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Lymphatic-type “Angiosarcoma” With Prominent Lymphocytic Infiltrate

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汇报人：韩 铭

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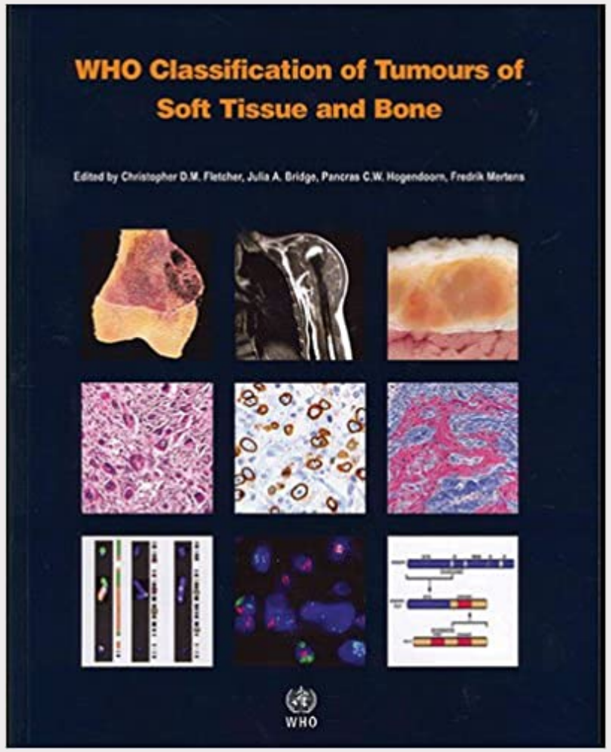
Vascular tumours

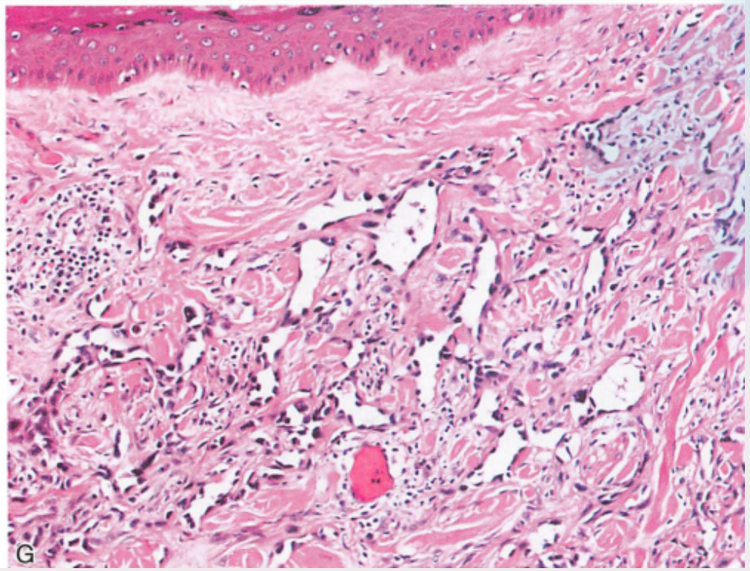


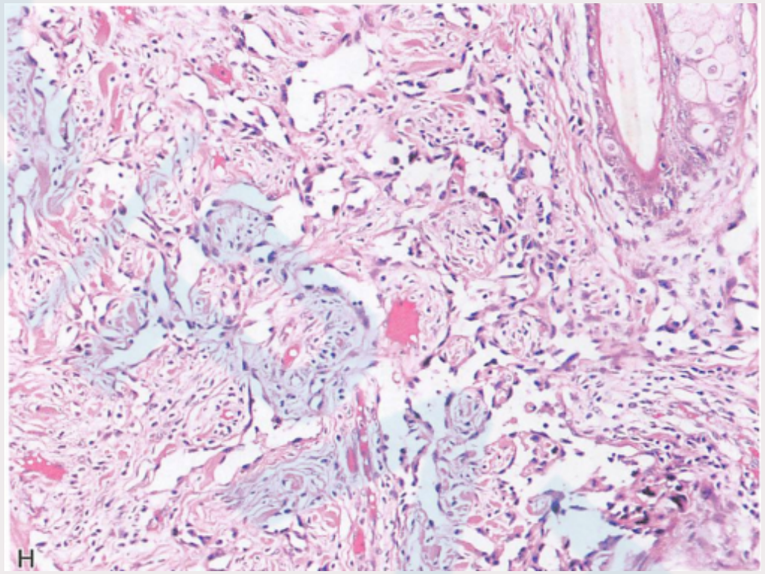
Benign	Intermediate	Malignant
Hemangioma epithelioid hemangioma Angiomatosis	Kaposiform hemangioendothelioma Kaposi sarcoma retiform hemangioendothelioma(RH) papillary intralymphatic angioendothelioma (Dabska Tumour) composite hemangioendothelioma pseudomyogenic hemangioendothelioma	epithelioid hemangioendoth-elioma angiosarcoma
lymphangioma	?	?

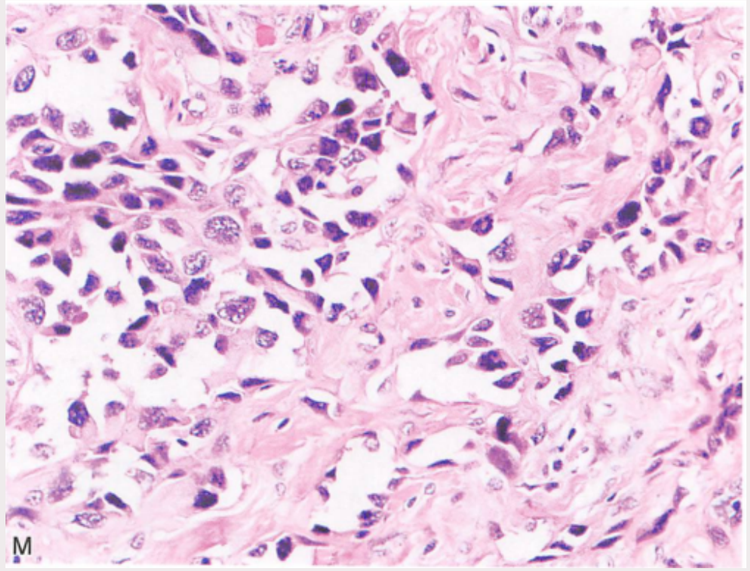
Angiosarcoma血管肉瘤

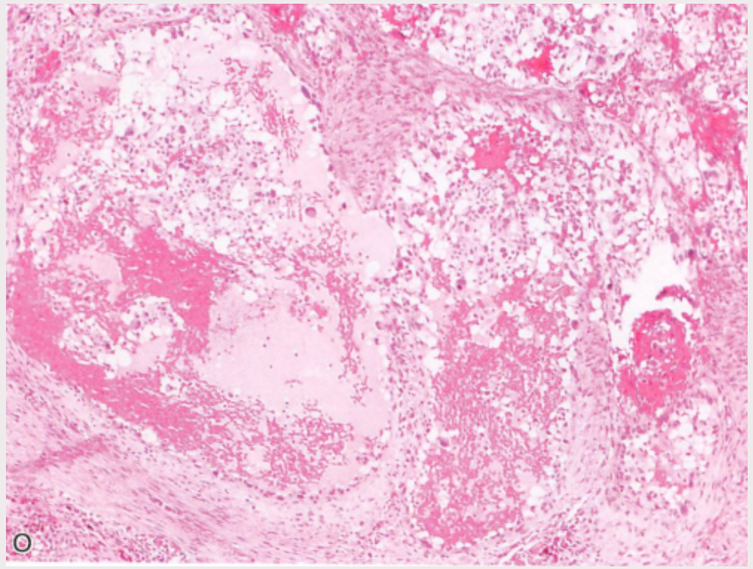
- Angiosarcoma is a malignant tumour that recapitulates the morphological and functional features of endothelium to a variable degree.
- 少见
- 老年人皮肤（头皮、面部）和软组织，也可见于骨、乳腺、心脏、肺、肝脏、脾脏及甲状腺等
- 形态上可有很大的差异
- 不规则血管腔相互吻合或沟通，呈浸润性或破坏性生长；
- 内皮细胞具有异型性

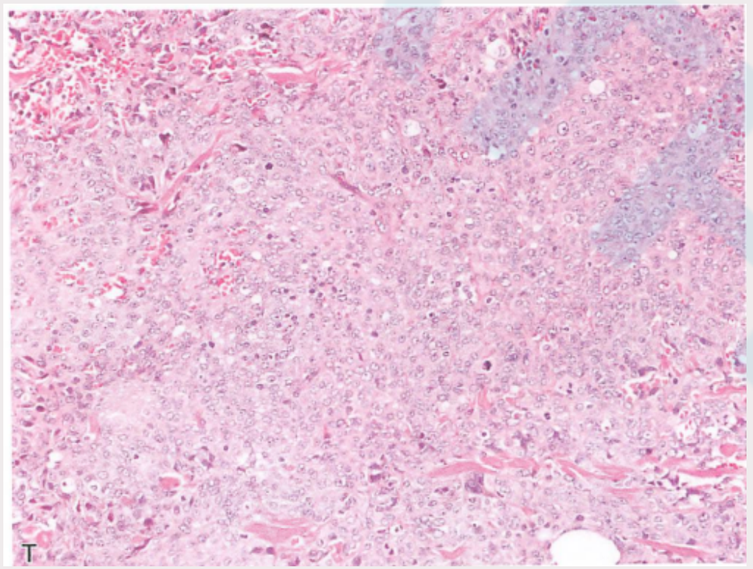
组织形态：不规则血管腔相互吻合或沟通

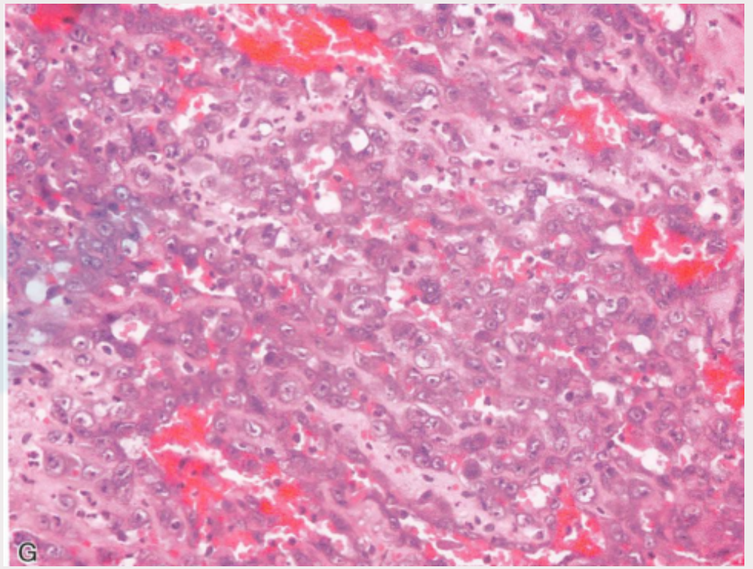










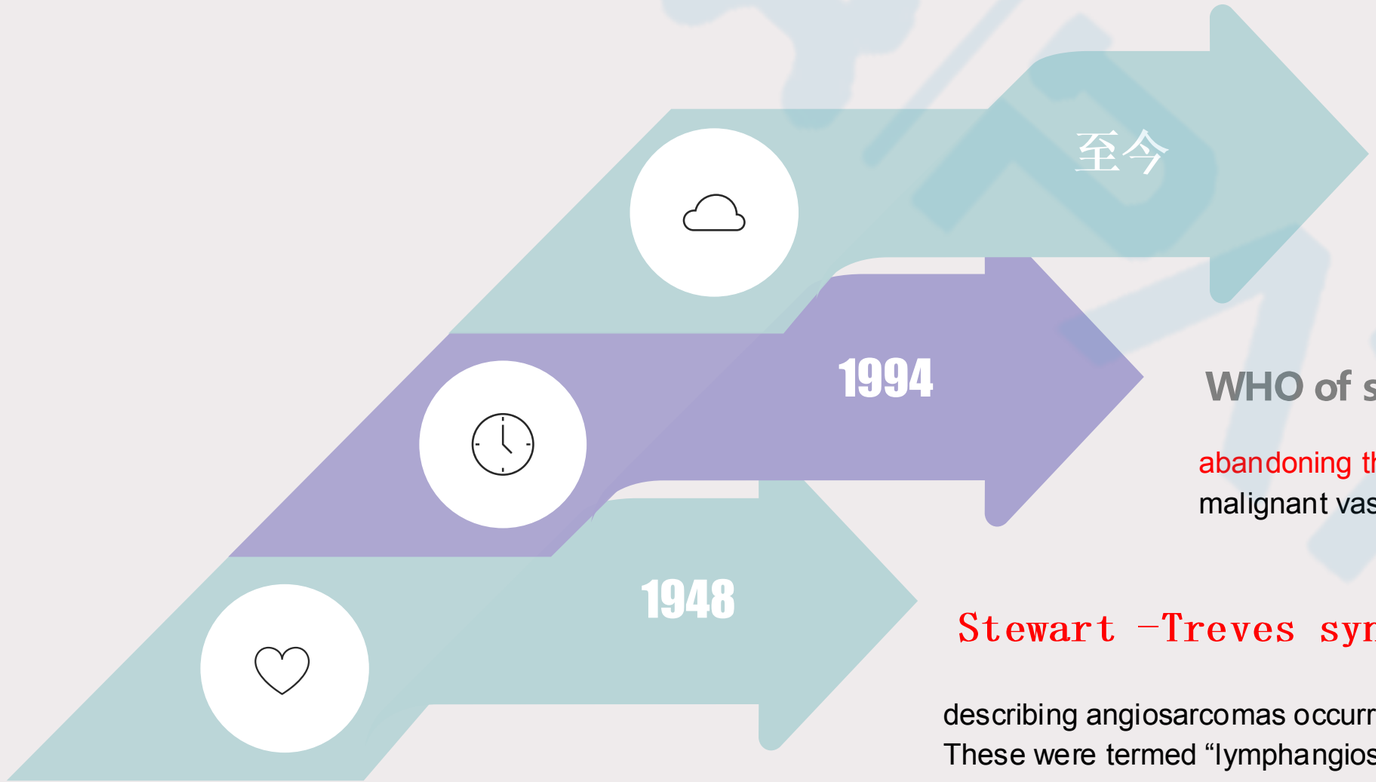


血管肉瘤

- 分类
  - 皮肤血管肉瘤不伴有肢体淋巴水肿：好发于头颈部，特别是头皮
  - 皮肤血管肉瘤伴长期肢体淋巴水肿：也称Stewart-Treves syndrome，曾被称为淋巴管肉瘤，90%的病例发生在乳腺癌根治术后
  - 深部软组织血管肉瘤
  - 乳房原发性血管肉瘤
  - 放疗相关性血管肉瘤：*MYC*基因扩增
  - 实质脏器血管肉瘤：心脏、脾脏、肝脏、胃、肺
  - 儿童和青少年血管肉瘤
- 免疫表型
  - 血管内皮标记物：CD31、CD34、ERG、Fli1
  - 少部分表达淋巴管内皮标记物：podoplanin、Prox-1（D2-40）

摘自王坚等《软组织肿瘤病理学》第2版

“lymphangiosarcoma (淋巴管肉瘤)”



Numerous biomarker studies

endothelial markers, lymphatic markers
Thus, the quest for a pure lymphatic-type angiosarcoma has been elusive. Whether such lesions exist or can be reliably separated morphologically and immunohistochemically from classic angiosarcoma remains unresolved.

WHO of soft tissue tumors, 2nd

abandoning the term “lymphangiosarcoma” altogether and using “angiosarcoma” for all malignant vascular tumors exclusive of Kaposi sarcoma.

Stewart -Treves syndrome

describing angiosarcomas occurring in the setting of postmastectomy lymphedema.
These were termed “lymphangiosarcomas” to distinguish them from the remainder believed to be derived from capillary endothelial cells and named “hemangiosarcoma.”

- Against this backdrop, we have observed a rare, but distinctive vascular tumor with growth characteristics of angiosarcoma, cytologic features of lymphatic differentiation (“hobnail” endothelium), a prominent lymphocytic infiltrate, and diffuse expression of a lymphatic marker (podoplanin [D2-40], Prox-1, or LYVE-1).

- This study details the clinicopathologic features of these tumors and explores the question of where they should be placed in the nosologic spectrum of vascular tumors.

MATERIALS AND METHODS

Case Selection

- the Emory University and Mayo Clinic
- from 1990 to 2017
- coded as “angiosarcoma” in which a prominent lymphocytic infiltrate
- coded as “atypical hobnail hemangioendothelioma”

- Slides were reviewed
  - angiosarcoma-like growth pattern (infiltrating, ramifying vessels),
  - cytologic features of lymphatic differentiation (cuboidal cells with high nuclear-cytoplasmic ratio, folded, or cleaved nuclei, occasional intranuclear inclusion),
  - a prominent intralesional or peripheral lymphocytic infiltrate,
  - diffuse expression of ≥1 lymphatic markers (podoplanin, PROX-1, LYVE-1).

- **“low grade”** , had focal architectural features (eg, elongated vessels) that at low power were reminiscent of retiform hemangioendothelioma (RHE).
  - Unlike the very uniform endothelial cells seen in RHE, the tumor cells were larger and more atypical. There was more piling up of endothelium within vessels and diffuse permeative growth.
- **“high grade”**, the tumor cells appeared frankly malignant with high-grade nuclear features and solid or medullary growth.

Immunohistochemistry

- podoplanin(D2-40),
- Prox-1,
- LYVE-1,
- CD31,
- CD34 ,
- Synaptophysin ,
- CD4 ,
- CD8,
- PDL-1 (SP263; Ventana).
  - PDL-1 was considered positive when there was membranous staining of >5% of tumor cells.

Molecular Genetics

- RNA sequencing: gene fusions and variant transcript detection
- Next-generation sequence: mutational analysis targeting 592 whole-gene
- Copy number variation: comparing the depth of sequencing of genomic loci to a diploid control as well as the known performance of these genomic loci.

RESULTS

Clinicopathologic Features

- 21 patients
- 12 males and 9 females (ratio=1.3:1)
- All lesions were located superficially in the dermis and/or subcutis
- 2 cases were associated with a preexisting postirradiation atypical vascular lesion (AVL).
  - laryngeal cancer
  - breast cancer

TABLE 1. Lymphatic-type Angiosarcoma Clinicopathologic Features

Features	n/N (%)
Age, median (range) (y)	65 (32-95)
Sex	
Male	12/21 (58)
Female	9/21 (43)
Site	
Head and neck	11/21 (53)
Lower extremity	5/21 (24)
Trunk	4/21 (19)
Upper extremity	1/21 (5)
Size, mean (range) (cm)	3 (0.8-8.5)
Depth	
Dermis only	10/21 (48)
Dermis and Subcutis	11/21 (53)
History of lymphedema	3/21 (14)
Preexisting AVL	2/21 (10)
MYC amplification	0/2 (0)
Cytology	
Low grade	10/21 (48)
High grade	11/21 (53)
Lymphatic immunophenotype	
Podoplanin	17/19 (89)
Prox-1	11/11 (100)
LYVE-1	5/10 (50)
PDL-1 positive	5/16 (31)
Follow-up, median (range) (mo)	41 (10-131)
ANED	10/17 (59)
AWD	5/17 (29)
DOD	1/17 (6)
DOC, NED	1/17 (6)
Local recurrence	9/17 (53)
Metastasis	2/17 (12)

ANED indicates alive no evidence of disease; AWD, alive with disease; DOC, died of other cause; DOD, died of disease.

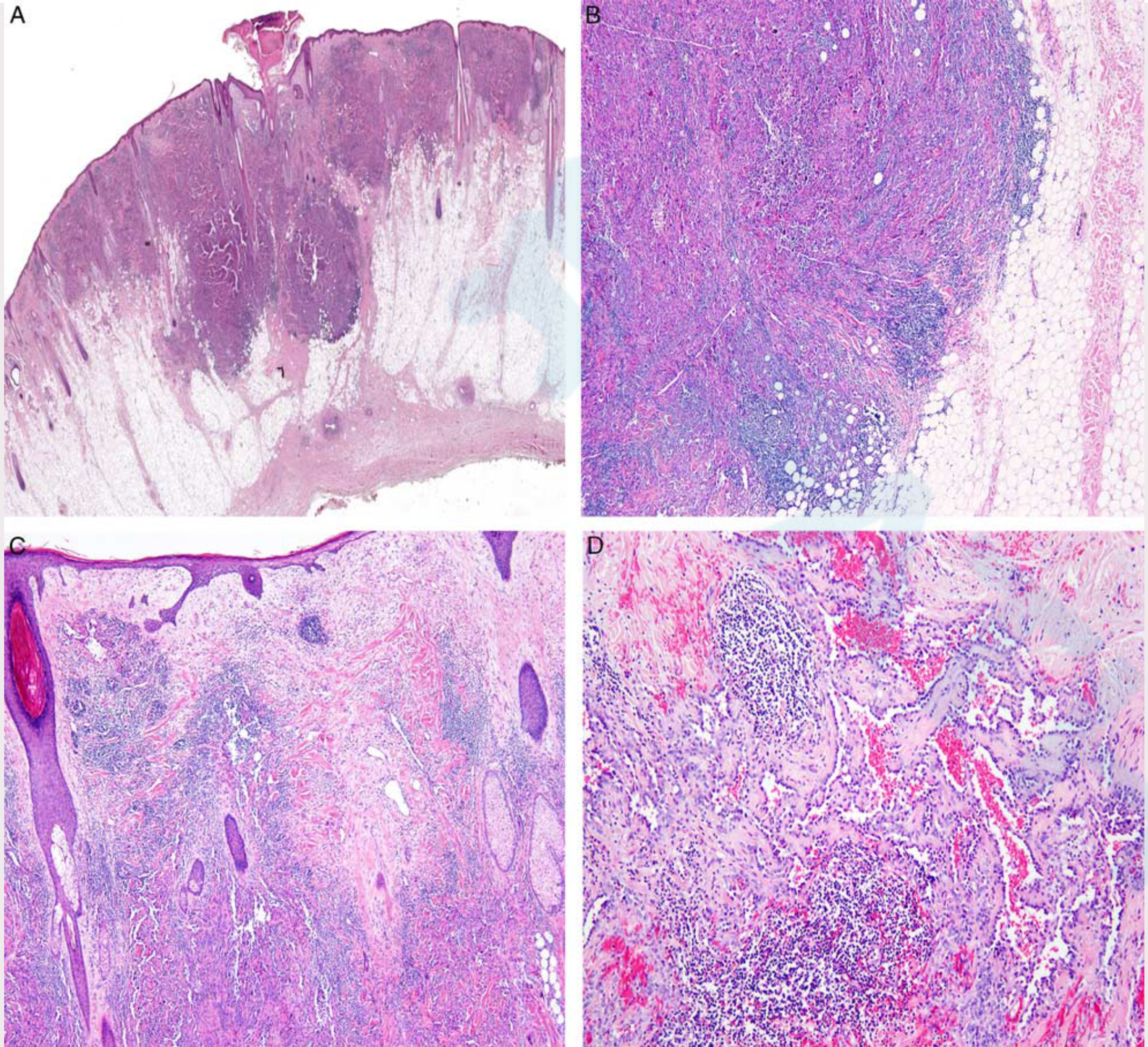


FIGURE 1. Low power view showing the deceptive pushing border (A) of many tumors and the dense, surrounding lymphocytic infiltrate (B). However, tumors actually grow in an infiltrative (C, D) pattern with ramifying vessels (D).

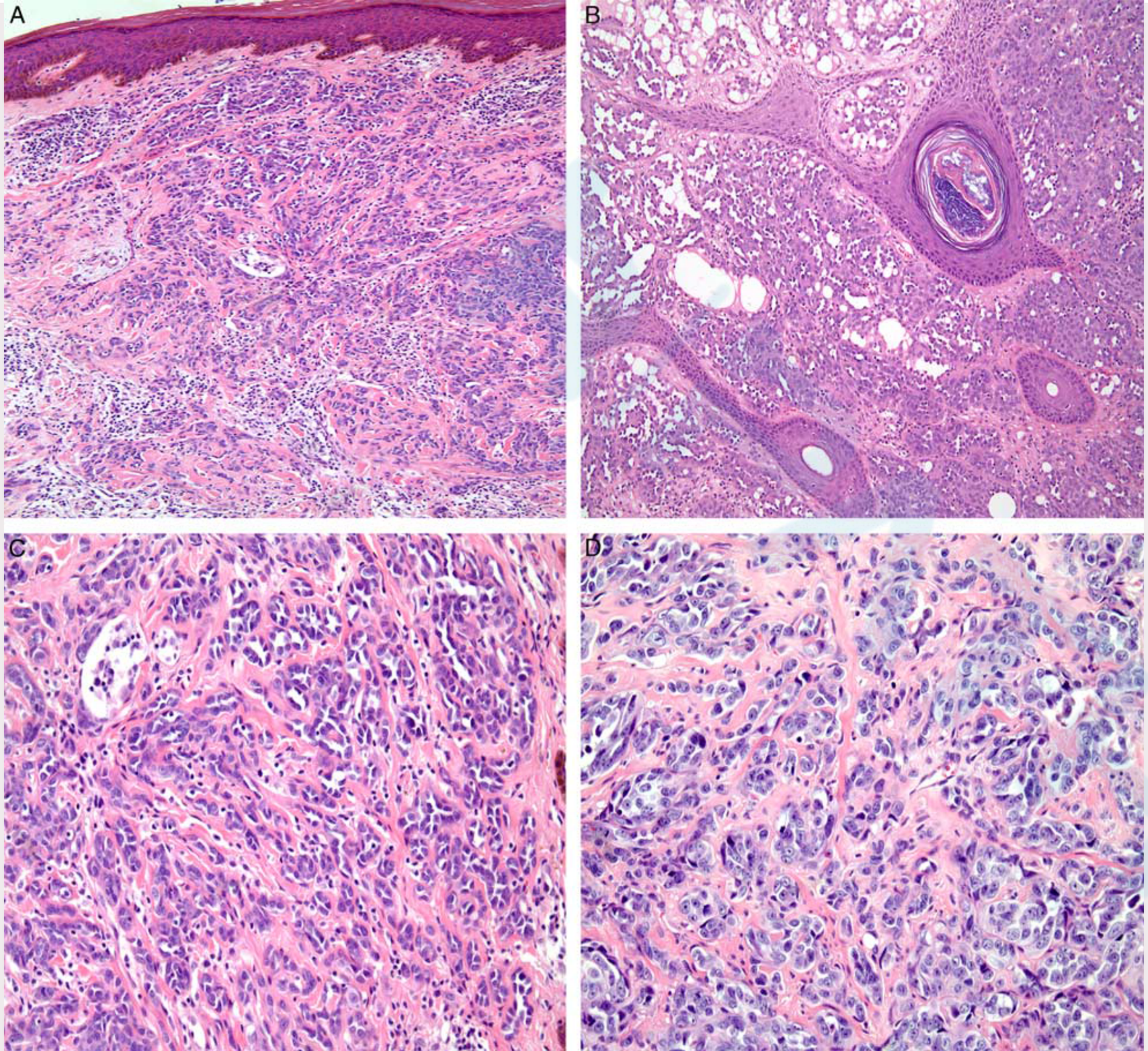


FIGURE 2. Case showing the spectrum of changes within the same tumor. Areas resembling hobnail hemangioendothelioma (A, C) consisting of attenuated vessels flanked by hyaline fibrosis blend with those having an irregularly ramifying pattern of vessels (B) with cells of higher nuclear grade (D).

“low-grade” tumor

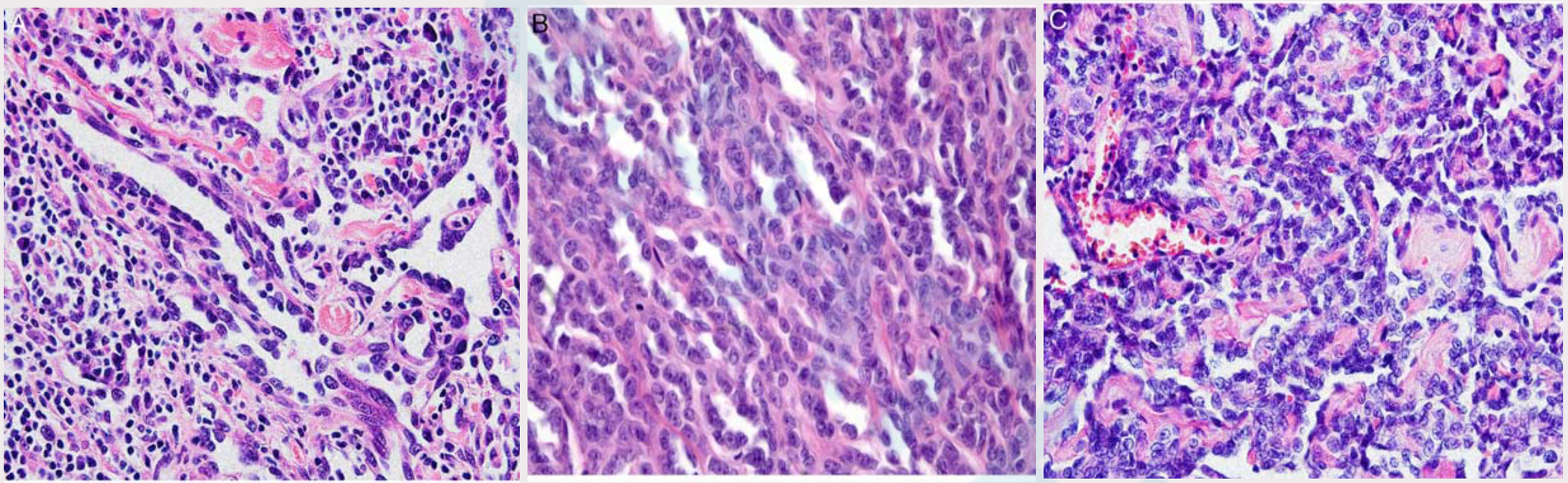


FIGURE 3. Example of a **“low-grade” tumor** with areas showing obvious vascular channel formation (A). In other areas, vascular channel formation is more subtle but the cells have hobnail endothelial features (B). In still other areas there is more piling up of endothelium in vessels (C).

“high-grade” tumor

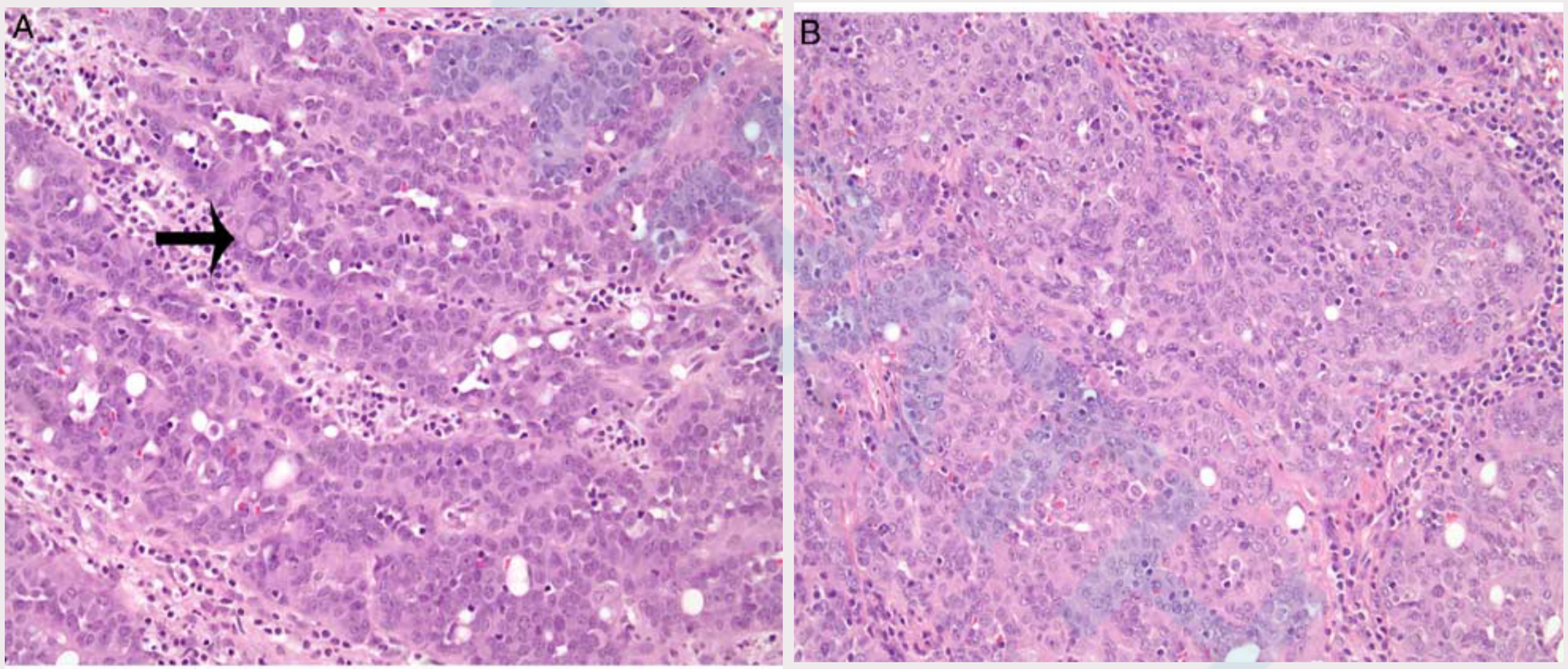


FIGURE 4. Example of “high-grade” tumor (A, B). The tumor grows in nests and sheets but cells typically retain cytologic features of hobnail endothelium including high nuclear-cytoplasmic ratio and intranuclear inclusions (arrow). The cells, however, never achieve the level of atypia of classic high-grade angiosarcoma.

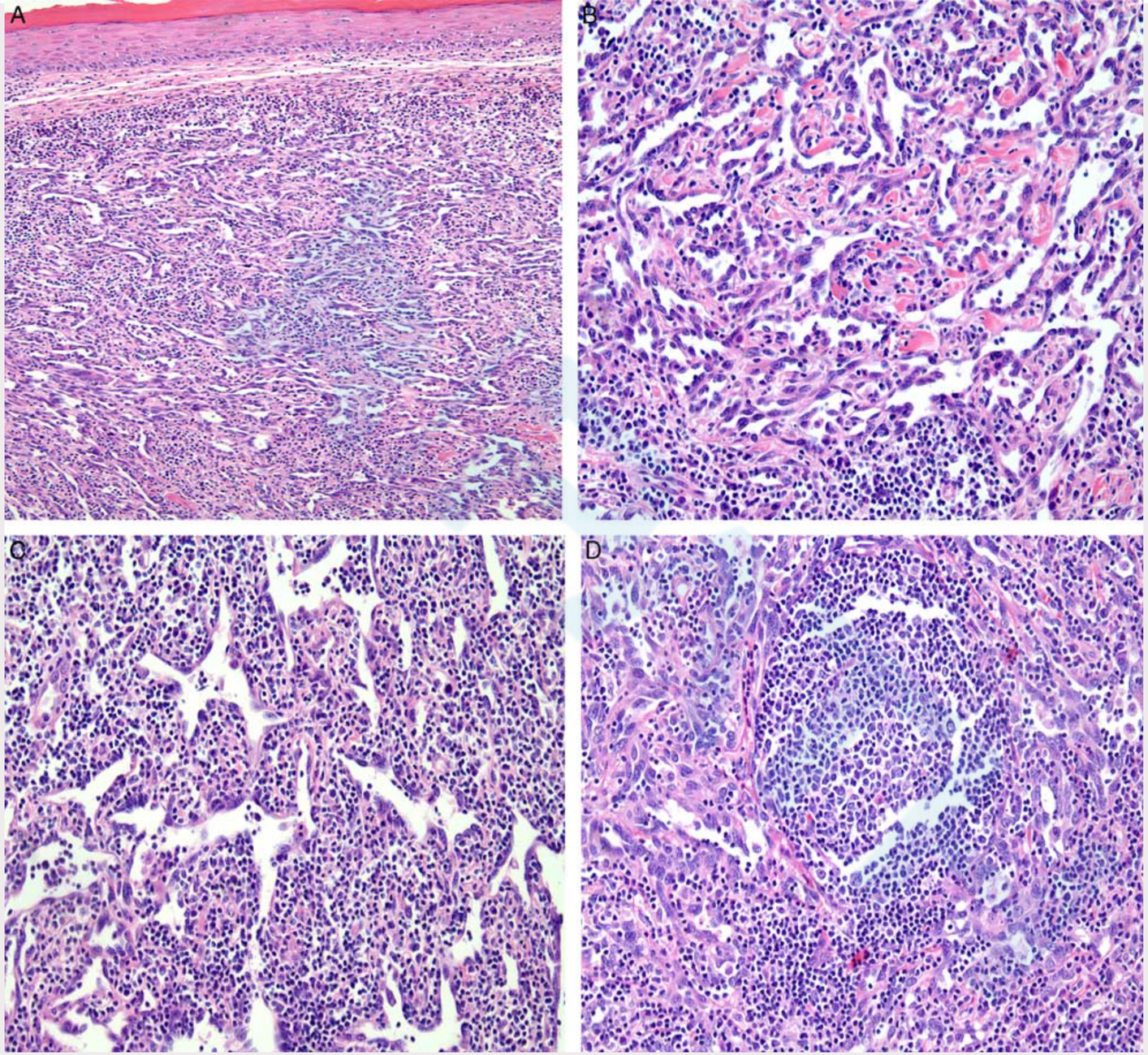


FIGURE 5. All cases had a striking lymphocytic infiltrate (A). Lymphocytes were present both within (B) and outside (C) vessels. Germinal centers were occasionally seen in the tumors (D).

Immunohistochemistry

Lymphatic immunophenotype

•All cases expressed at least 1 lymphatic marker (21/21; 100%).

•Podoplanin 17/19 (89)

•Prox-1 11/11 (100)

•LYVE-1 5/10 (50)

PDL-1 positive 5/16 (31)

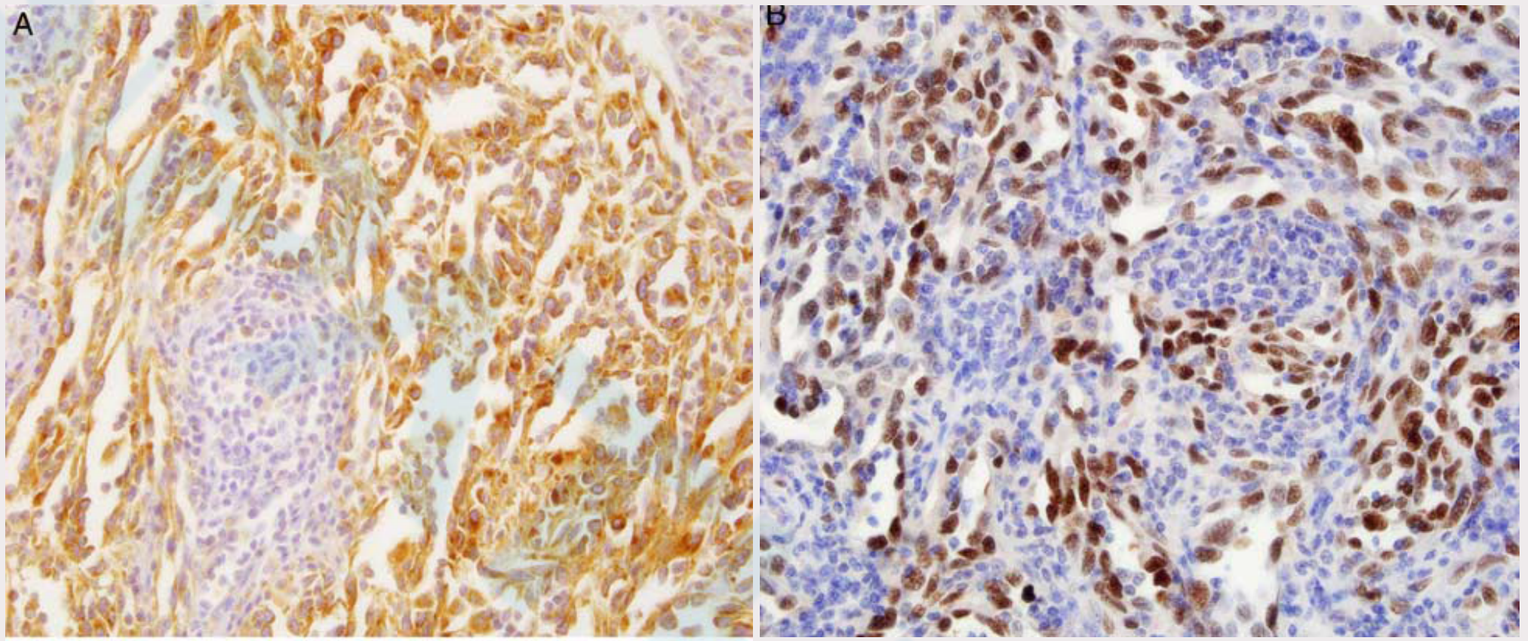


FIGURE 6. Nearly all tumors strongly and diffusely expressed podoplanin (D2-40) (A), and all tested expressed PROX-1 (B).

Molecular Genetic Analysis

TABLE 2. Lymphatic-type Angiosarcoma Molecular Results

Case No.	Mutation	Amplification
3	Indeterminate (low-quality DNA)	Indeterminate
4	*TP53* c.403delT [C135fs]; *POT1* c.1682delA [D561fs]	*CRKL; SMARCB1; CLTCL1*; BCR
5	*NRAS* c.64C > A [Q22K]	*MYC*
8	Indeterminate (low-quality DNA)	Indeterminate
14	QNS	QNS

QNS indicates quantity not sufficient.

Cases: 5

Case 4 showed a *POT1* pD561fs mutation involving exon 17, a *TP53* p.C135fs mutation involving exon5 and CRKL amplification.

Case 5 showed an NRAS p.Q22K mutation on exon 2 as well as MYC amplification.

TABLE 3. Lymphatic-type Angiosarcoma "High-grade" Cases

Case No.	Age (y)	Sex	Location	Size (cm)	Depth	Treatment	LR	Met	Status	F/U (mo)
1	NA	M	Face	NA	Subcutis	NA	NA	NA	NA	NA
4	76	M	Right face	1	Dermis	WLE+RT	Y	N	AWD	16
5	57	F	Suprapubic/left groin	2.4	Subcutis	WLE+CT	N	N	ANED	114
6	36	M	Left thigh	3	Subcutis	WLE+RT	N	N	ANED	131
7	82	M	Knee	NA	Subcutis	WLE	N	N	ANED	25
9	73	F	Forehead	NA	Subcutis	WLE+CT+RT	N	N	ANED	10
12	89	M	Scalp	2.5	Subcutis		NA	NA	NA	NA
15	53	M	Back	0.8	Dermis	WLE	Y	N	AWD	49
16	68	M	Face	NA	Dermis	WLE	NA	NA	NA	NA
18	68	F	Right temporal(头皮右颞部)	3.5	Subcutis	WLE	Y	Y	DOD	76
19	57	F	Left chest	8.5	Subcutis	WLE+CT	Y	N	AWD	96
11 cases	(36-89)	(7M4F)	头面部 6例	(0.8~3.5)	皮下组织	局部扩大切除术	4例复发	1例转移	1例死于疾病	edian: 63

ANED indicates alive no evidence of disease; AWD, alive with disease; BKA, below-knee amputation; CT, chemotherapy; DOD, died of disease; F, female; F/U, follow-up; HG, high grade; LR, local recurrence; M, male; Met, metastasis; N, no; NA, not available; RT, radiotherapy; WLE, wide local excision; Y, yes.

TABLE 4. Lymphatic-type Angiosarcoma Low-grade Cases

Case No.	Age (y)	Sex	Location	Size (cm)	Depth	Treatment	LR	Met	Status	F/U (mo)
2	41	F	Right lower leg	1.9	Subcutis	BKA+CT	Y	N	ANED	87
3	60	F	Left thigh	NA	Dermis	WLE	N	N	ANED	54
8	95	M	Right anterior orbital	NA	Subcutis	WLE	N	N	ANED	10
10	72	F	Right breast	4.5	Dermis	WLE	N	N	ANED	11
11	50	M	Left periepiglottic fold	NA	Dermis	NA	Y	NA	NA	NA
13	61	M	Right nasal tip	NA	Dermis	WLE+CT	Y	N	ANED	36
14	89	M	Scalp	NA	Dermis	WLE+RT	N	N	DOC, NED	16
17	49	F	Wrist	1.8	Subcutis	WLE+CT	Y	Y	AWD	126
20	32	M	Left thigh	3.1	Dermis	WLE	N	N	ANED	18
21	86	F	Left nasal rim	NA	Dermis	WLE+CT	Y	N	AWD	41
10 cases	(32-89)	(5M5F)	头面部 5例	(1.8~4.5)	真皮	局部扩大切除术	5例复发	1例转移	1例死于其他疾病	dian: 36

ANED indicates alive no evidence of disease; AWD, alive with disease; BKA, below-knee amputation; CT, chemotherapy; DOC, died other cause; F, female; F/U, follow-up; LG, low grade; LR, local recurrence; M, male; Met, metastasis; N, no; NA, not available; RT, radiotherapy; WLE, wide local excision; Y, yes.

DISCUSSION

“lymphangiosarcoma”

- Stewart and Treves first described “lymphangiosarcoma” in 1948 as a sequela of postradical mastectomy lymphedema. Initially quite popular, this term was abandoned since, with the exception of the underlying lymphedema, these “lymphangiosarcomas” were morphologically similar to classic angiosarcoma.
- The distinction was further blurred by the observation that angiosarcoma in general can express lymphatic markers to a variable (but usually minor) degree leading to the conclusion that they have a mixed or indeterminate phenotype.

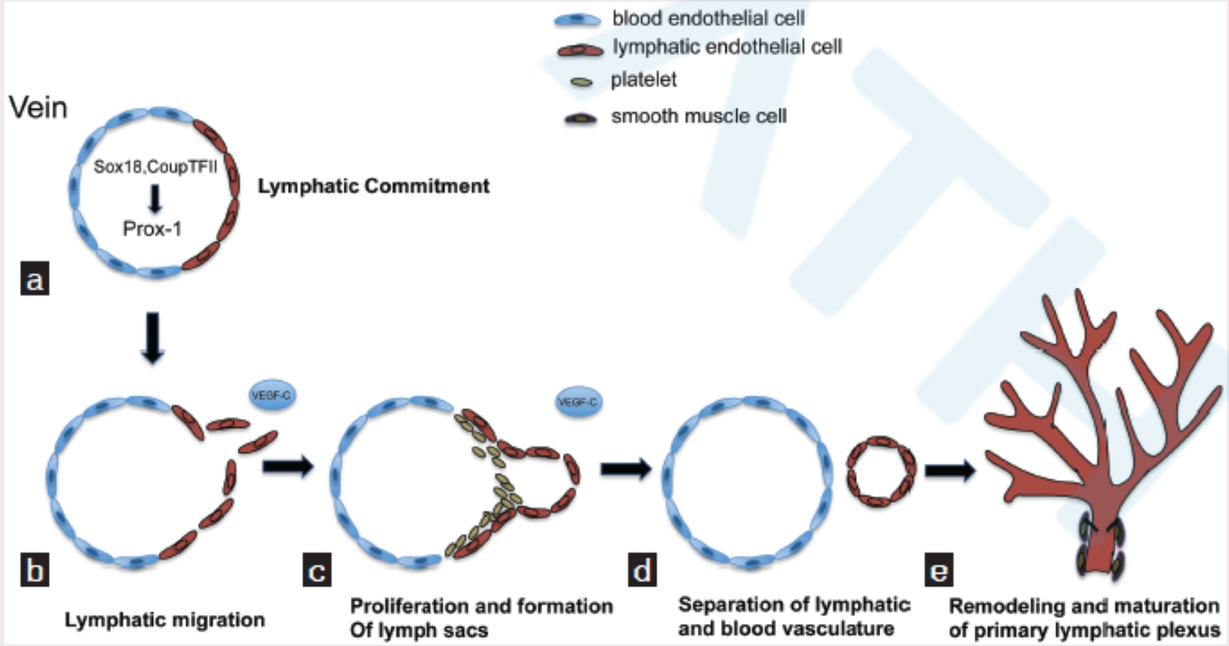
Lymphatic-type “Angiosarcoma”

- In this study, we report a subset of reproducibly recognized angiosarcomas which we believe are lymphatic based on
- (1) cytologic features traditionally associated with lymphatic differentiation (hobnail endothelium) as seen in certain lymphatic tumors (eg, RHE)
  - slightly elongated vessels lined by hobnail endothelium
  - the majority of the tumors had vessels of more complex arrangement, multilayering of atypical endothelial cells (some of which appeared frankly malignant), features associated with angiosarcoma.

- (2) the presence of a dense peritumoral and intraluminal lymphocytic infiltrate
  - composed of a relatively equal portion of CD4 and CD8 T cells. In a few cases, the vessels were filled with lymphocytes to the virtual exclusion of other cell types, recapitulating the close relationship between lymphatic vessels and lymphocytes in the normal setting.

“lymphatic-type angiosarcomas,” VS “lymphangiosarcomas,”

- (3) expression of multiple lymphatic markers, and whose natural history appears to be more indolent than that of conventional angiosarcoma.



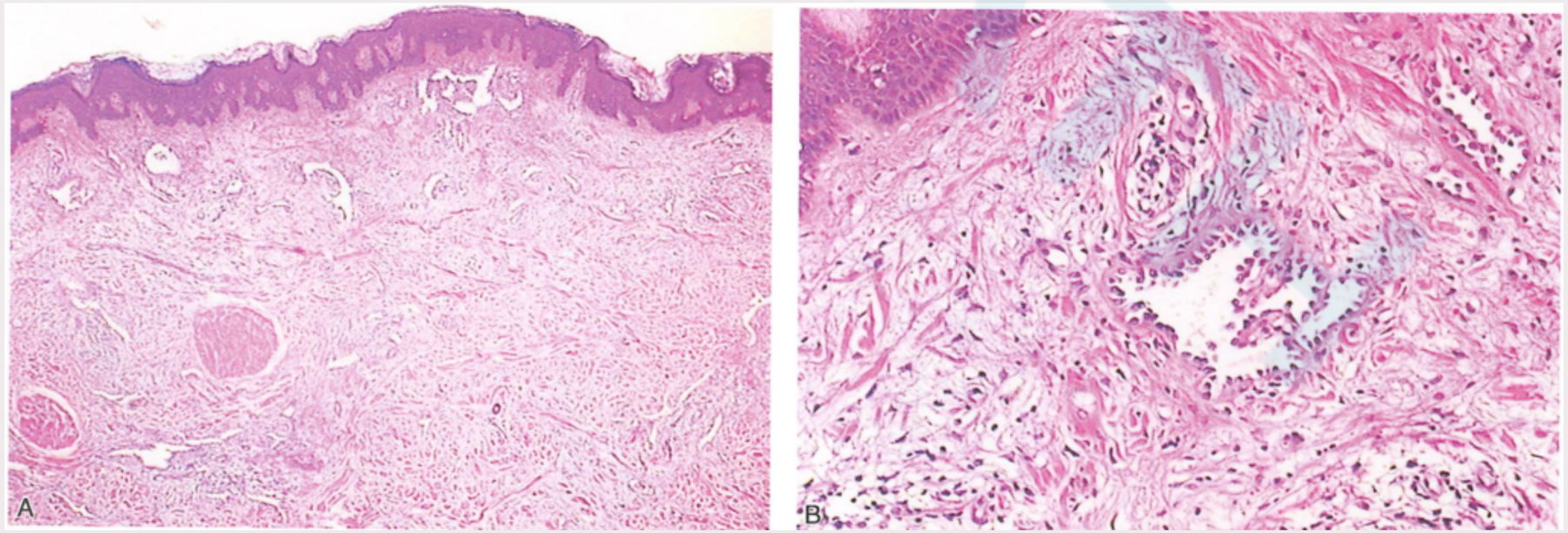
J Cardiovasc Dis Res. 2011 Jul-Sep; 2(3): 141 - 152.

Where they fall in the nosologic classification of vascular tumors ?

- angiosarcomas: the classic angiosarcoma-like pattern of ramifying vessels infiltrating adjacent structures and the level of atypia (nucleomegaly, prominent nucleoli).
- differ from classic angiosarcoma: they affect a broader age range of patients, invariably present as a unifocal masses, and appear to have a much better prognosis.
  - one half recurred, only 2 patients developed metastases
  - Angiosarcomas have recurrence rates of 70% to 80% and 5-year survival of 30% to 40%.
  - the high-grade group versus the low-grade group showed essentially similar outcomes, suggest that these lesions are more indolent than conventional angiosarcoma

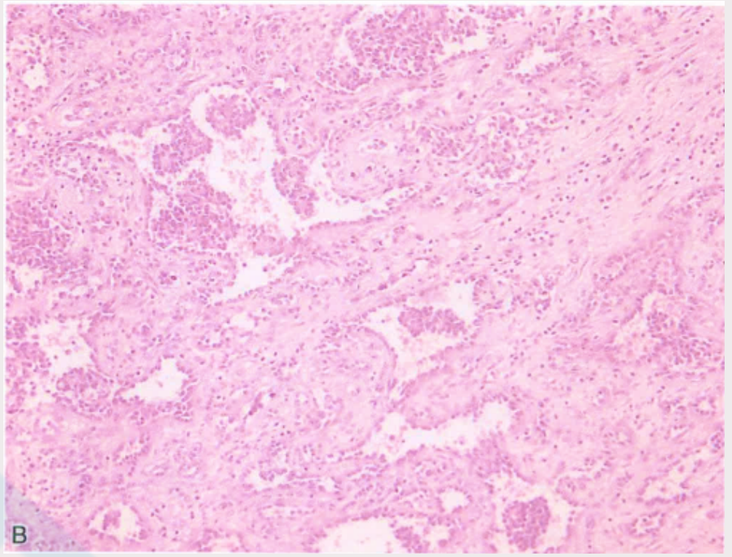
鉴别诊断-鞋钉样血管瘤

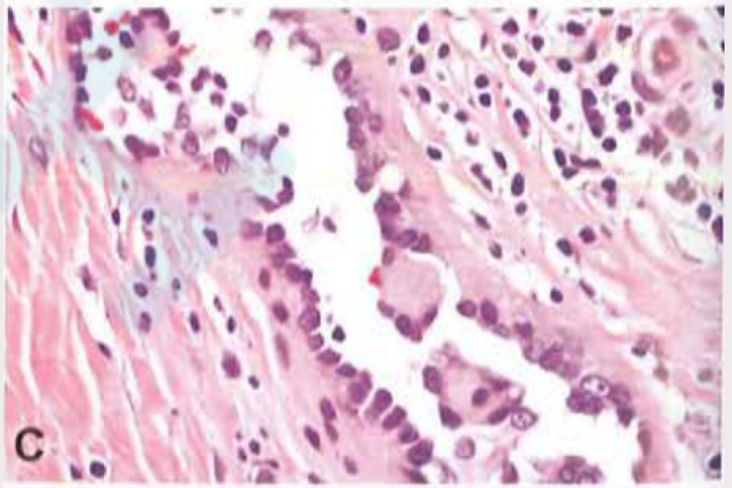
- 良性肿瘤，好发于年轻人
- 近半数发生于下肢，特别是大腿和臀部
- 病变位于真皮层，呈双相性的生长
- 鞋钉样内皮细胞表达CD31、CD34、D2-40



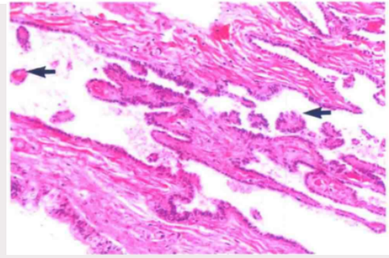
鉴别诊断-乳头状淋巴管内血管内皮瘤
(Papillary intralymphatic angioendothelioma)

- 又称Dabska瘤
- 主要发生于儿童，部分发生于血管畸形、慢性淋巴水肿和局限性淋巴管瘤的基础上
- 由大小不一、形态不规则的扩张性薄壁脉管组成，腔内内皮细胞呈乳头状排列，表面衬覆鞋钉样内皮细胞，中央为玻璃样变性的轴心
- 内皮细胞表达CD31、CD34，多数表达D2-40和VEGFR3
- 缺乏多层结构的内皮，未见高级别核的细胞，以及弥漫浸润性生长

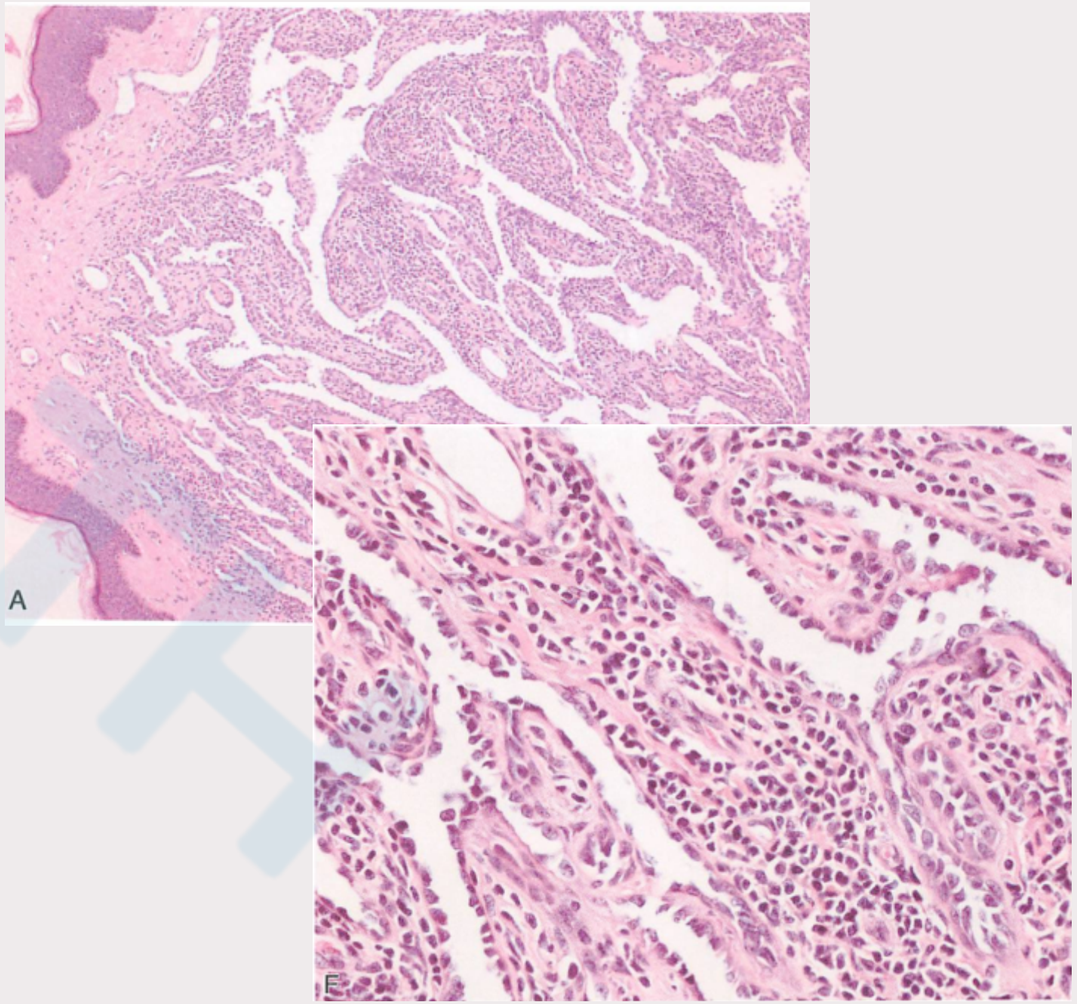




鉴别诊断-网状血管内皮瘤
Reliform haemangioendothelioma，RH



- 多见于中青年
- 好发于四肢远端
- 由细长的分支状血管组成，形成特殊的网状结构，类似于人体正常的睾丸网
- 内皮细胞单层排列，似鞋钉样，无异型性及核分裂象
- 偶可见条索状、梁索状或实性结构
- 血管周围淋巴细胞浸润，伴有胶原化
- 缺乏多层结构的内皮，未见高级别核的细胞，以及弥漫浸润性生长



In summary

- we have described a distinctive subset of angiosarcomas showing clinical, morphologic, and immunohistochemical features of lymphatic endothelial differentiation for which we propose the term “lymphatic-type angiosarcoma.”

- Although these tumors have some morphologic features reminiscent of RHE, they have significant differences as well as a more aggressive course.

- On the basis of clinical follow-up to date, the natural history of lymphatic-type angiosarcoma appears to be more favorable than other forms of cutaneous angiosarcoma.

Thanks