西京医院 XIJING HOSPITAL

PATH
第四军医大学病理学教研室
DEPARTMENT OF PATHOLOGY
FOURTH MILITARY MEDICAL UNIVERSITY

PRDM10-rearranged Soft Tissue Tumor

A Clinicopathologic Study of 9 Cases

Florian Puls, MD, FRCPath, Nischalan Pillay, MB, ChB, FRCPath, PhD,†‡*
Henrik Fagman, MD, PhD, Anne Palin-Masreliez, BSc,* Fernanda Amary, MD, PhD,†*
Magnus Hansson, MD, PhD, Lars-Gunnar Kindblom, MD, PhD,**
Tom A. McCulloch, BM, BS, FRCP, FRCPath,§ George Meligonis, MBBCh, FCPath(SA),‖
*Ronald Muc, MBBCh, FRCPath,¶ Pehr Rissler, MD, PhD,# Vaiyapuri P. Sumathi, FRCPath,***
Roberto Tirabosco, MD,† Jakob Hofvander, MSc,†† Linda Magnusson, MSc,††
Jenny Nilsson, MSc,†† Adrienne M. Flanagan, MB, BCh, PhD, FRCPath,†‡
and Fredrik Mertens, MD, PhD#††

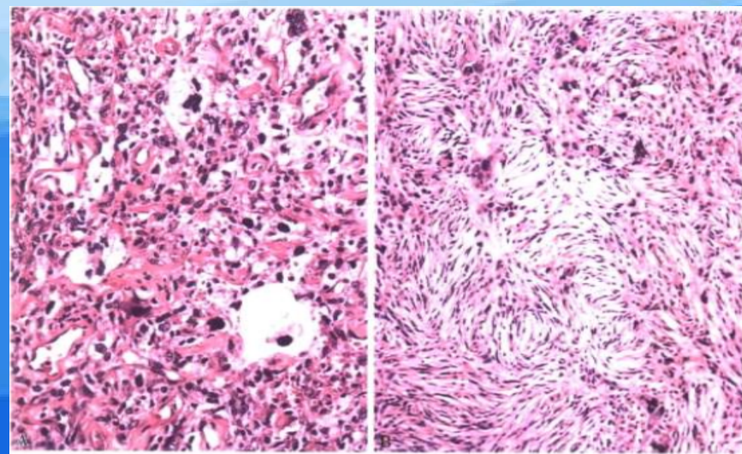
汇报人：徐梦微

西京医院 病理科

BACKGROUND

undifferentiated pleomorphic sarcomas (UPS)

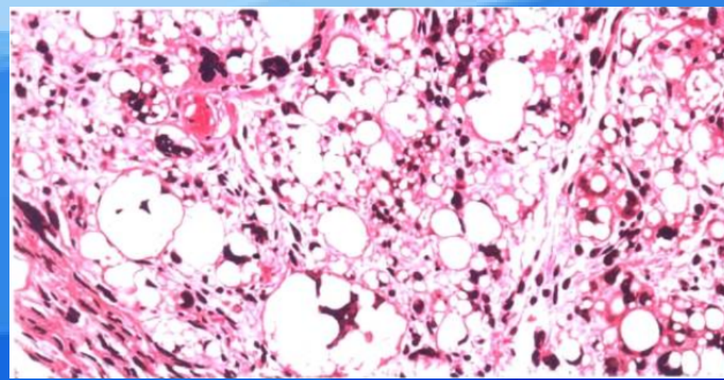
- ICD-O编码：8830-3
- 男：女=1.2：1；中老年多见；好发于四肢、躯干、腹膜后。
- 肿瘤多位于深部组织，常为孤立性结节，无包膜，浸润性生长，常伴出血、坏死和囊性变。
- 镜下：瘤细胞呈现多形性和异型性。瘤细胞包括纤维母细胞、组织细胞、泡沫状组织细胞、杜顿巨细胞、破骨样多核巨细胞、未分化原始间充质细胞、具有含铁血黄素的巨噬细胞和炎细胞，并可见奇异形巨细胞。瘤细胞排列成旋涡状、席纹状、束状或弥漫分布。



BACKGROUND

pleomorphic liposarcoma

- ICD-O编码：8854-3
- 是一种多形性的高度恶性肉瘤，含有数量不等的多形性脂肪母细胞，非典型性脂肪肉瘤(高分化脂肪肉瘤)和其他分化区域。
- 好发于四肢，较少见于躯干和腹膜后。
- 大多位于深部软组织，也可位于皮下；质硬，为多结节状，切面白色至黄色，可见黏液样区域和坏死区域。
- 肿瘤由多形性梭形肿瘤细胞和束状排列的较小的圆形细胞构成，混杂有多核巨细胞和多形性多空泡脂肪母细胞(奇异型核，染色质深）。常见细胞内和细胞外嗜酸性透明小滴。



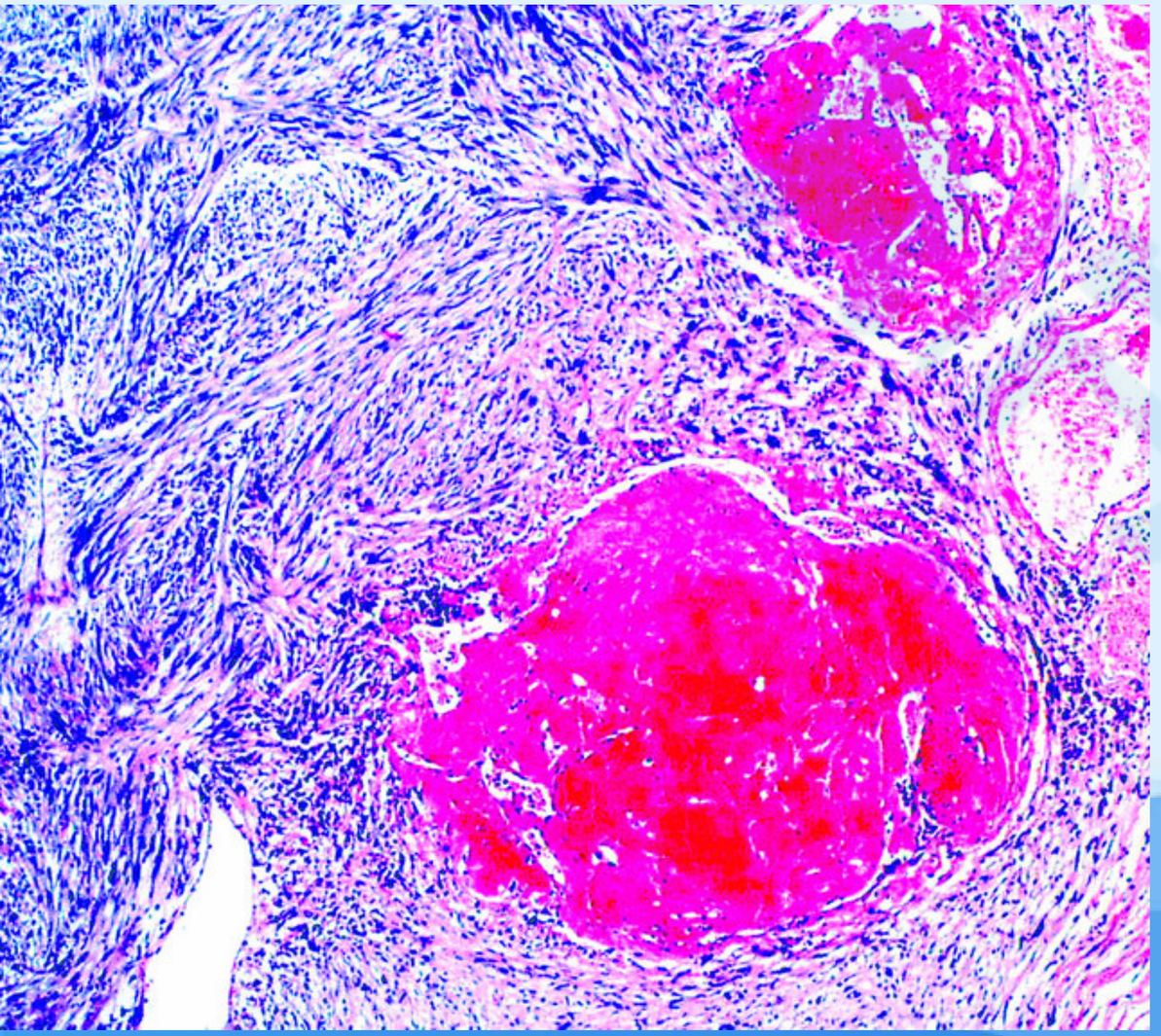
BACKGROUND

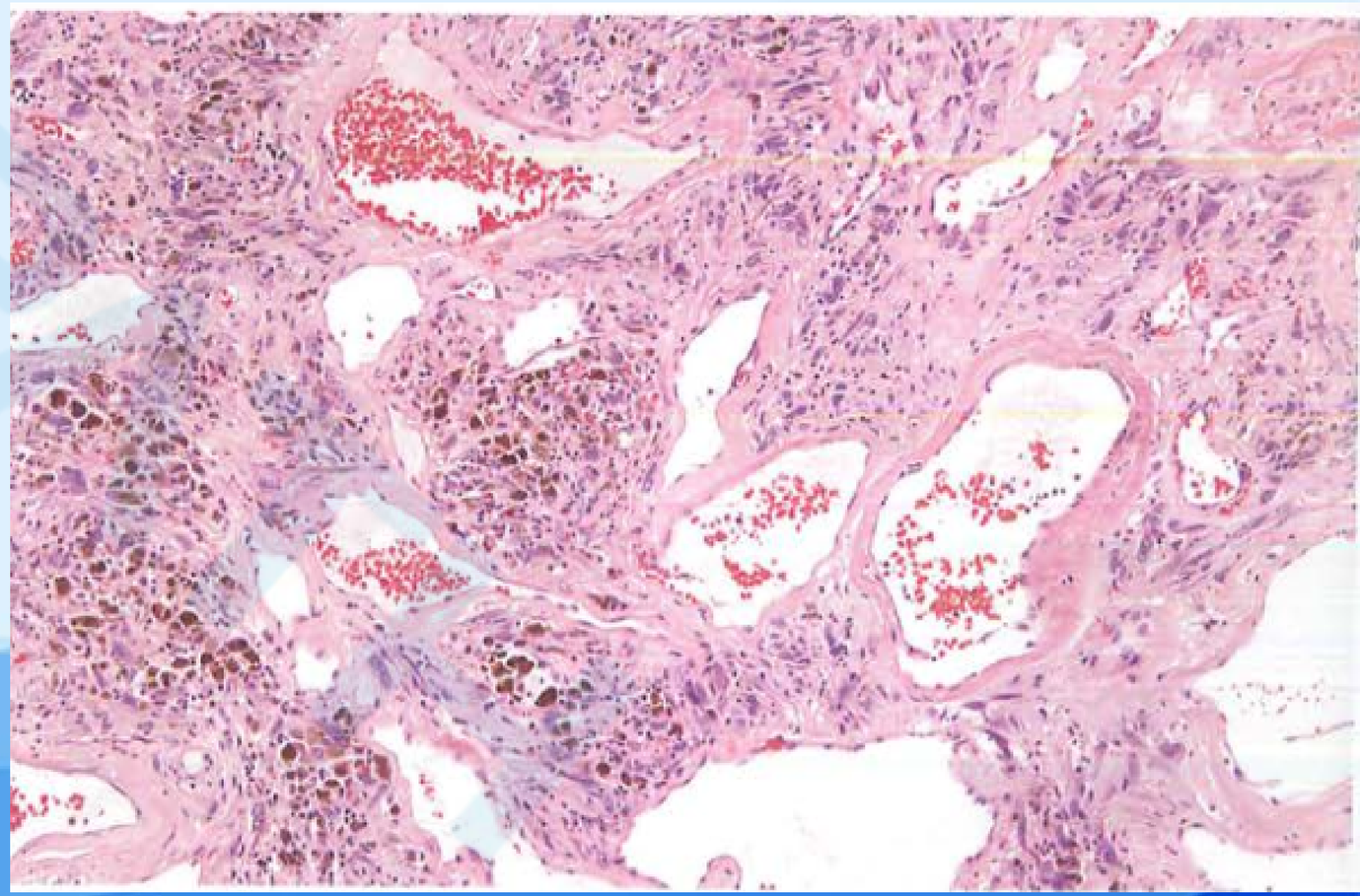
pleomorphic hyalinizing angiectatic tumor（PHAT）

多形性玻璃样变血管扩张性肿瘤

- ICD-O编码：8802-1
- 一种分类尚未确定的非转移性肿瘤，含有扩张的、血管壁有明显纤维素沉着的薄壁血管簇，血管簇周围有惰性分化的多形性梭形肿瘤性间质细胞，含有不同程度炎性成分。
- 成人低度恶性肿瘤（中位年龄51岁）；好发于四肢、躯干。分叶状浸润性生长，浅棕色至栗色。
- 镜下：整个片状增生的梭形细胞病变中散在薄壁扩张的血管。血管内皮细胞下方有一层厚的无定形玻璃样物质将肿瘤细胞包围并形成间质玻璃样变区，血管内常有机化血栓，间质细胞梭圆形或圆形，有深染的多形性核，核分裂象少(<1/50HPF)，肿瘤内可有数量不等的肥大细胞、淋巴细胞、浆细胞和嗜酸性粒细胞浸润。
- IHC:CD34(+)、Vim(+)

BACKGROUND





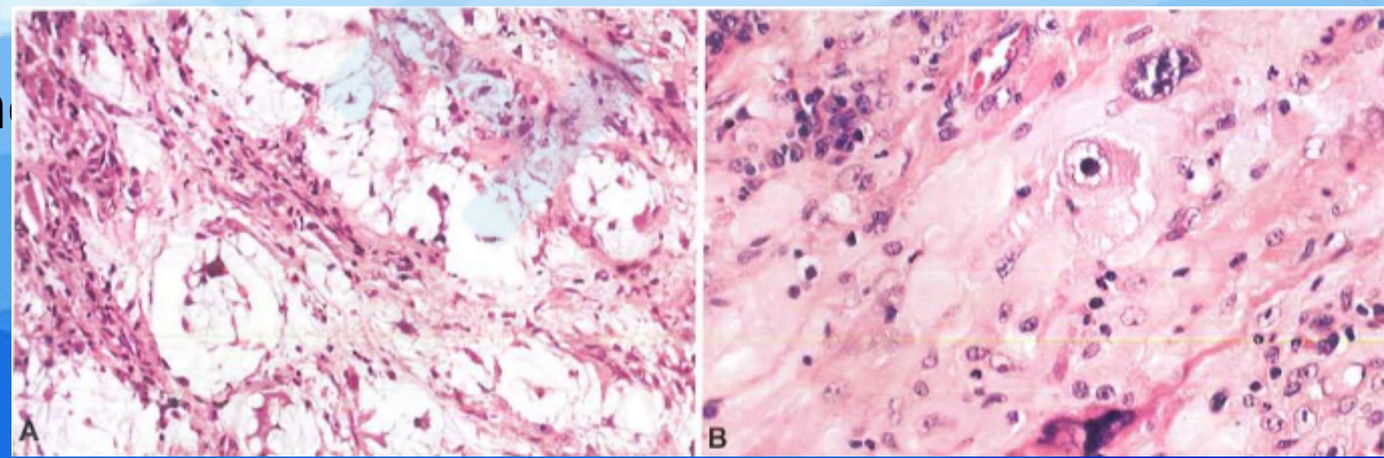
BACKGROUND

superficial CD34-positive fibroblastic tumor (SCD34FT)

•a rare mesenchymal neoplasm of borderline malignancy.
•located in the dermis and extended into the subcutis.
•The tumor was composed of spindle to polygonal cells with pleomorphic nuclei arranged in a sheet-like or fascicular pattern.
• Immunohistochemical examination revealed that the tumor cells were strongly positive for CD34.

myxoinflammatory fibroblastic sarcoma(MIFS)

•Rare low grade sarcoma of hands and feet with myxoid stroma, inflammation and virocyte-like cells .
•Also called inflammatory myxohyalin
virocyte or Reed-Sternberg-like cells,
sarcoma.



BACKGROUND

PRDM10

- The protein encoded by this gene is a transcription factor that contains C2H2-type zinc-fingers.
- PRDM10 (PR/SET Domain 10) is a Protein Coding gene. Diseases associated with PRDM10 include Undifferentiated Pleomorphic Sarcoma and Diffuse Idiopathic Skeletal Hyperostosis.

Hofvander J, Tayebwa J, Nilsson J, et al. Recurrent PRDM10 gene fusions in undifferentiated pleomorphic sarcoma. Clin Cancer Res. 2015;21:864–869.

Clinical Cancer Research

Recurrent *PRDM10* Gene Fusions in Undifferentiated Pleomorphic Sarcoma

Jakob Hofvander[1], Johnbosco Tayebwa[1], Jenny Nilsson[1], Linda Magnusson[1], Otte Brosjö[2], Olle Larsson[3], Fredrik Vult von Steyern[4], Nils Mandahl[1], Christopher D.M. Fletcher[5], and Fredrik Mertens[1]

约5%的UPS存在PRDM10融合,涉及转录因子PRDM10作为3’伴侣，MED12或CITED2作为5’伴侣基因。形态学分级较低，无一例出现转移。因此，PRDM10融合阳性肉瘤可能构成UPS的一个重要临床亚型。

Abstract

Purpose: Undifferentia…*D12* or *CITED2* as the 5′ defined as a sarcoma with… soft tissue sarcomas for tifiable line of differentiat… revealed one more UPS with a metastatic rate of… of these genes has been rearrangement has been id… fusions before. be used for treatment str… at *PRDM10* fusions are transcriptome sequencing … ough the fusion-positive fusions.

Experimental design: RNA-Seq, FISH, and/or various PCR methodologies were used to search for gene fusions and rearrangements of the *PRDM10* gene in 84 soft tissue sarcomas.

Results: Using RNA-Seq, two cases of UPS were found to display novel gene fusions, both involving the transcription factor … nuclear pleomorphism and lack of differentiation as other UPS, it is noteworthy that all three were morphologically low grade and that none of the patients developed metastases. Thus, *PRDM10* fusion-positive sarcomas may constitute a clinically important subset of UPS.

Clin Cancer Res; 21(4); 864–9.

MATERIALS AND METHODS

Cases

Sahlgrenska University Hospital Gothenburg, Sweden

- low-grade UPS
- PHAT
- MIFS
- SCD34FT
- pleomorphic liposarcoma

PRDM10 IHC(RE7116,Novocastra, Newcastle, UK)

- negative, weak, moderate, or strong
- the extent of immunoreactivity was graded to the percentage of immunopositive tumor cell cytoplasm/nuclei (0, <5%; 1+, 5% to 25%; 2+, 26% to 50%; 3+, 51% to 75%; or 4+,> 75%).

FISH and RNA-Seq

RESULTS

RESULTS

TABLE 1. Clinical Features of *PRDM10*-rearranged Tumors

Case	Age (y)*/ Sex	Site	Size (mm)	Treatment	Follow-up (mo)
1†	41/F	Shoulder	30	CR	NED (61)
2†	58/F	Foot	30	CR	NED (41)
3†	30/M	Shoulder	10	CR of LR	NED (231), LR (180)
4‡	61/M	Thigh	50	CR	NED (84)
5	42/F	Knee	30	CR	NED (18)
6	42/M	Trunk	20	CR	NED (204)
7	20/M	Thigh	35	CR	NED (12)
8	32/F	Thigh	45	CR	NED (48)
9	48/M	Perineum	60	CR	NA

*Age at diagnosis.

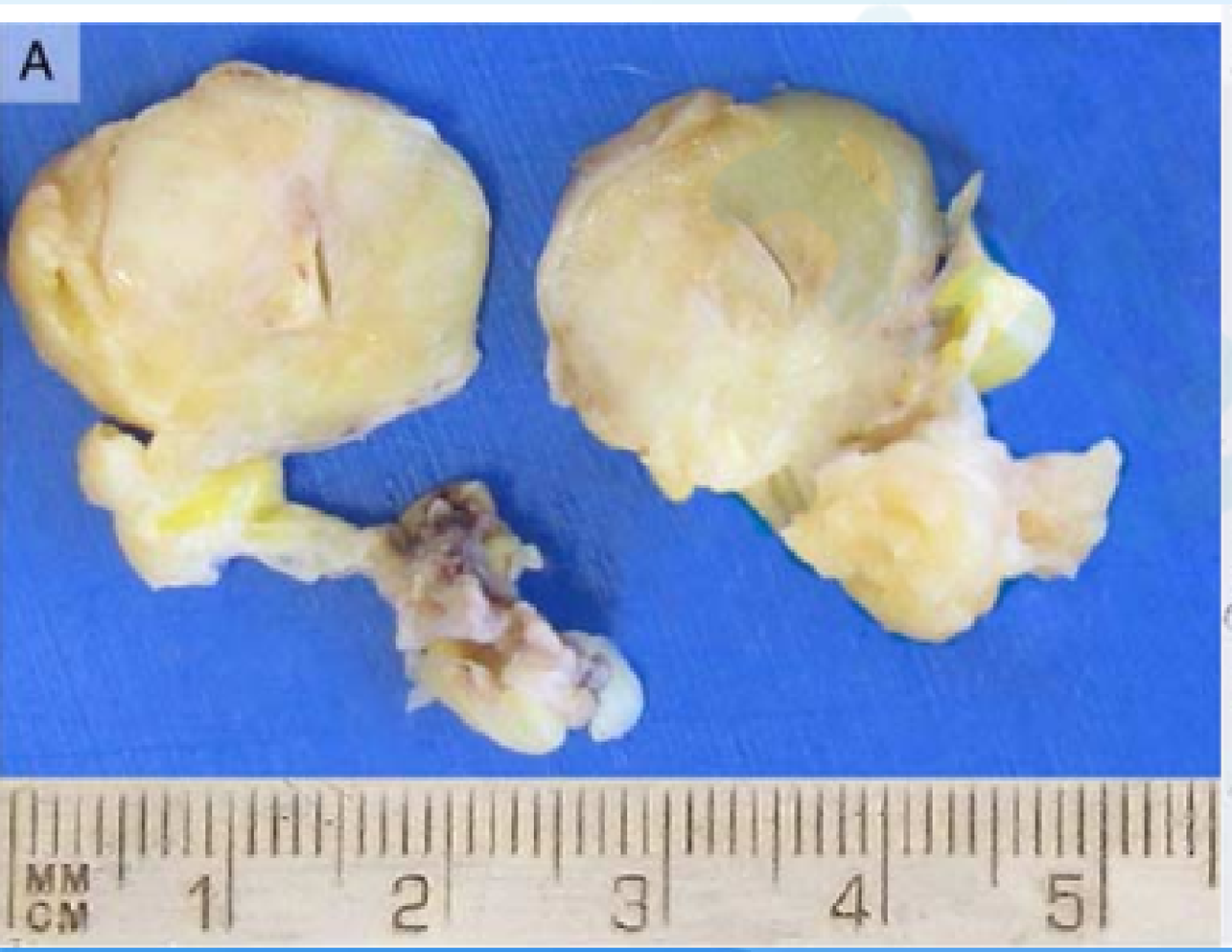
†Previously published.[9]

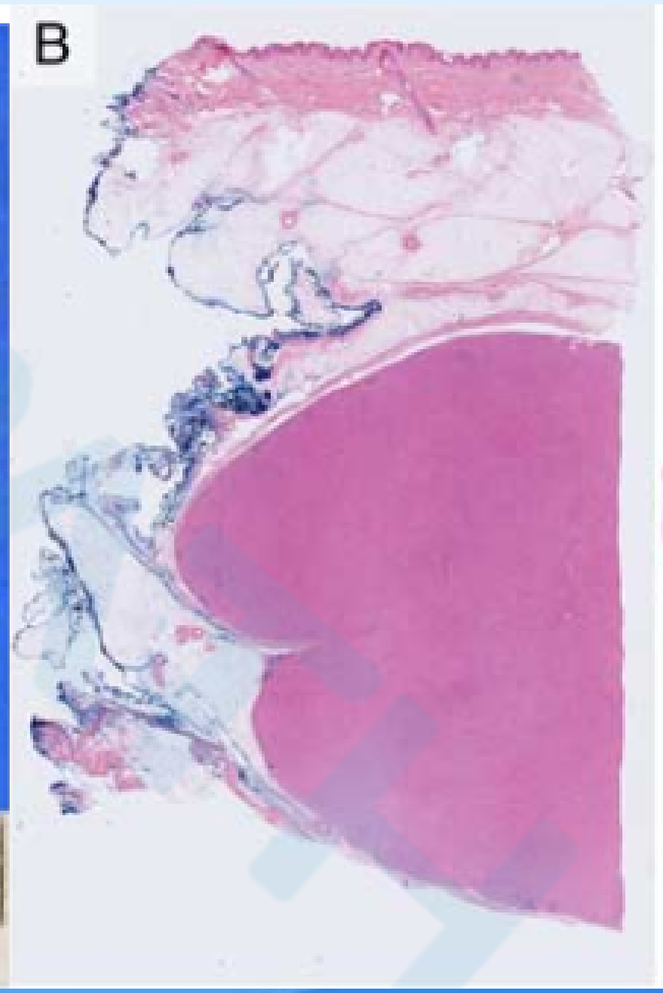
‡Previously published as leiomyosarcoma, reclassified as pleomorphic liposarcoma.[8,17]

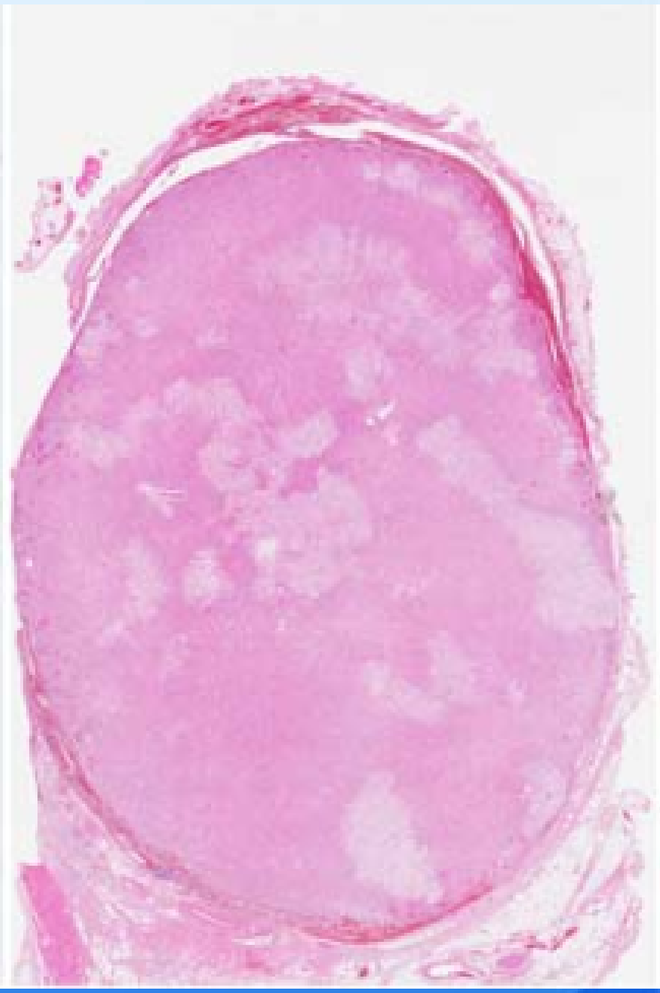
CR indicates complete resection; F, female; LR, local recurrence; M, male; NED, alive; no evidence of recurrent disease/metastasis.

- 9例：5男4女
- 年龄20 ~ 61岁(中位数=42)
  9例中有3例以前已发表
- 5例位于四肢(4例位于大腿或膝盖区域，1例位于足部)，2例位于肩膀，1例位于躯干和腹股沟）
- 肿瘤大小范围为10 - 60mm(平均= 36mm)

RESULTS







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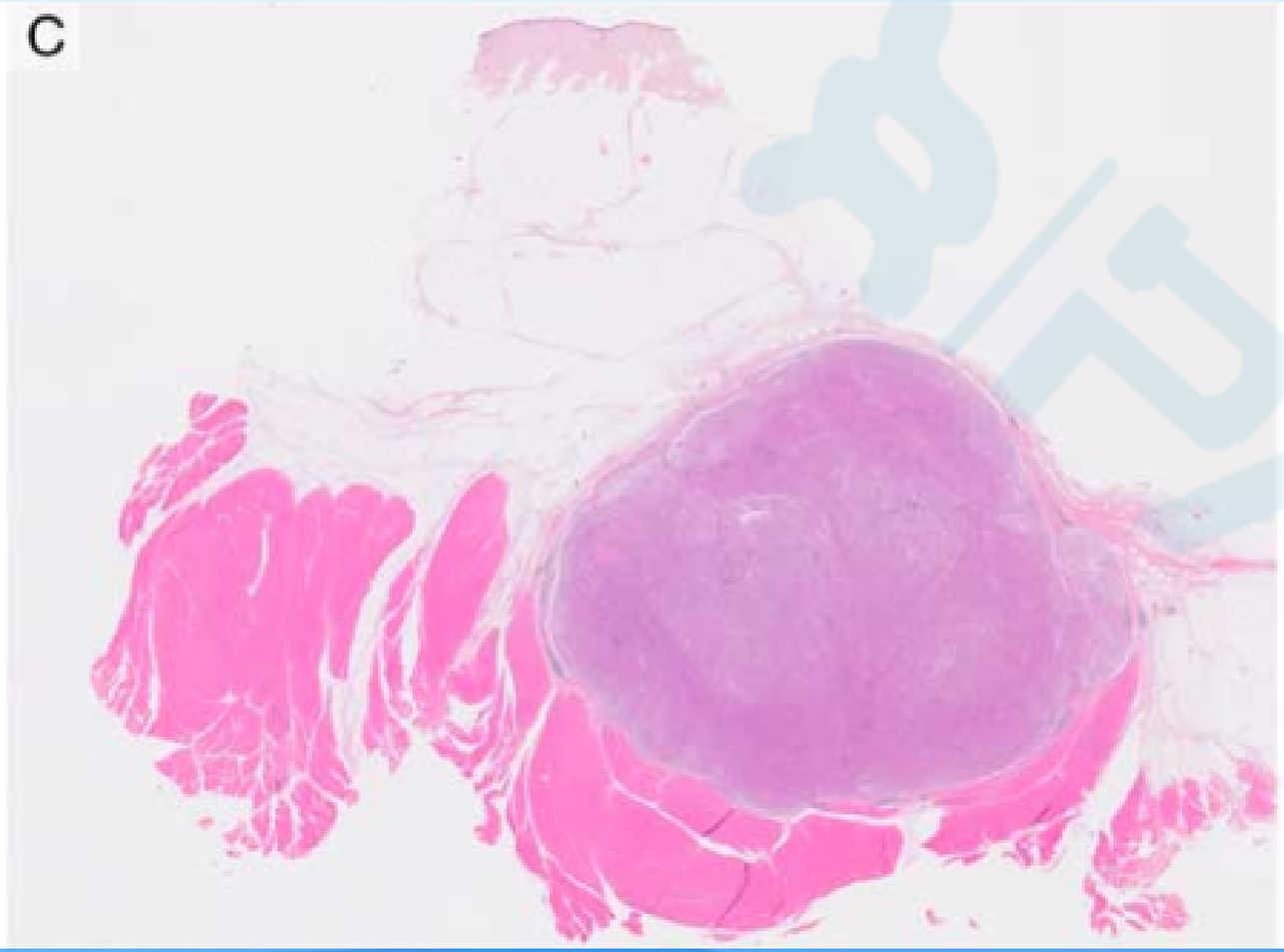

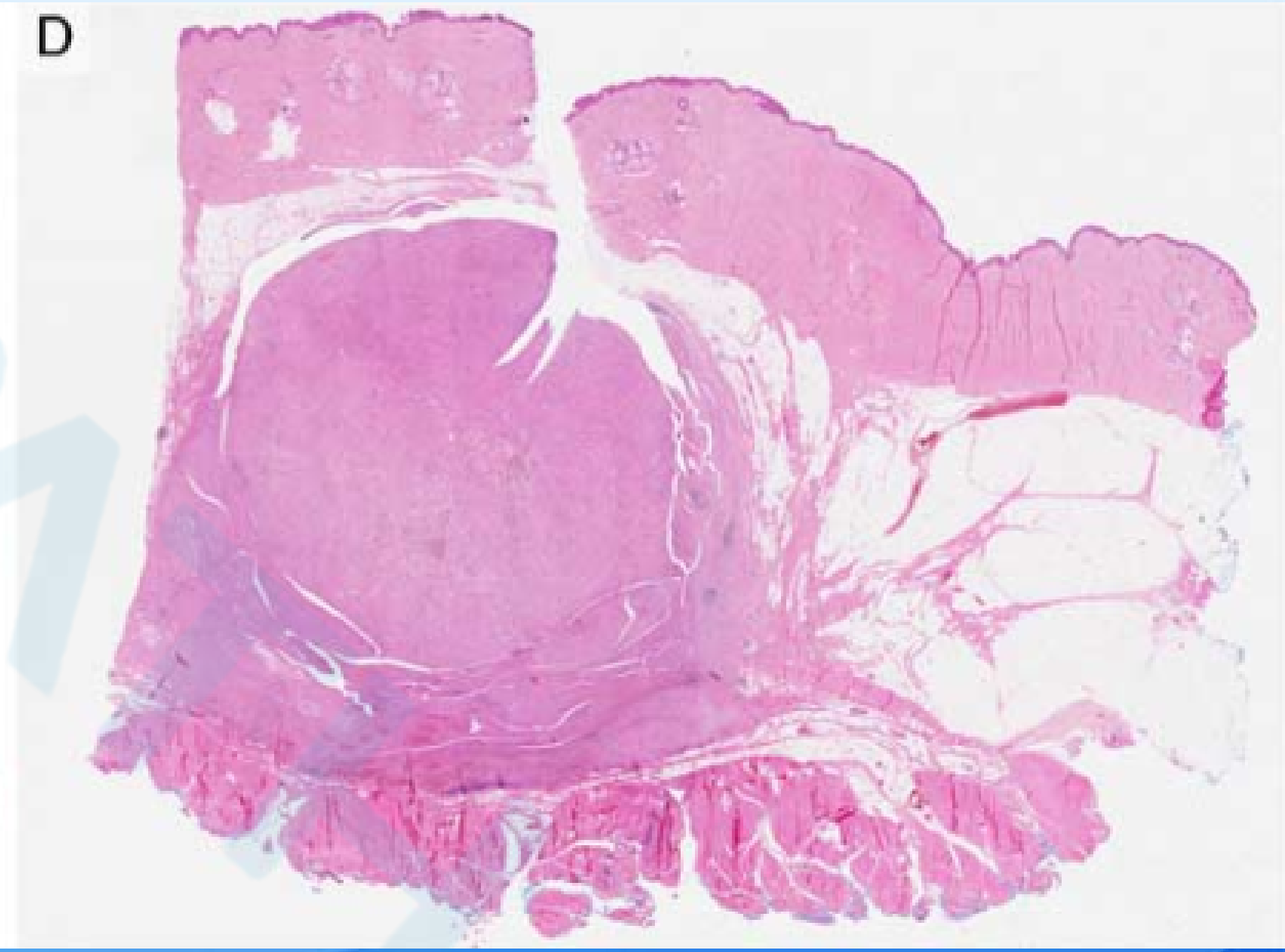

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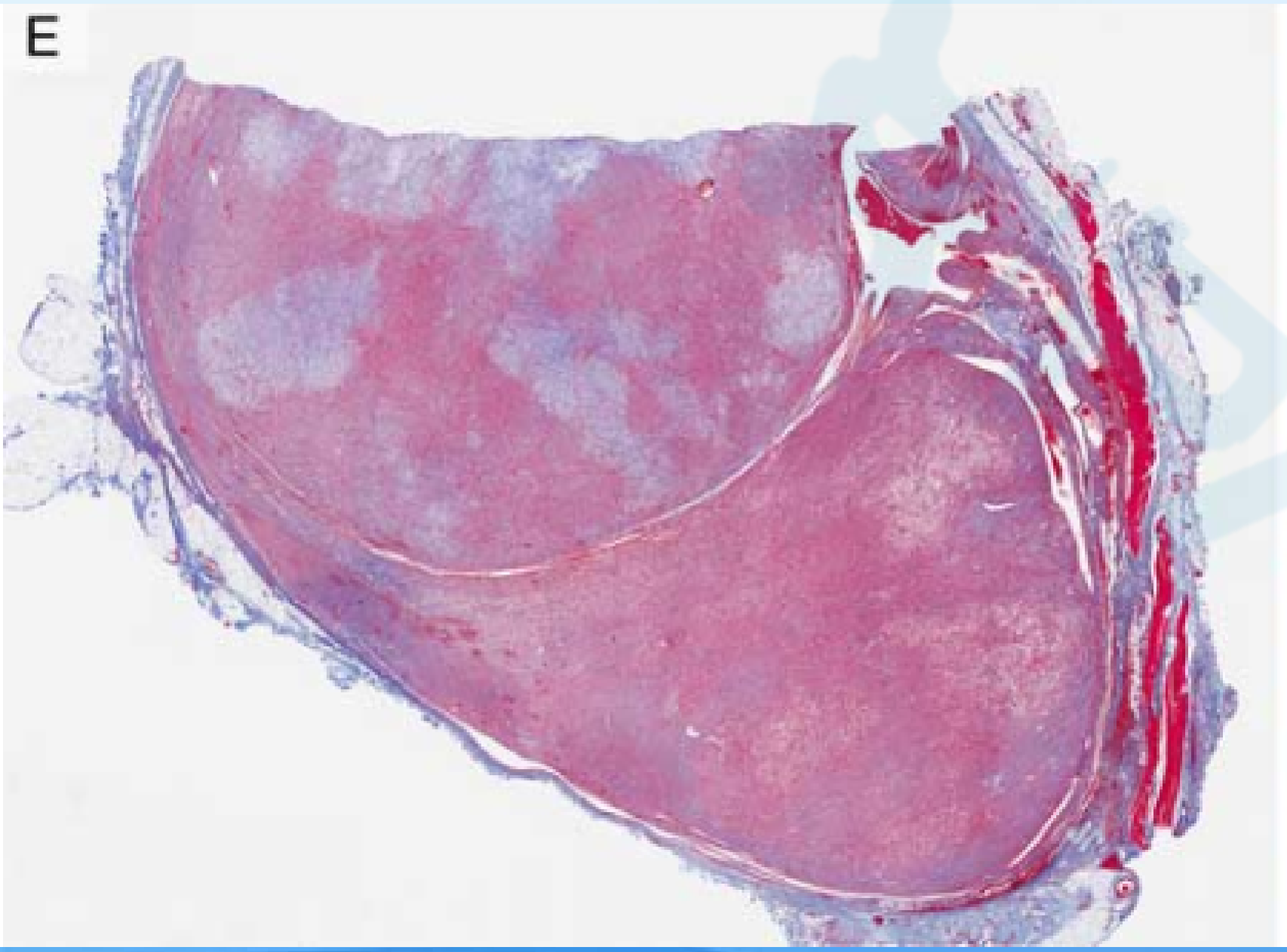
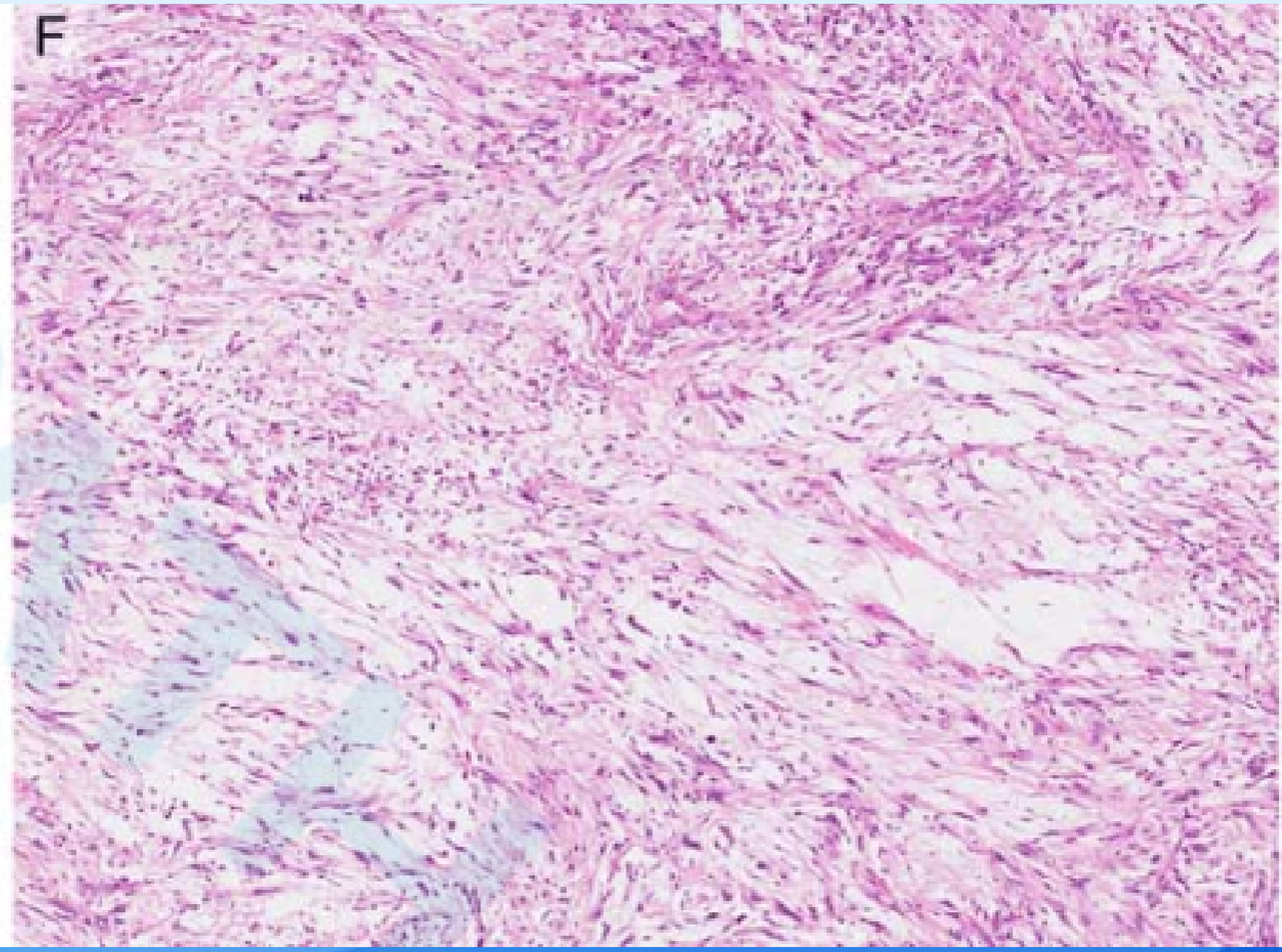




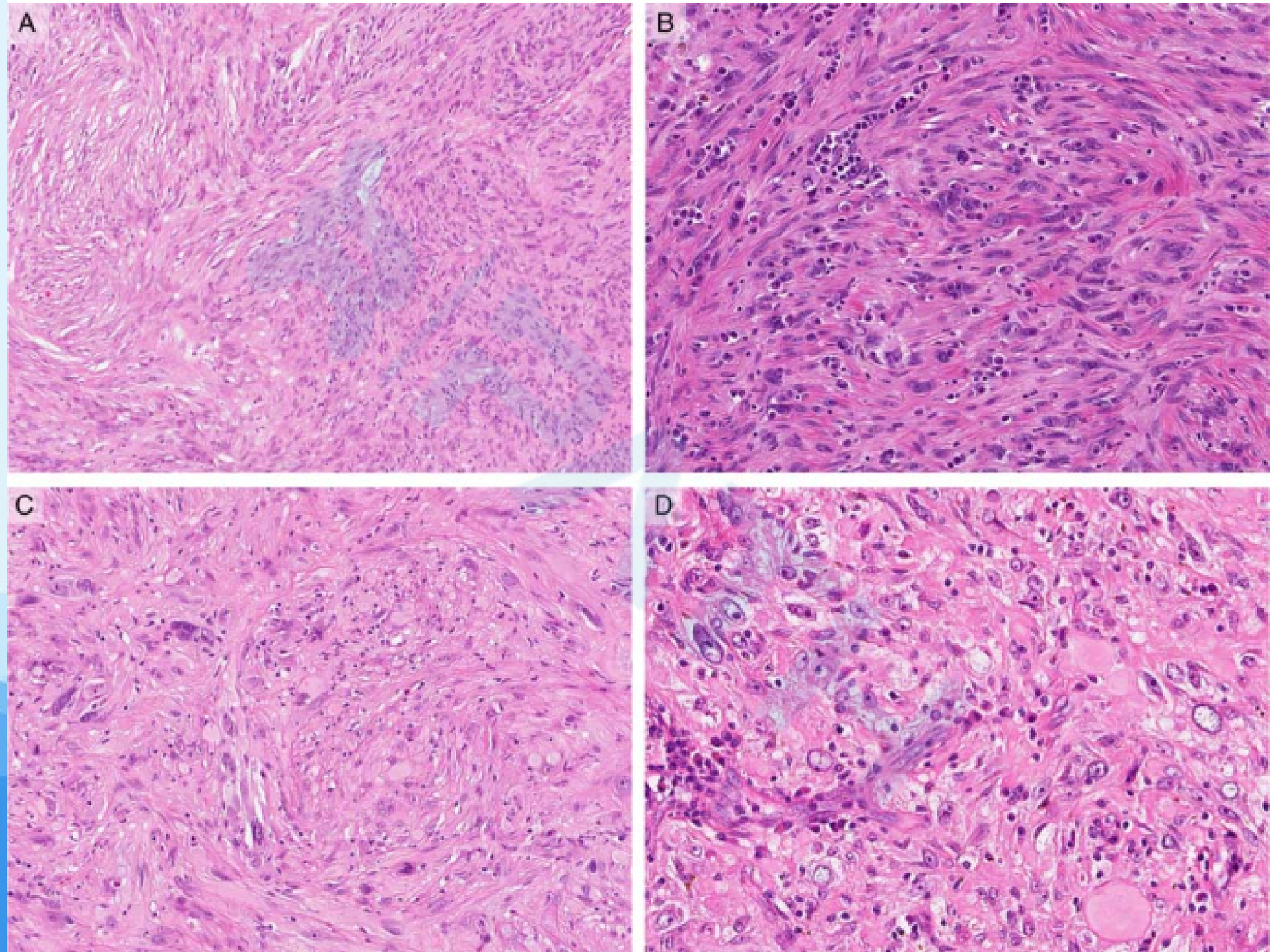
RESULTS

TABLE 2. Morphologic Features of *PRDM10*-rearranged Tumors

Case	Demarcation	Myxoid Areas	Multinucleated Giant Cells	Pseudovascular Spaces	Vacuolization	Mitoses/ 50 hpf*	Original Diagnosis
1	Well demarcated	Present	Absent	Absent	Absent	7	UPS, low grade
2	Focal infiltrative	Absent	Present	Absent	Absent	7	UPS, low grade
3	Focal infiltrative	Present	Absent	Present	Single cells	1	UPS, low grade
4	Well demarcated	Present	Absent	Present	Prominent	0	PLS
5	Focal infiltrative	Present	Absent	Present	Single cells	3	PHAT
6	Well demarcated	Present	Absent	Present	Prominent	4	PLS
7	Well demarcated	Absent	Present	Absent	Single cells	7	SCD34FT
8	Focal infiltrative	Present	Present	Absent	Single cells	2	SCD34FT
9	Well demarcated	Entirely myxoid	Absent	Absent	Absent	3	SCD34FT

*Mitoses were counted in 50 ×40 objective fields (field area of 0.238 mm^2).
PHAT indicates pleomorphic hyalinizing angiectatic tumor; PLS, pleomorphic liposarcoma.

RESULTS



RESULTS

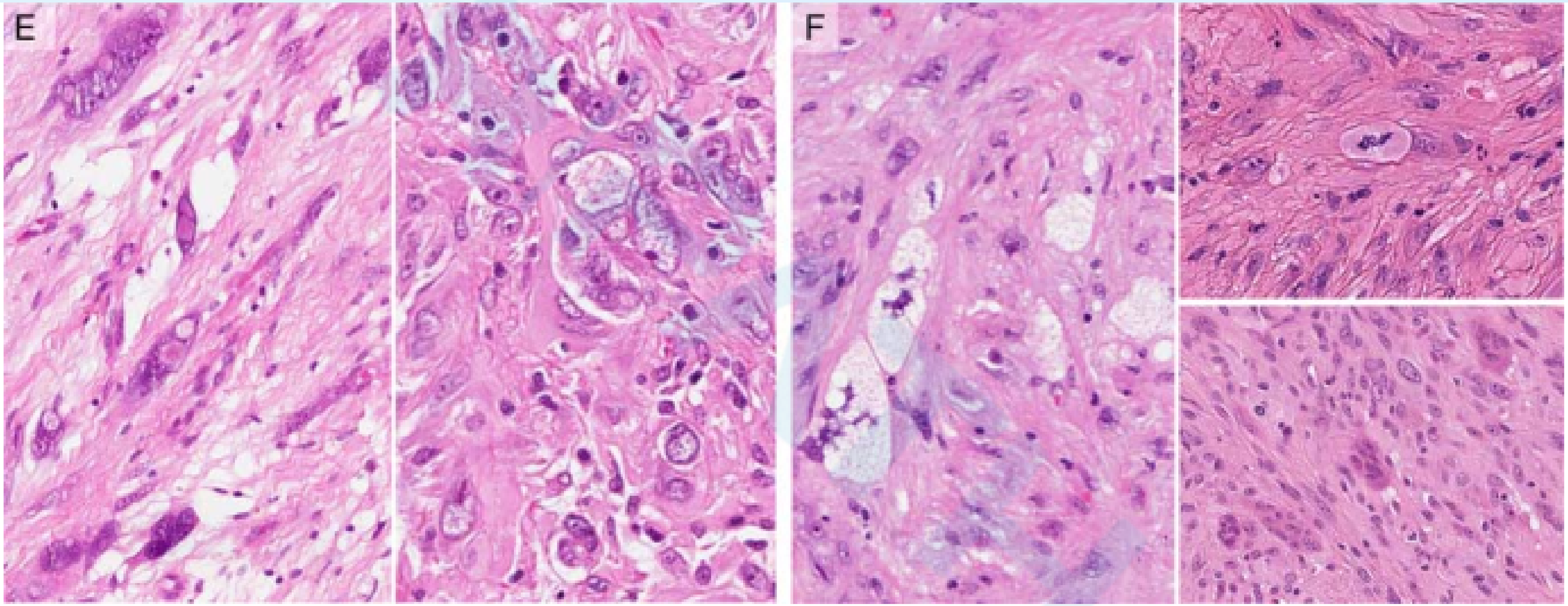
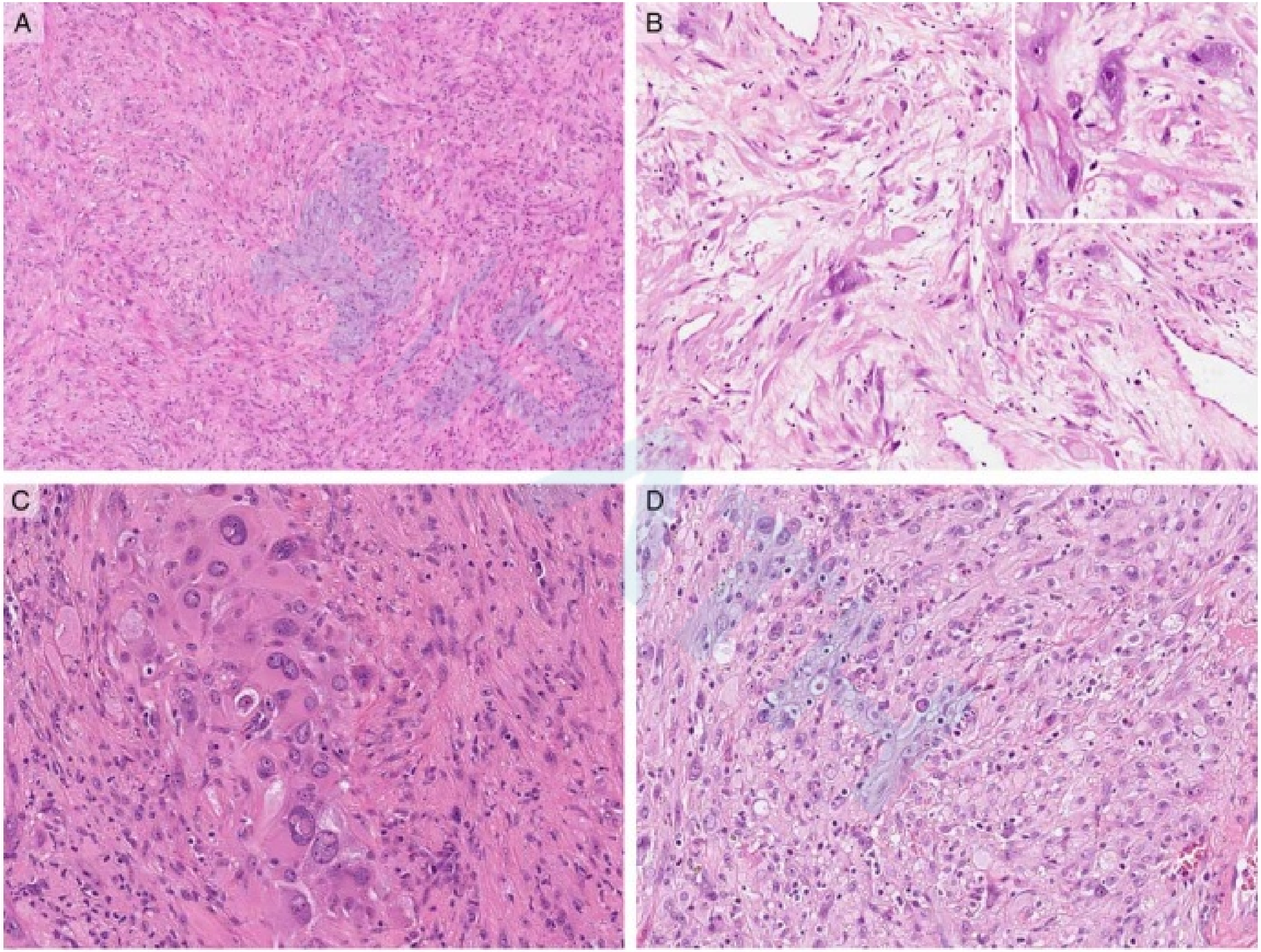


FIGURE 2. Medium and high-power appearances of the *PRDM10*-rearranged tumor. A, Generally, tumors were cellular, composed of spindle cells arranged in fascicles (case 8). B, An inflammatory infiltrate with plasma cells and lymphocytes was invariably present (case 4). C and D, The tumor cells showed marked pleomorphism; areas with glassy cytoplasm and well-defined cell borders were frequently seen (cases 7 and 2). E, "Virocyte"-like cells with intranuclear inclusions (cases 5 and 1). F, Focal cytoplasmic vacuolization was seen in 6 cases (case 8); all tumors showed a low mitotic count; multinucleated giant cells were seen in 3 cases (case 7).

RESULTS



RESULTS

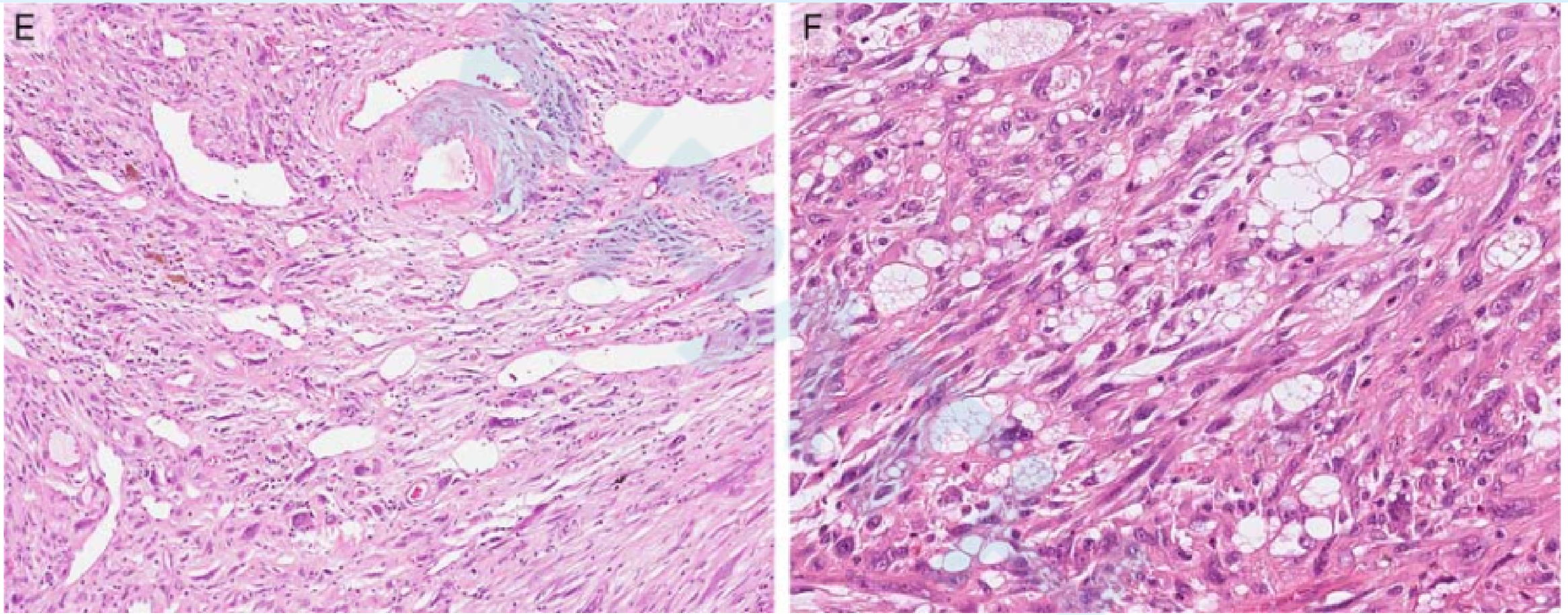


FIGURE 3. Morphologic spectrum of the *PRDM10*-rearranged tumor. A, Focal vaguely storiform architecture similar to deep fibrous histiocytoma with atypia (case 7). B, Myxoid background with bizarre "virocytes" simulating myxoinflammatory fibroblastic sarcoma high magnification (case 8). C and D, Focal epithelioid morphology with glassy cytoplasm mimicking a carcinoma or epithelioid sarcoma (cases 7 and 1, respectively). E, Hyalinized gaping vessels and hemosiderin reminiscent of pleomorphic hyalinizing angiectatic tumor (case 5). F, Focally vacuolized cytoplasm suggestive of pleomorphic liposarcoma (case 4).

RESULTS

TABLE 3. Immunohistochemical and Molecular Features

Case*	CD34	Cytokeratins AE1/AE3 or MNF116	S100 Protein	Ki-67 (%)	PRDM10 Cytoplasmic	PRDM10 Nuclear	FISH†	Fusion Transcript	Fusion Junction‡
1	Pos	Pos (focal)	Neg	5	1+ weak	4+ strong	Pos (68%)	*CITED2-PRDM10*	ex2-ex14
2	Pos	NA	NA	NA	1+ weak	3+ moderate§	Pos (93%)	*MED12-PRDM10*	ex43-ex14
3	Pos	NA	NA	NA	1+ weak	3+ moderate§	ND	*MED12-PRDM10*	ex43-ex13
4‖	Pos	NA	Neg	5	1+ weak	4+ strong	ND	*CITED2-PRDM10*	ex2-ex14
5	Pos	Pos (focal)	Neg	<5	1+ weak	3+ moderate	Pos (36%)	Neg	NA
6	Pos	Pos (focal)	Neg	5	1+ weak	4+ strong	Pos (17%)	ND¶	NA
7	Pos	Pos (focal)	Neg	5	1+ weak	4+ moderate	Neg (8%)	*MED12-PRDM10*	ex42-ex14
8	Pos	Pos (focal)	Neg	NA	1+ weak	3+ moderate	Pos (26%)	*MED12-PRDM10*	ex43-ex13
9	Pos	Neg	Neg	NA	1+ weak	4+ strong	Neg (13%)	*CITED2-PRDM10*	ex2-ex14

*Cases 1, 2, and 3 correspond to cases 2, 27, and 1 in Hofvander et al.[9]

†Interphase FISH using a break-apart probe for *PRDM10*.

‡Fusion junction based on RNA-seq and/or RT-PCR results.

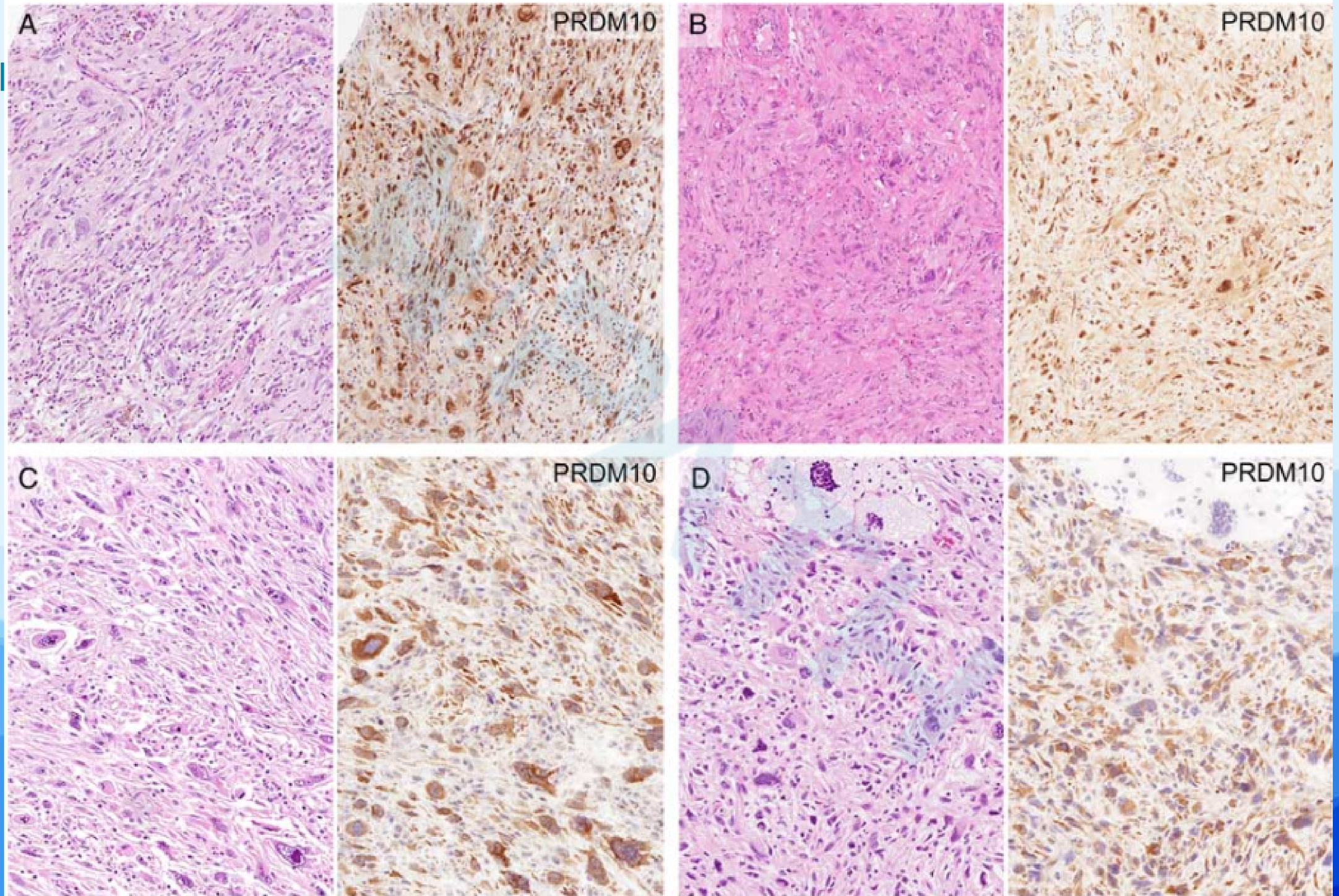
§PRDM10 antibody dilution 1:25.

‖The karyotype supported the finding of a fusion between *CITED2* (maps to chromosome band 6q24) and *PRDM10* (11q24): 73-90,XXY,-Y,del(3)(p25)x2,del(6)(q23)x2, add(11)(q25)x2,add(20)(p13)x2, inc (case 240 in Mertens et al[8]).

¶Extracted RNA was of too poor a quality (Dv200 value 23%).

NA indicates not available; ND, not done; Neg, negative; Pos, positive.

RESUL



RESULTS

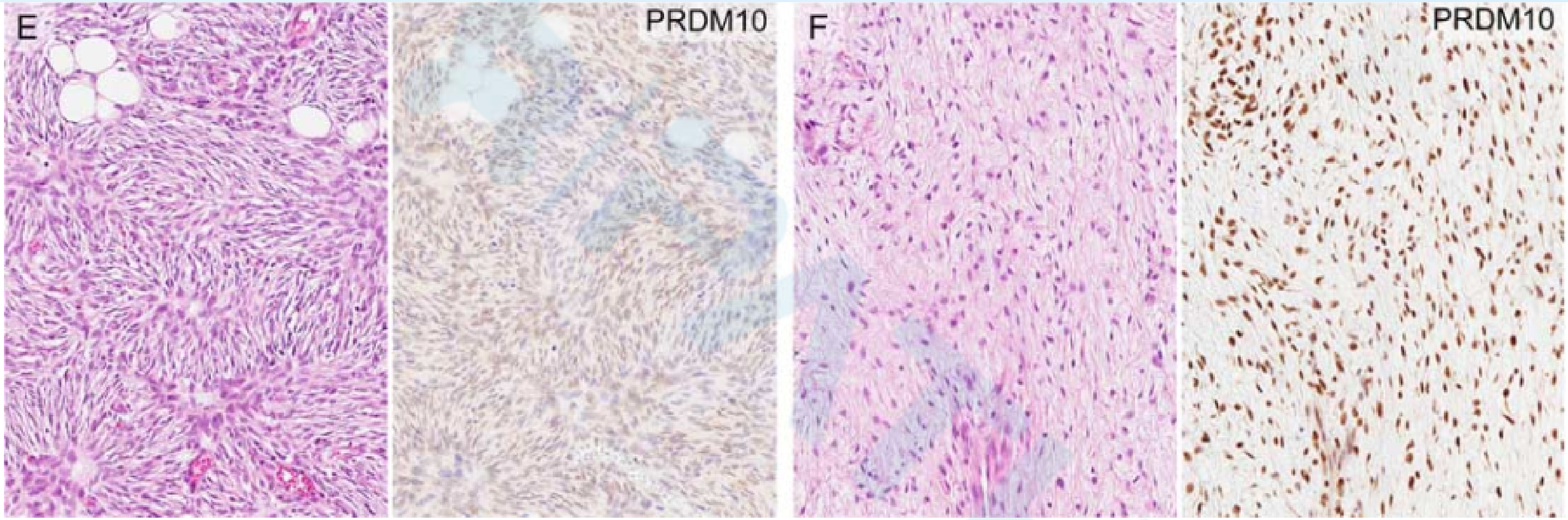


FIGURE 4. PRDM10 immunohistochemistry. A and B, Nuclear PRDM10 positivity in *PRDM10*-rearranged tumor (A case 4, B case 7). C and D, Strong and moderate cytoplasmic PRDM10 positivity in UPS. The nuclei are negative. E, Weak nuclear positivity was noted in dermatofibrosarcoma protuberans. F, Low-grade myxofibrosarcoma with nuclear PRDM10 positivity.

DISCUSSION

◆PRDM10-rearranged tumors displayed recurrent and distinctive morphologic and clinical features:

✓middle-aged adults (20 to 61 y, median: 42 y);located in the subcutis

✓very low level of mitotic activity

✓a fibrous matrix, myxoid changes, and a chronic inflammatory infiltrate

✓The absence of metastases after a median of 54 months of follow-up

◆SCD34FT :

✓a borderline superficial lesion characterized by pronounced pleomorphism and low mitotic count

✓it seems reasonable to assume that SCD34FT and PRDM10-rearranged tumor overlap

◆PHAT:

✓The shared features of PRDM10-rearranged tumor and PHAT are positivity for CD34, low mitotic rate, and cellular pleomorphism

DISCUSSION

PRDM10

◆It is involved in the embryonic development of both mesenchymal tissues and the central nervous system.

◆It belongs to the PRDM family of transcription factors, most of which share an N-terminal PR domain with potential methyltransferase activity and multiple C2H2-type zinc-finger domains providing sequence-specific DNA binding.

◆PRDM10 is predominately present in the cytoplasm in hepatocytes, the exocrine pancreas, and renal proximal tubular epithelial cells.

◆In normal soft tissue components, immunostaining of PRDM10 is comparatively weak.

CONCLUSION

◆The PRDM10-rearranged soft tissue tumors described here are relatively well-circumscribed neoplasms arising in the deep subcutis of the extremities in young to middle-aged individuals.

◆They are characterized by pleomorphic morphology, very low mitotic rate, and CD34 positivity and appear to overlap with SCD34FTs.

◆Immunohistochemical detection of nuclear PRDM10 and demonstration of PRDM10 rearrangement are helpful in recognizing this rare soft tissue tumor.

Thanks for your attention