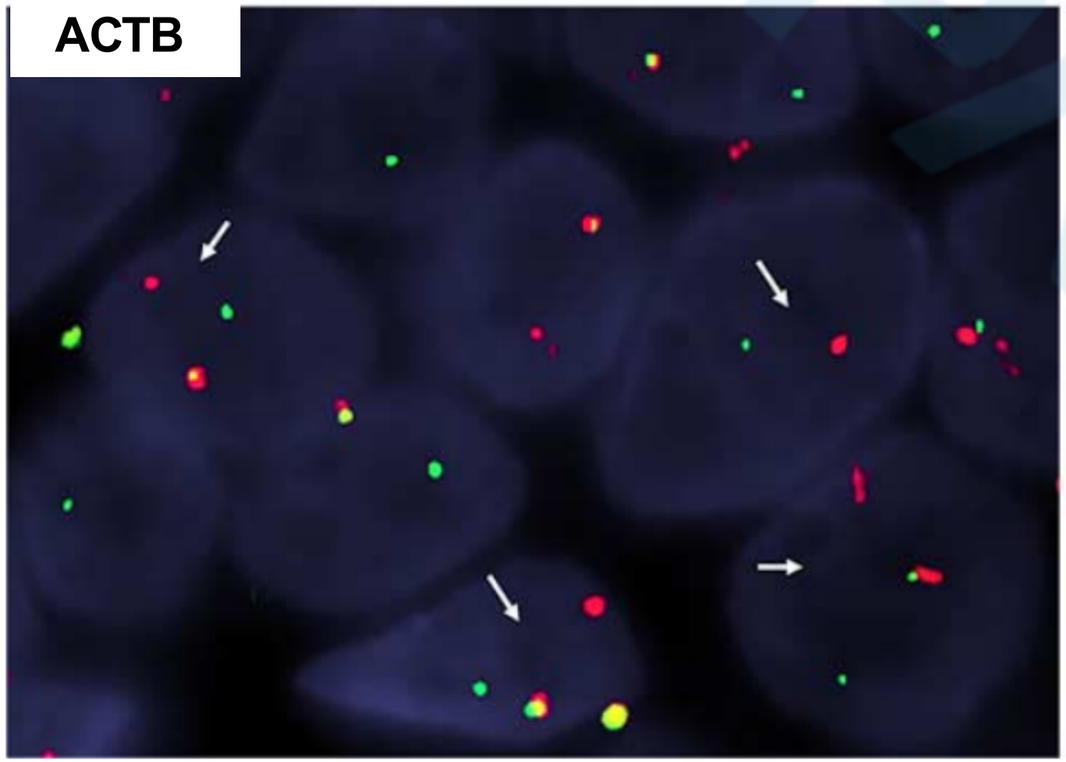
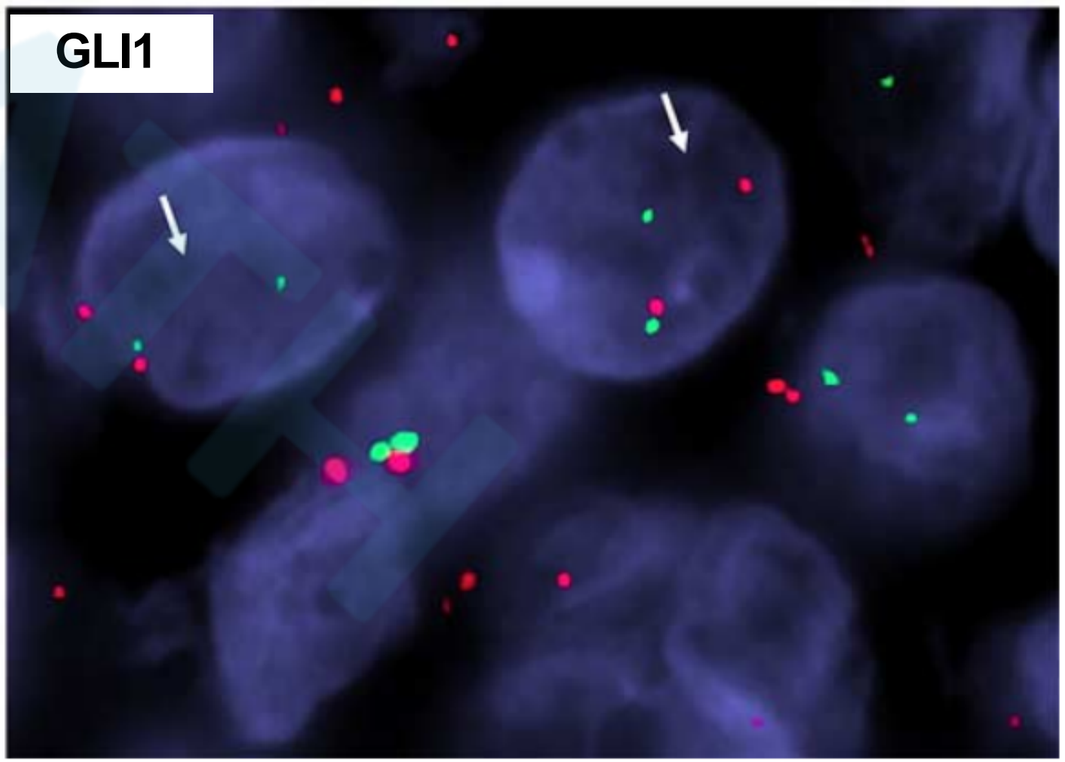
免疫组化及分子分析：

TABLE 2. Imunohistochemical Profiles of Each Tumor

	SMA	MSA	Desmin	S100	EMA	Pan-Keratin	CD99	WT1	CD10	Ki-67
#1	+ (f)	+ (r)	–	–	+ (w, f)	–	+ (w, f)	–	–	35%
#2	+/+ (f)	+ (f)	–	–	–	–	+/–	–	NP	NP
#3	+ (f)	–	–	+ (f)	+	+	–	–	+	1%

Refer to the main text for a complete description of all immunohistochemistry performed.
(f) indicates focal; (r), rare cells; (w), weak; NP, not performed; x/x, different results between initial and subsequent specimens.

- 



治疗及预后：

- 治疗：
  - 新辅助治疗后手术

- 预后：
  - 诊断后27个月，患者出现胸壁疼痛，X线片显示第八肋骨的破坏性病变。
  - 穿刺活检和肋骨大面积切除标本证实与胫骨肿瘤相似的形态学特征。

Case2

- 男，62y，右肩部肿块；
- MRI显示一6×8×10cm实性肿块，伴右肩胛骨骨质破坏；

- 大体标本：肩胛骨区一7.5cm的肿块；有多个卫星结节与主要肿块分开，并有明显的血管侵犯；
- 显微镜下：肿瘤细胞由圆形到椭圆形的小细胞组成，染色质细腻，胞质透明，背景中可见微血管，肿瘤呈腺样排列，核分裂像罕见（1/50HPF）；间质局部粘液样变，无坏死。

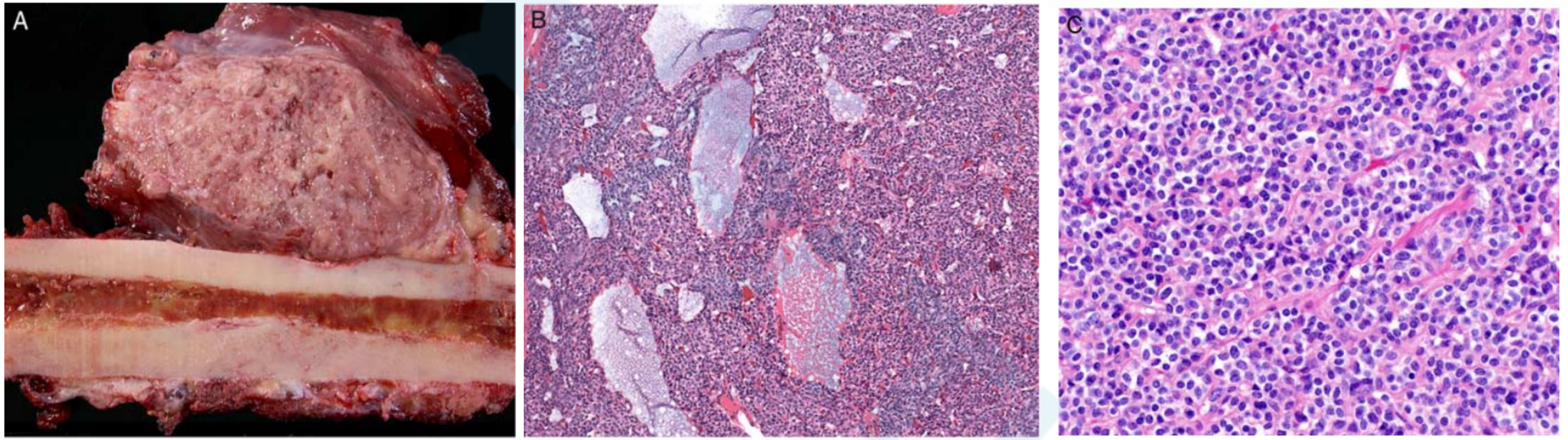


FIGURE 3. Case 2, Pathologic findings. A, Gross examination of the resected thigh metastasis shows a well-demarcated, soft, red_x0002_white ovoid mass within the skeletal muscle that focally erodes the adjacent cortex of the femur. B, On low power, the neoplastic cells are arranged in small groups with a delicate background vascula_x0002_ture and foci of myxoid stroma (hematoxylin and eosin). C, A high_x0002_power image shows a proliferation of cytologically uniform small cells with round-to-ovoid nuclei, dispersed chromatin, and small nucleoli with variably distinct cell borders (hematoxylin and eosin).

免疫组化及分子分析：

TABLE 2. Imunohistochemical Profiles of Each Tumor

	SMA	MSA	Desmin	S100	EMA	Pan-Keratin	CD99	WT1	CD10	Ki-67
#1	+ (f)	+ (r)	−	−	+ (w, f)	−	+ (w, f)	−	−	35%
#2	+/+ (f)	+ (f)	−	−	−	−	+/−	−	NP	NP
#3	+ (f)	−	−	+ (f)	+	+	−	−	+	1%

Refer to the main text for a complete description of all immunohistochemistry performed.
(f) indicates focal; (r), rare cells; (w), weak; NP, not performed; x/x, different results between initial and subsequent specimens.

- FLI-1、calponin、myogenin、MyoD1、CD45、syn和CgA均阴性；

- EWSR1的FISH检测阴性。

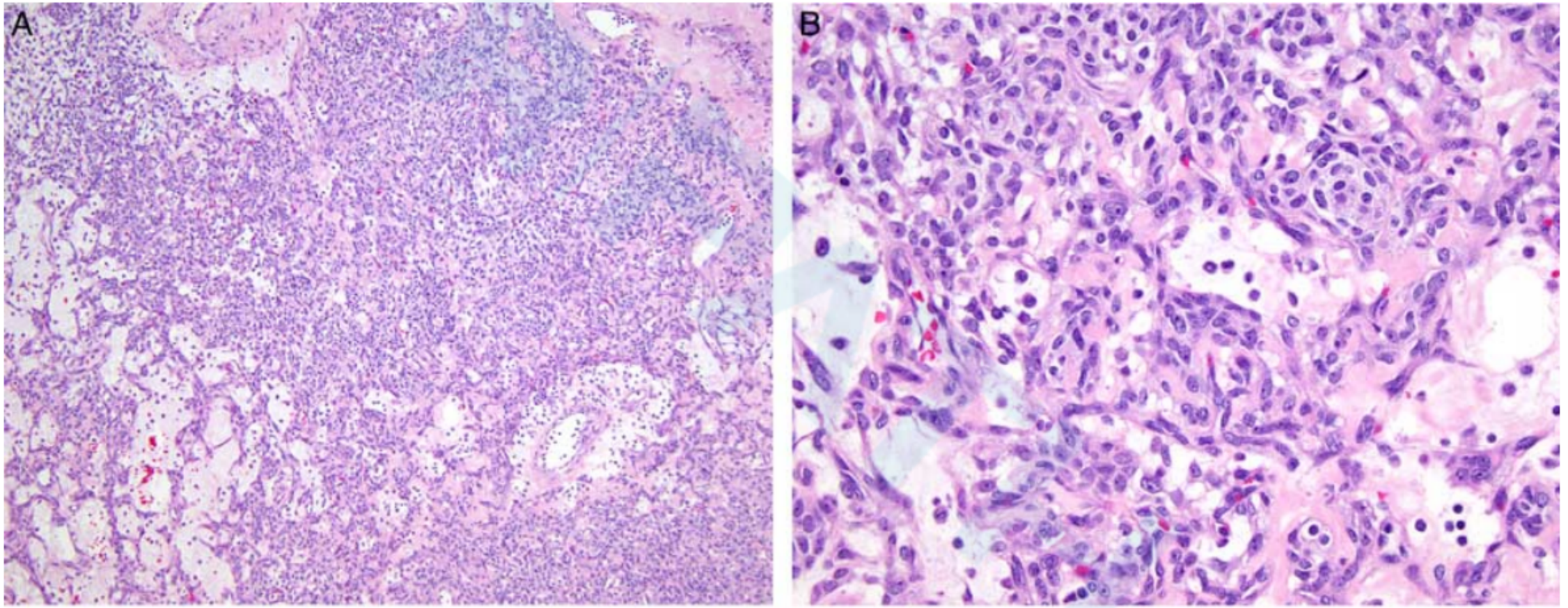
治疗及预后：

- 手术，术后放疗；
- 术后7年，左肺出现转移瘤，与原肿瘤形态相似；
- 术后9年，右肺出现转移瘤，进行了手术切除；
- 术后15年，右大腿发现一包块，包块切除后肿瘤组织学形态及免疫表型均与原肿瘤一致，且用PCR方法检测到了ACTB和GLI1基因的融合；

Case3

- 女,41y,因偶然发现左卵巢囊肿而就诊，患者无异常阴道流血、盆腹腔疼痛、腹胀、泌尿或肠道习惯等的改变；
- MRI显示左侧附件内有一囊实性肿块，大小约5.5×7.4×5.5cm；行全子宫及双附件切除术；

- 大体检查：左侧卵巢肿块部分破裂，大小约7.0×4.5×3.0cm，表面光滑；切面为囊实性，灰褐色，坏死少见，无残存的正常卵巢组织。
- 显微镜下：肿瘤由均匀的卵圆形细胞组成，细胞密集区与水肿区交替出现。间质内血管丰富，局部可见坏死，但核分裂罕见（1个/50HPF）。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#2	+/+ (f)	+ (f)	−	−	−	−	+/−	−	NP	NP
#3	+ (f)	−	−	+ (f)	+	+	−	−	+	1%

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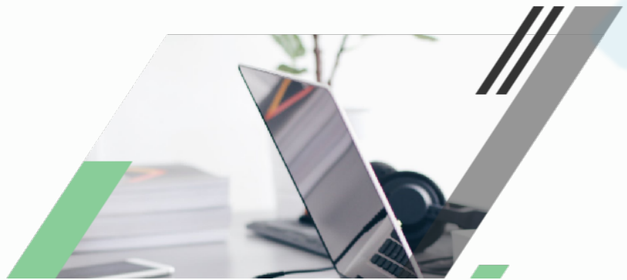
- PAX8、SF-1、inhibin、SALL4、β-catenin、HMB45、Melan A和syn均阴性；

- 分子检测：NGS显示仅t（7；12）GLI1-ACTB重排。

- **本例患者术后无其它治疗，目前随访14个月无复发。**

讨论：

1. 伴t（7；12）周细胞瘤



- 本文提出了3例与微血管相关、由圆形至卵圆形细胞组成的肿瘤，其免疫表型至少局灶性有肌源性分化（表达SMA），同时有ACTB-GLI1基因的融合，我们暂时将其命名为“伴t（7；12）周细胞瘤”。

- 伴t（7；12）周细胞瘤目前被认为是伴有ACTB-GLI1基因融合的肌性周细胞瘤的一个特殊亚型。

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	Antonescu et al[4]	Female	30	Foot	1.5	NA		+S100 −SMA, CK, EMA	NA	AWD, LN met (21)
	Antonescu et al[4]	Female	79	Retroperitoneum	NA	NA		−S100, SMA, CK, EMA	NA	AWD, LN met (interval NA)
	Antonescu et al[4]	Female	38	Chest wall (muscle)	NA	NA		+CK (f) −S100, SMA, EMA	NA	NA
12 (2018)	Koh et al[9]	Female	11	Ovary	15.0	Abdominal pain and distension	"Round to spindle"; alternating hypocellular and hypercellular, cystic, pushing border; necrosis; "rare" mitoses; +subendothelial tumor proliferation. Biological potential not specified	+S100 −Desmin, SMA, CK, EMA	Left salpingooph-orectomy	NED (24)*
13-15	Current cases	Female	57	Bone (tibia)	9.8	Painless mass	Round-to-ovoid; richly vascularized stroma; myxoid stroma in 1 case. Low to intermediate grade malignant	+SMA (f), EMA (f) −S100, CK, desmin	Neoadjuvant chemo+resection	AWD, bone met (27)
		Male	62	Bone (scapula)	7.5	Palpable mass		+SMA (+/f) −S100, EMA, CK, desmin	Resection +adjuvant radiotherapy	AWD, lung met (84) and soft tissue/bone met (180)
		Female	41	Ovary	7.0	Incidental ovarian cyst	Ovoid; alternating hypocellular and hypercellular, solid/cystic; necrosis. Biological potential not clear	+SMA (f), S100 (f), EMA, CK −Desmin	Total abdominal hysterectomy with bilateral salpingooph-orectomy	NED (14)

*Per personal communication with the prior author(s).
AWD indicates alive with disease; IHC, immunohistochemistry; LN, lymph node; met, metastasis; NA: not available; NED, no evidence of disease; S100, S100 protein; chemo, chemotherapy.

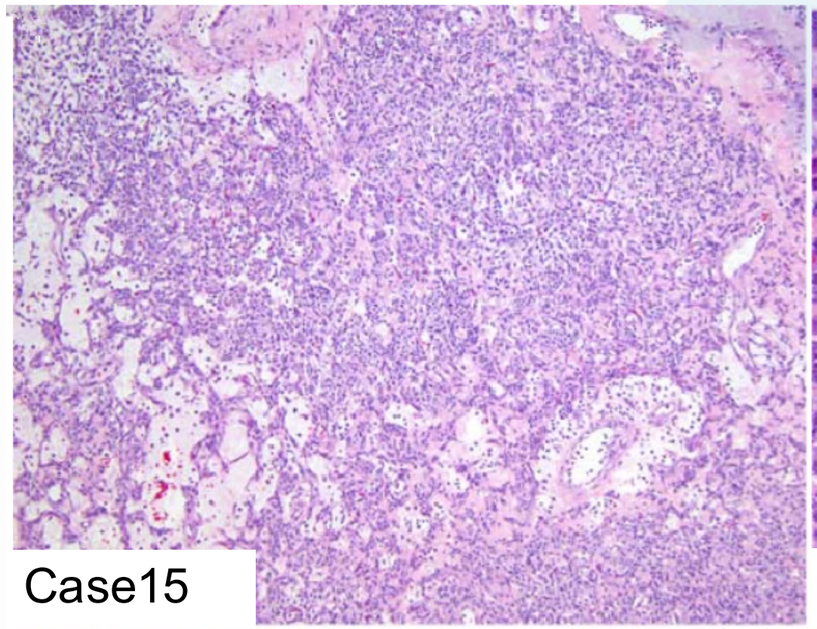
临床病理特征：

- 女性多于男性（女：男=2：1）；
- 年龄9-79y，平均年龄39岁；
- 肿瘤大小从0.8-15cm，平均大小约5.5cm；
- 好发于软组织（4例）、舌头（3例）和骨（3例），少见部位有胃（2例）、卵巢（2例）和腹膜后（1例）；

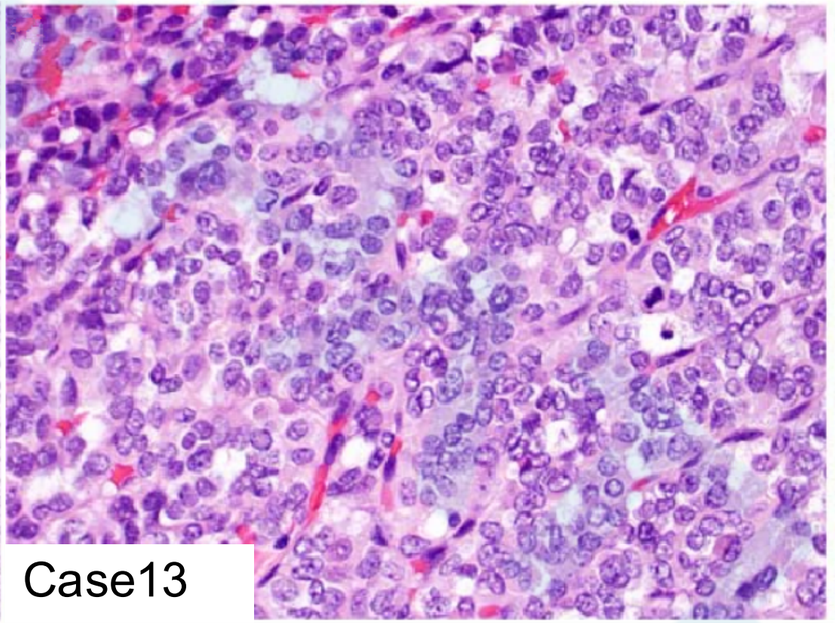
- 镜下肿瘤主要由相对一致的卵圆形至梭形细胞组成，大部分病例以卵圆形细胞为主，围绕血管生长。

- 肿瘤细胞体积较小，胞质嗜酸性或透明，核为圆形或卵圆形，无明显非典型性，可见小核仁，但核分裂像少见（0-5个/HPF）。

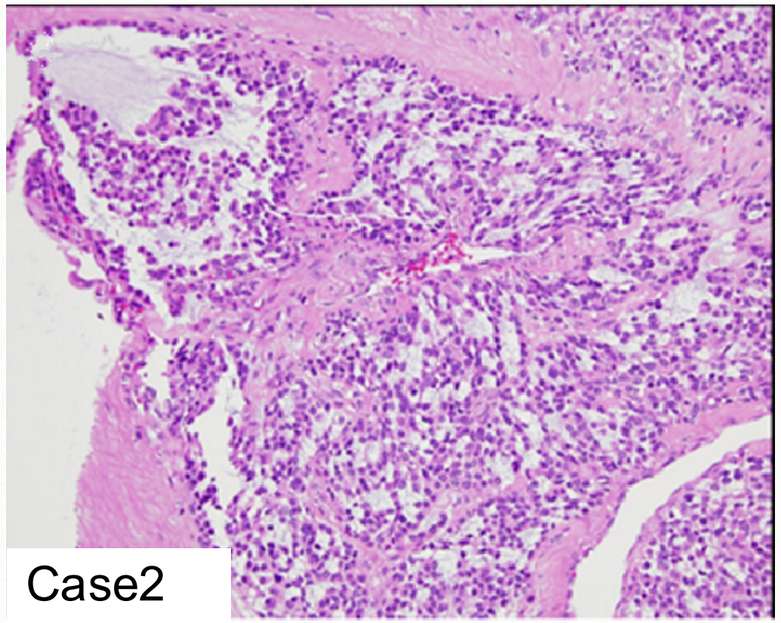
- 大多数肿瘤呈浸润性生长，约一半病例伴局灶性粘液样间质，偶见坏死（20%，n=3/15）。



Case15



Case13



Case2

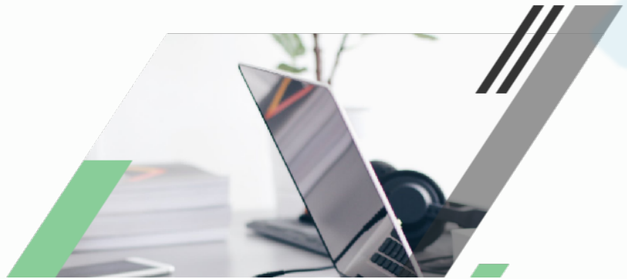
- 免疫组化：肿瘤细胞表达SMA，但DES、S-100、CK、EMA常阴性。

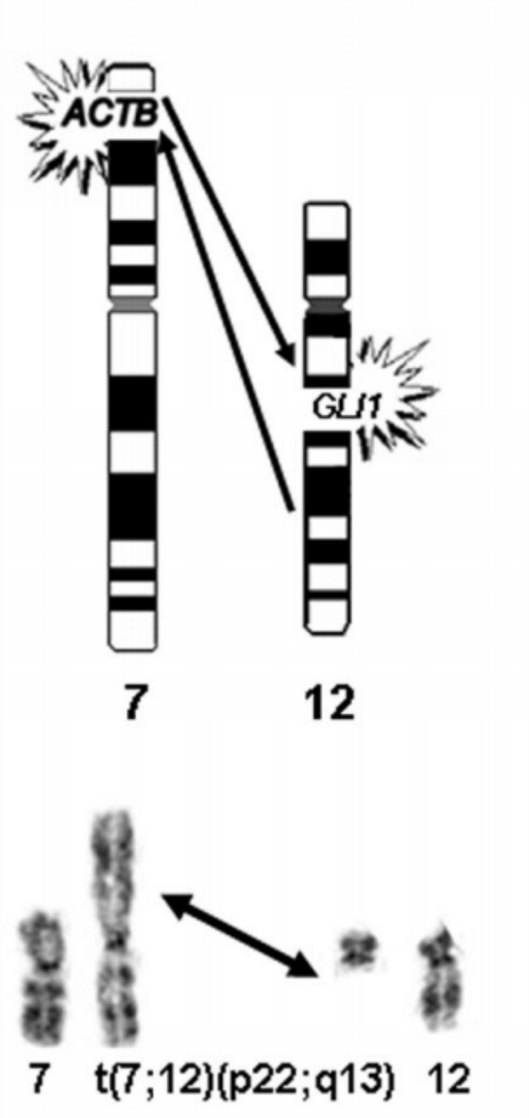
- 具有独特的细胞遗传学特征： t(7;12)(p22;q13)，导致位于7p22上的ACTB基因与位于12q13上的GLI基因的融合。

- 预后：11/15患者无病生存，虽然有4例有淋巴结或远处转移，但都存活，提示其多数为良性。

讨论：

2.ACTB和GLI1基因





- t(7;12)(p22;q13)移位导致ACTB与GLI1基因的融合，从而使表达的ACTB基因的启动子驱动了GLI1表达的增加；进而导致下游靶基因的转录激活和再调控，最终影响细胞的周期调控、细胞粘附、凋亡、信号转导和细胞增殖等。

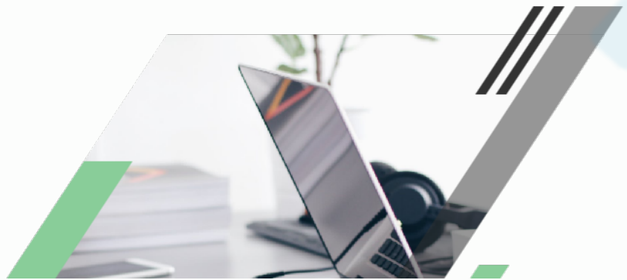
- GLI1基因的过表达可见于多种肿瘤中，如胶质母细胞瘤和横纹肌肉瘤等，其主要作用在于参与了SHH信号通路，而与其相关的治疗靶点正在研究中。

Rimkus TK, Carpenter RL, Qasem S, et al. Targeting the Sonic Hedgehog signaling pathway: review of smoothened and GLI inhibitors. Cancers (Basel). 2016;8:22–45.

- ACTB-GLI1基因融合在其它肿瘤中罕见报道。

- 仅Antonescu等人报道了4例与ACTB-GLI1融合相关的“恶性上皮样肿瘤”；

总结



- 本文报道了3例伴有 t(7;12）周细胞瘤，其形态学表现为肿瘤细胞呈圆形到卵圆形，排列在薄壁血管周围，肿瘤细胞表达SMA，但不表达DES、S-100、CK、EMA，有ACTB-GLI1基因的融合。

- 具有这种遗传学异常的肿瘤常表现为侵袭性的生物学行为，但之前的报道和本文都证实了，虽然有转移的病例，但治疗后却无明显进展。

- 本文扩展了我们对ACTB-GLI易位相关肿瘤的认识，其基因靶点可能为此类肿瘤提供新的治疗方向。

感谢聆听