Clinicopathologic Diversity of Undifferentiated Sarcoma With BCOR-CCNB3 Fusion

Analysis of 11 Cases With a Reappraisal of the Utility of Immunohistochemistry for BCOR and CCNB3

汇报人　　高慎茹
指导老师　　徐红

Undifferentiated Sarcoma With BCOR-CCNB3 Fusion

- Recently, the CIC or BCOR rearrangement was detected in a subset of small round or spindle cells sarcomas

- CIC-rearranged sarcomas that harbor CIC-DUX4 or CIC-FOXO4 account for two-thirds of EWSR1-negative small round cell sarcomas

- Undifferentiated sarcomas with BCOR-CCNB3 fusion, first described by Pierron et al3 in 2012, account for 4% to 13% of undifferentiated small round cell sarcomas without an EWSR1 rearrangement

- other fusion partners of the BCOR gene including MAML3 and ZC3H7B

BCOR–CCNB3 基因融合的未分化肉瘤

- 主要发生于儿童–年轻人（<25y）
- 绝大多数为男性
- 部位：骨、深部软组织
- 形态
  - 原始未分化小细胞–细胞核不规则（非典型尤文肉瘤）
  - 主要为梭形细胞组成
- 免疫组化：CCNB3+，CD99染色模式不典型
- 具有*BCOR – CCNB3*基因融合
- 与肾脏透明细胞肉瘤具有重叠的特征

- **BCOR基因**

  The X-linked BCL-6 co-repressor gene

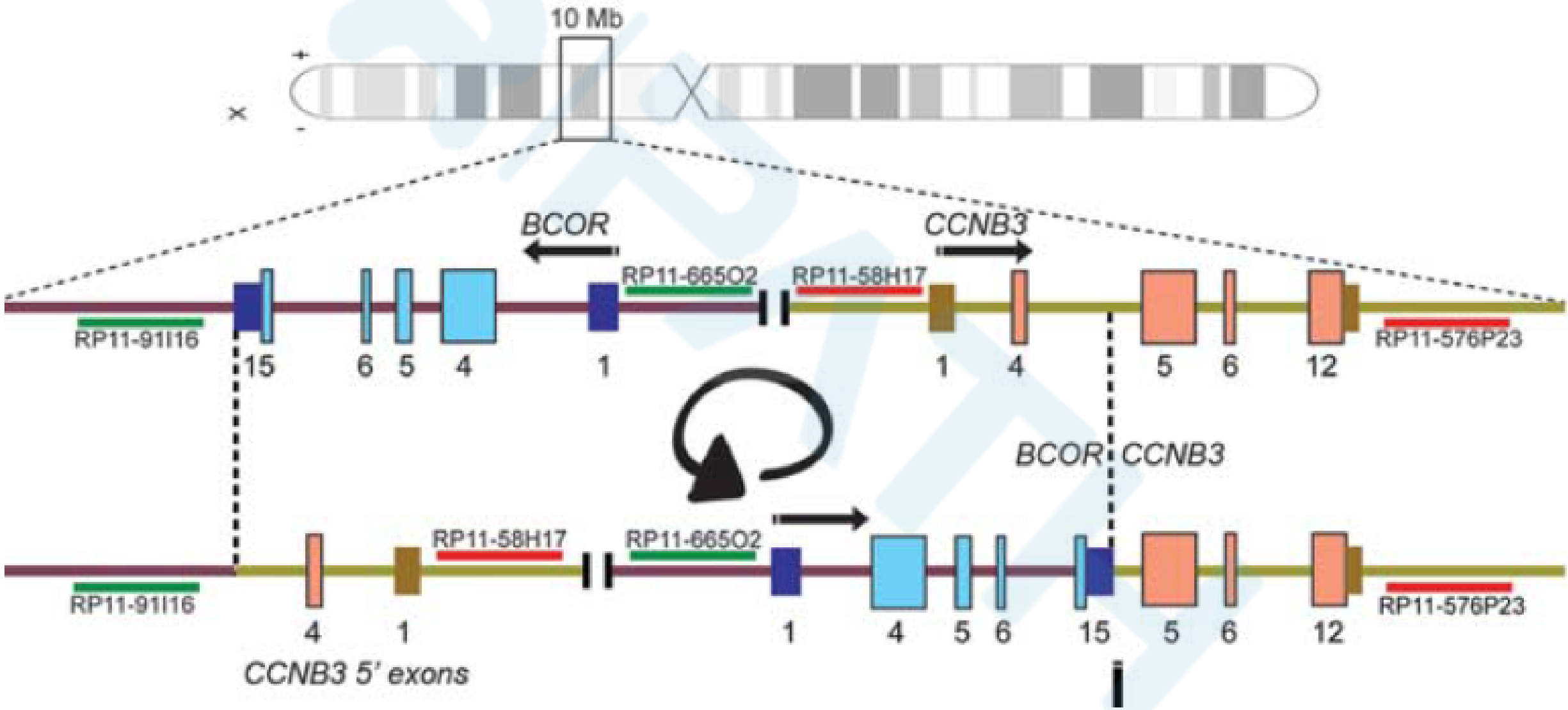
  Polycomb repressive complex (PRC)2的关键组成成分

- **CCNB3基因**

  编码cyclin B3蛋白

  Cyclin家族成员，与细胞周期依赖蛋白激酶CDK相互作用，促进细胞周期进展

BCOR–CCNB3 基因融合的未分化肉瘤



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MATERIALS AND METHODS

- Case Selection

  ---85 small round or spindle cell tumors without SS18-SSX, EWSR1-FLI1, EWSR1-ERG, ETV6-NTRK3, and/or EWSR1/TAF15/TCF12-NR4A3 fusion gene transcripts by RT-PCR

  ---412 small round or spindle cell tumors other than BCOR-CCNB3 sarcoma were also retrieved and analyzed

MATERIALS AND METHODS

- RNA Sequencing
- Reverse Transcription-Polymerase Chain Reaction

MATERIALS AND METHODS

- Immunohistochemistry

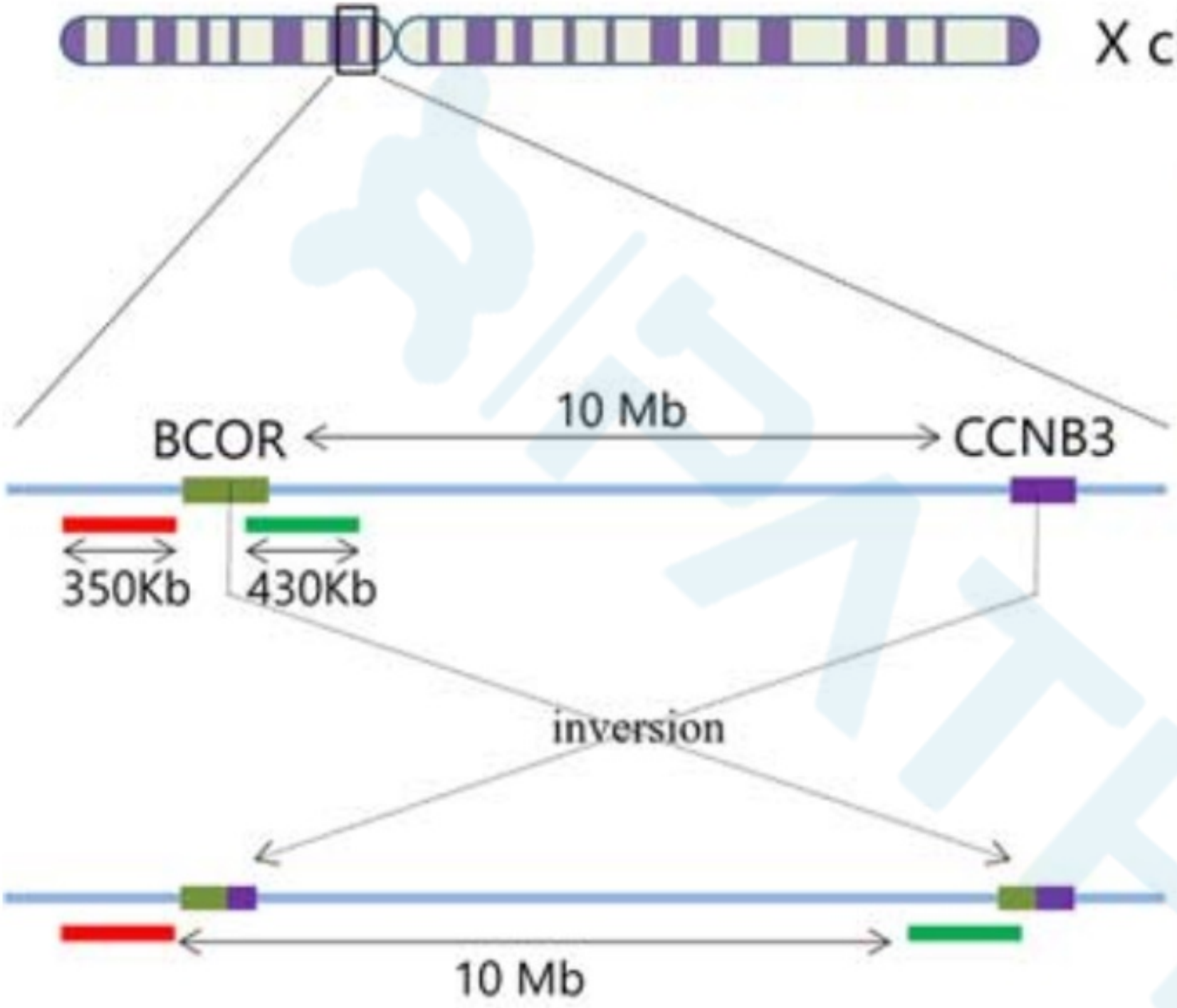
---CCNB3 (HPA000496, polyclonal, 1:200; Sigma-Aldrich, St. Louis, MO)

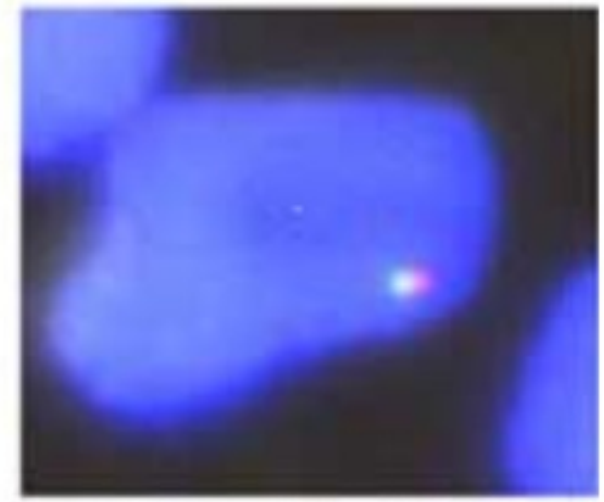
---BCOR (C-10, monoclonal, 1:300, Santa Cruz, Dallas, TX)

---α-SMA、AE1/AE3、bcl-2、CAM5.2、CD34、CD56、CD99、cyclin D1、desmin、NKX2.2、S-100、syn、TLE1、WT-1

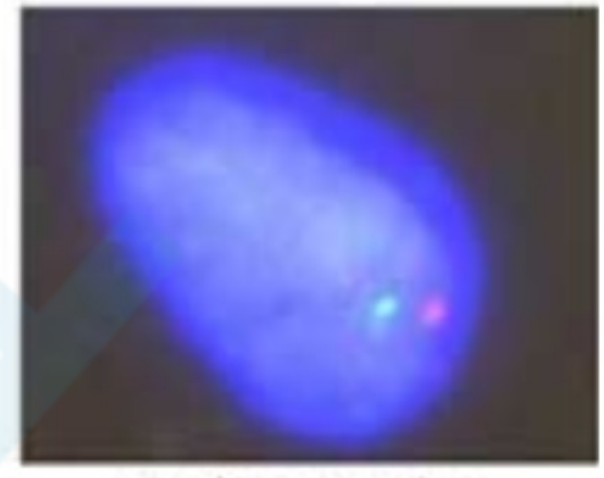
MATERIALS AND METHODS

- Fluorescence In Situ Hybridization
  ---BCOR split probes





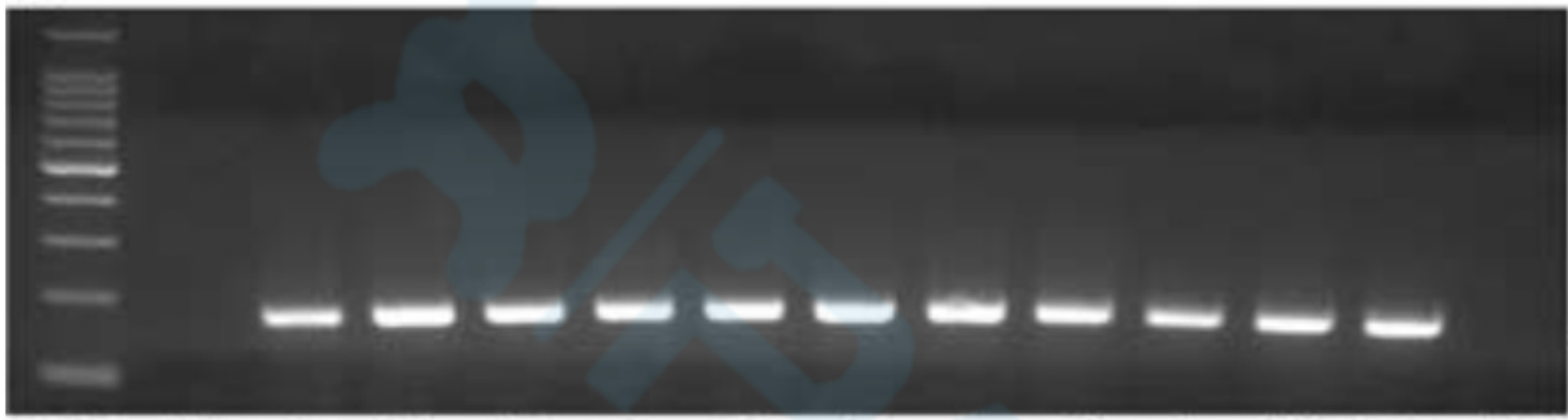
Normal, male



Split, male

RESULTS

A


← 170 bp
M N 1 2 3 4 5 6 7 8 9 10 11 SS

B

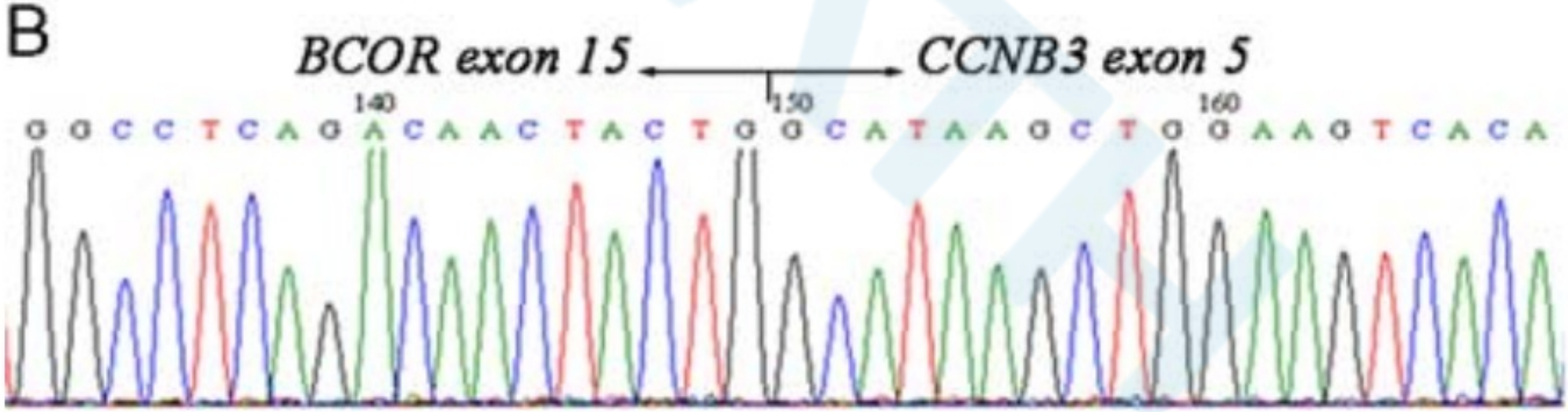
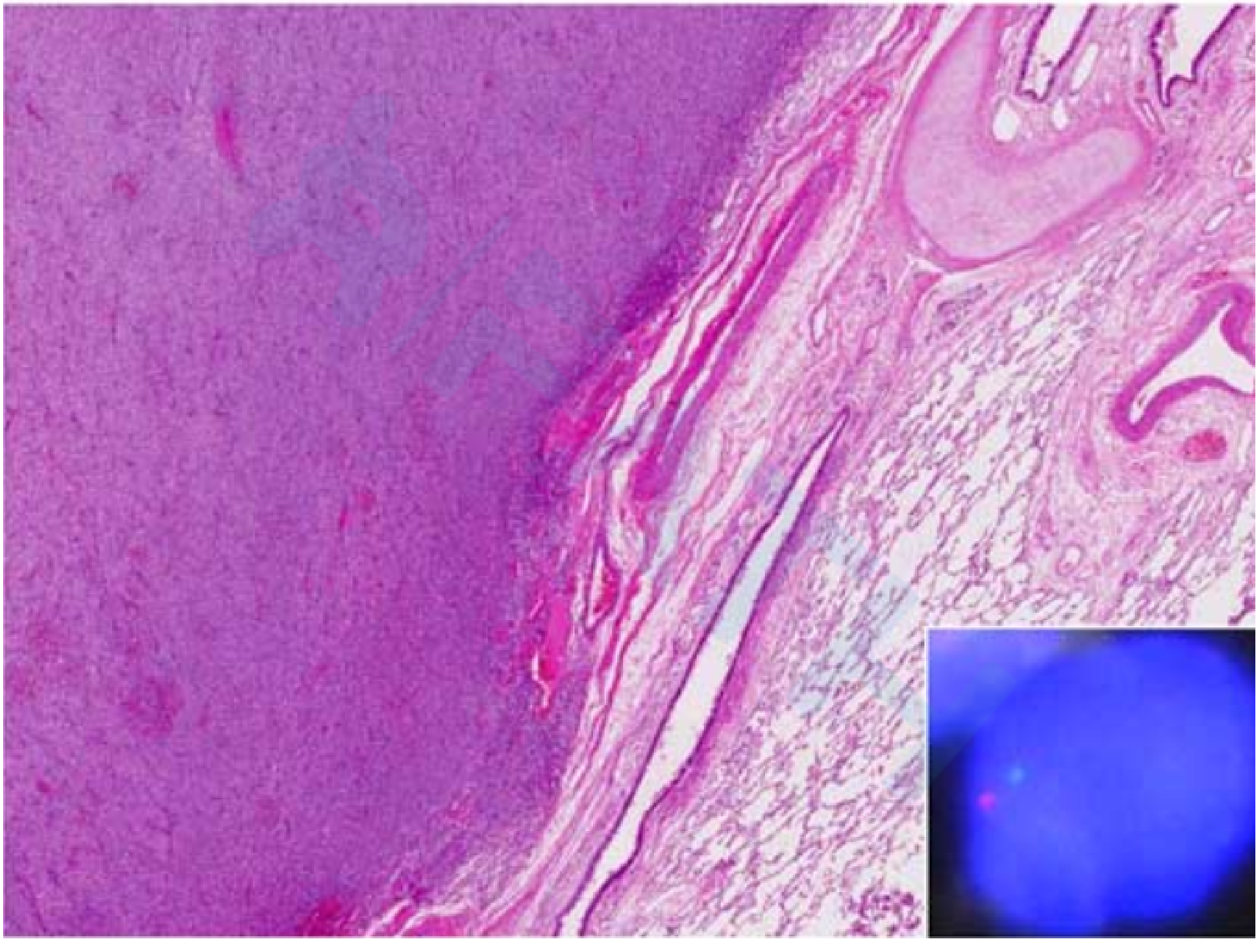

BCOR exon 15
CCNB3 exon 5
140
150
160
G G C C T C A G A C A A C T A C T G G C A T A A G C T G G A A G T C A C A

TABLE 1. Clinicopathologic Features of Undifferentiated Sarcomas With *BCOR-CCNB3* Fusion

Case	Age (y)	Sex	Location	Size (cm)	Metastasis	Outcome (Months of Follow-up)	CCNB3 IHC	BCOR IHC	*BCOR* FISH
1	14	M	Foot	3.5	None	NA	Positive	Positive	Split
2	9	M	Thigh	4	None	NA	Positive	Positive	Split
3	14	M	Calcaneum	3	Lung	NED (165)	Positive	Positive	Split
4	16	M	Paranasal sinus	6	None	NA	Positive	ND	ND
5	16	M	Foot	1.5	None	NED (99)	Positive	Positive	ND
6	31	M	Thigh	15	Lung, liver, retroperitoneum	DOD (51)	Negative	Positive	Split
7	15	M	Sacral region	14	None	NED (126)	Positive	Positive	Split
8	7	M	Thigh	4	None	NED (66)	Negative	Positive	Split
9	18	M	Lung	10	None	NED (29)	Positive	Positive	Split
10	6	M	Vertebra (Thoracic)	6	None	NED (25)	Positive	Positive	Uninformative
11	16	M	Sacral region	>15	None	NED (24)	Positive	Positive	Split

DOD indicates dead of disease; IHC, immunohistochemistry; M, male; NA, not available; ND, not done; NED, no evidence of disease.

A



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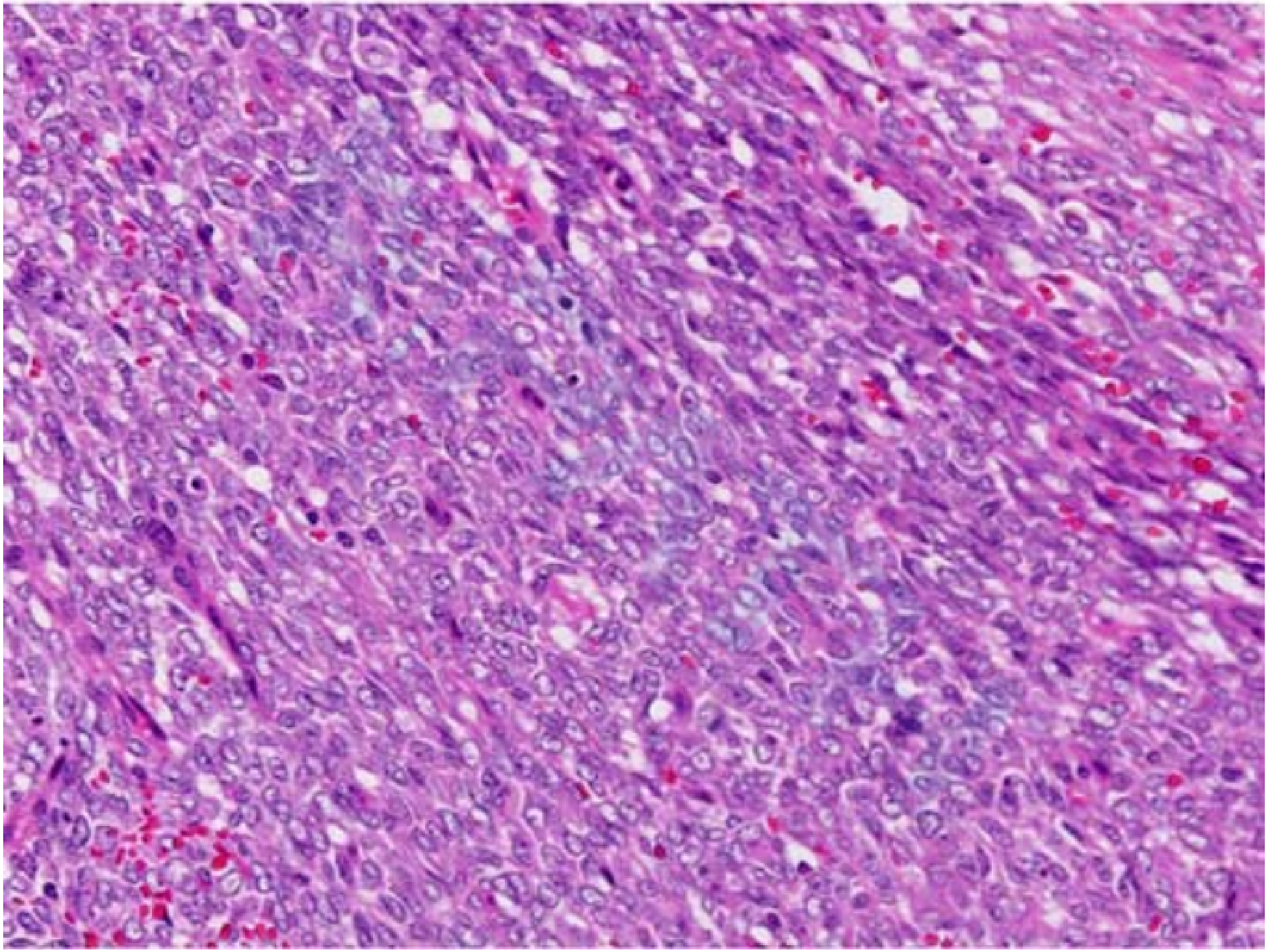

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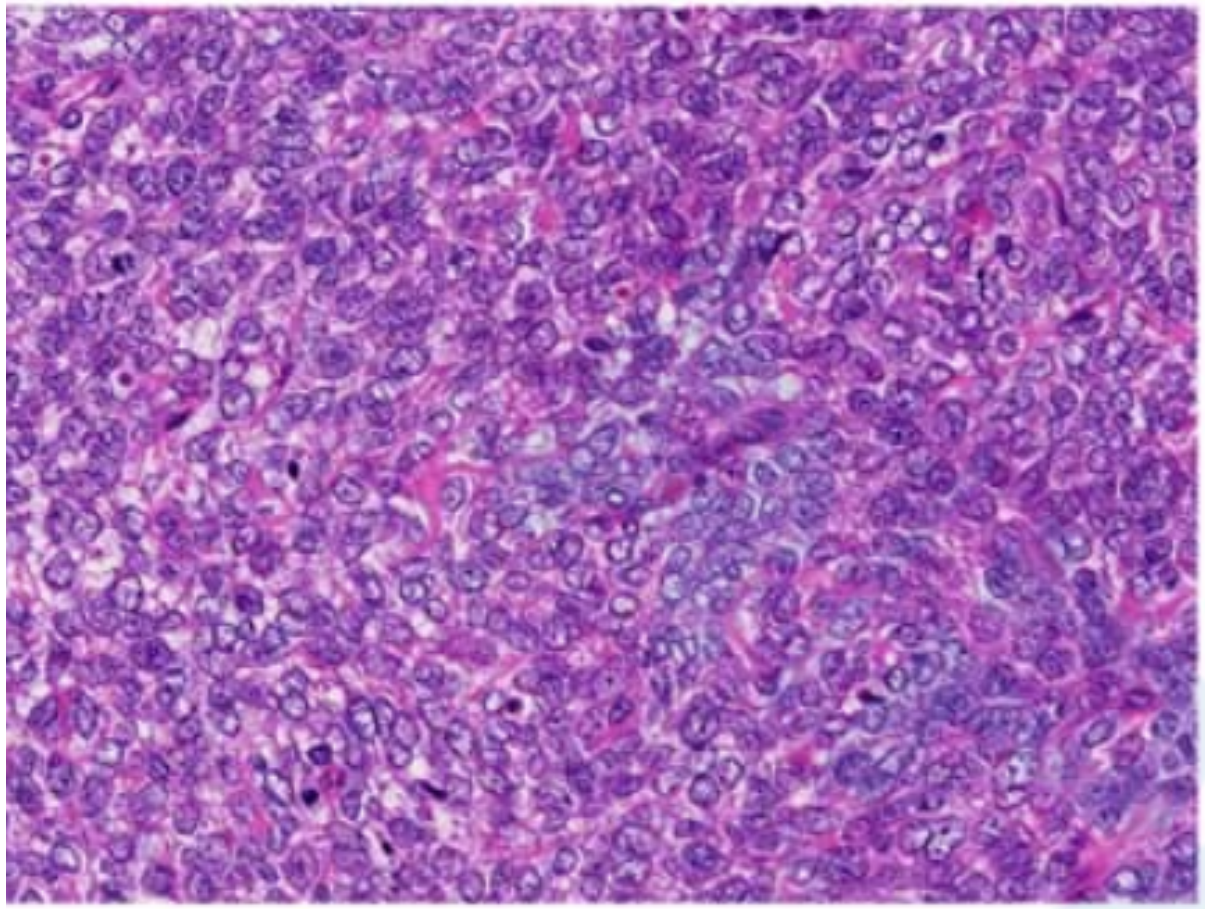

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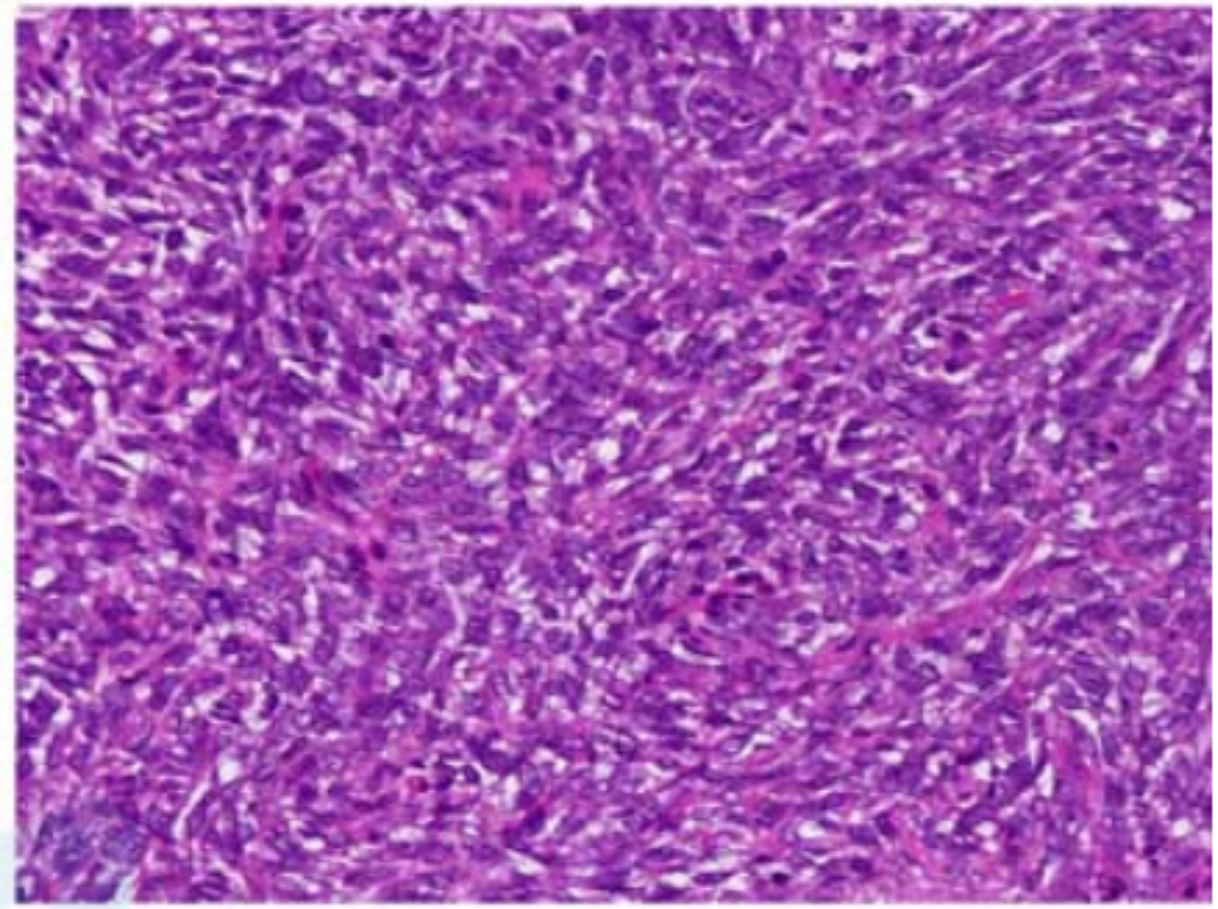

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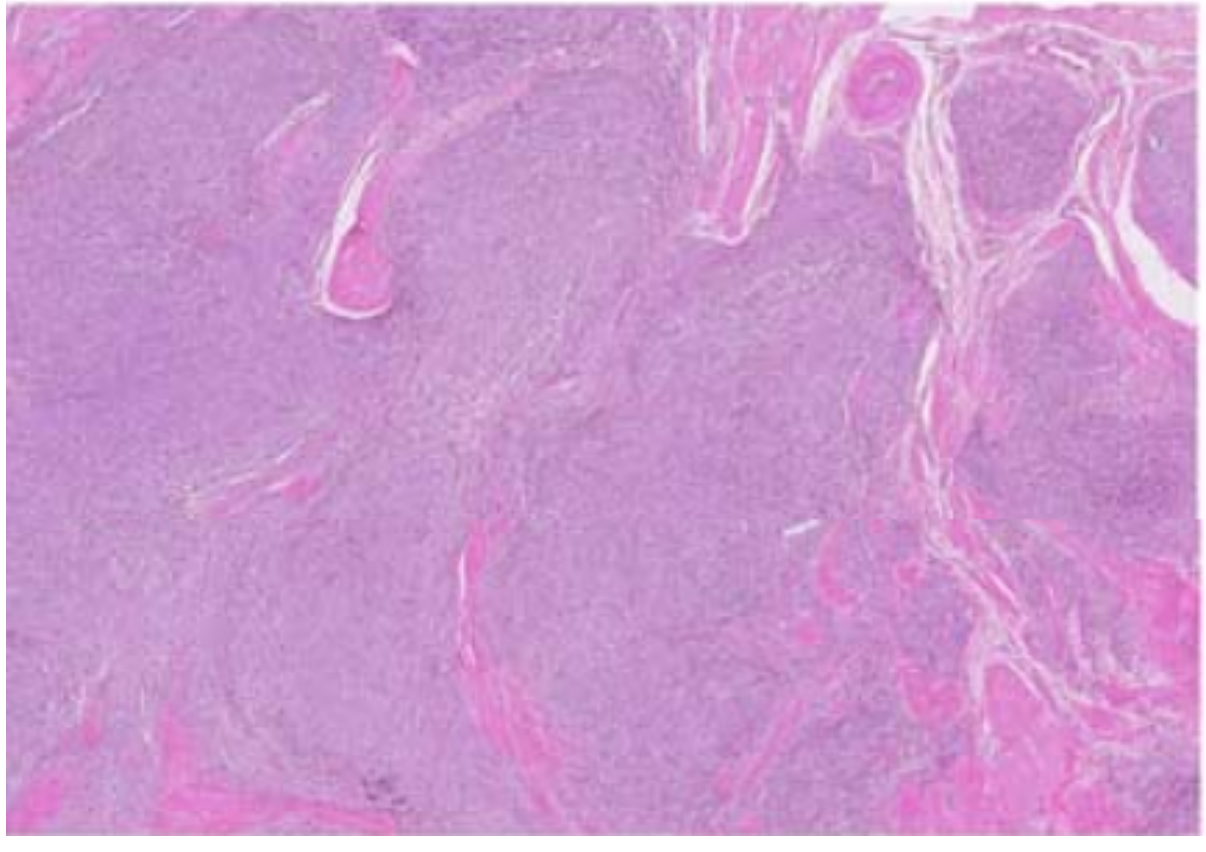

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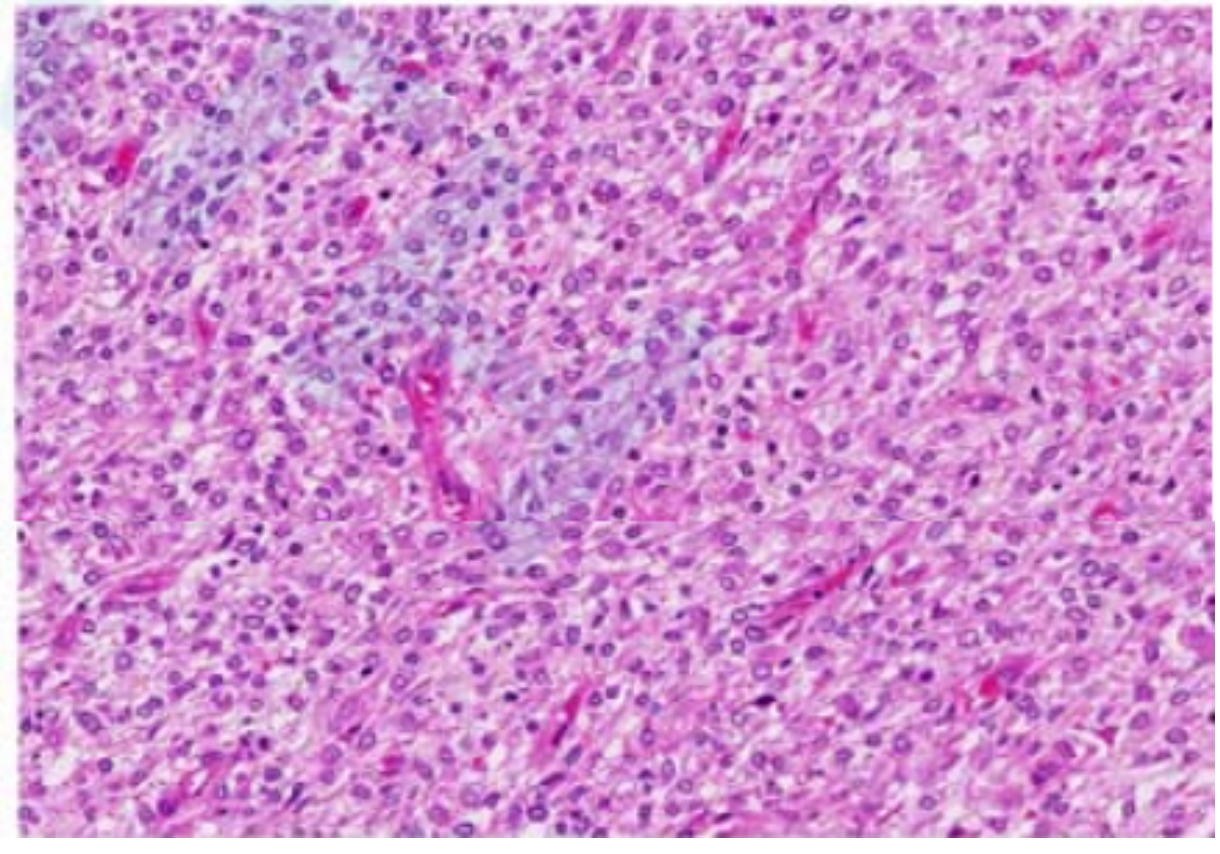

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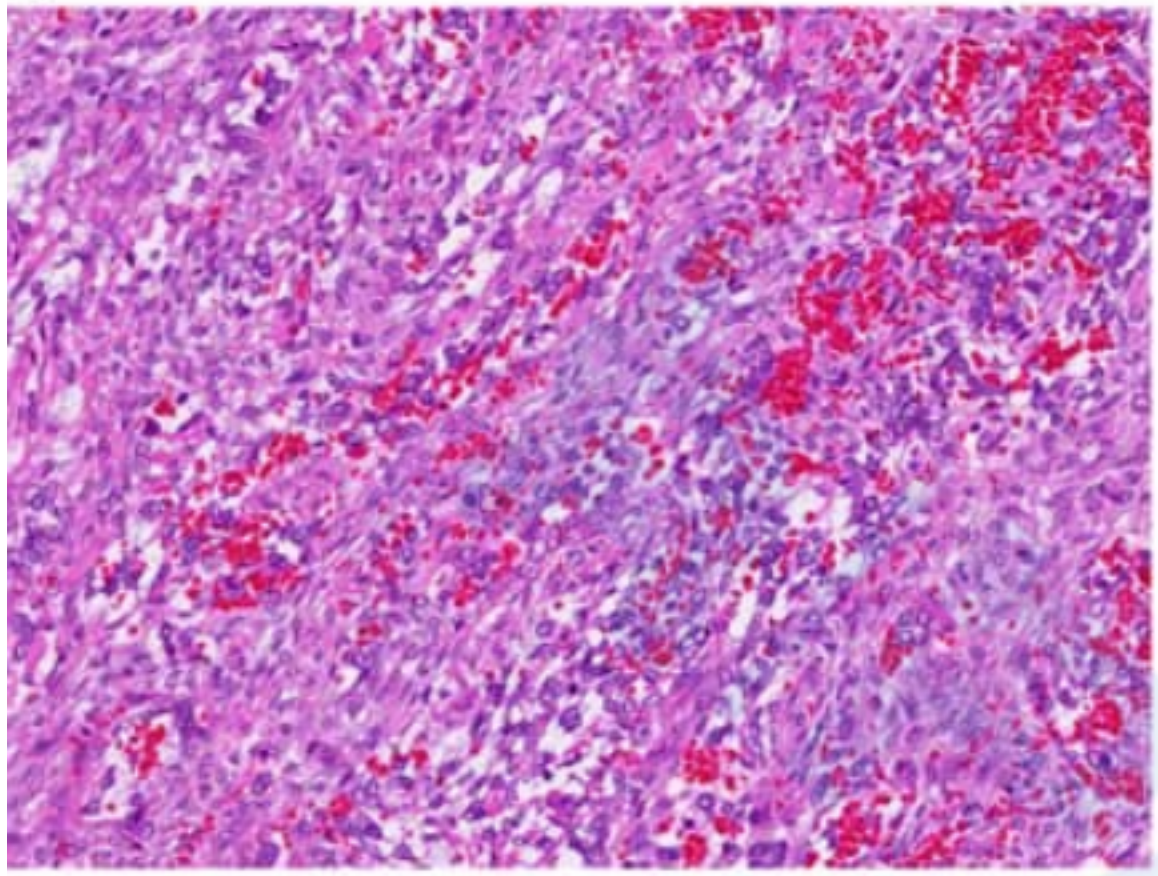

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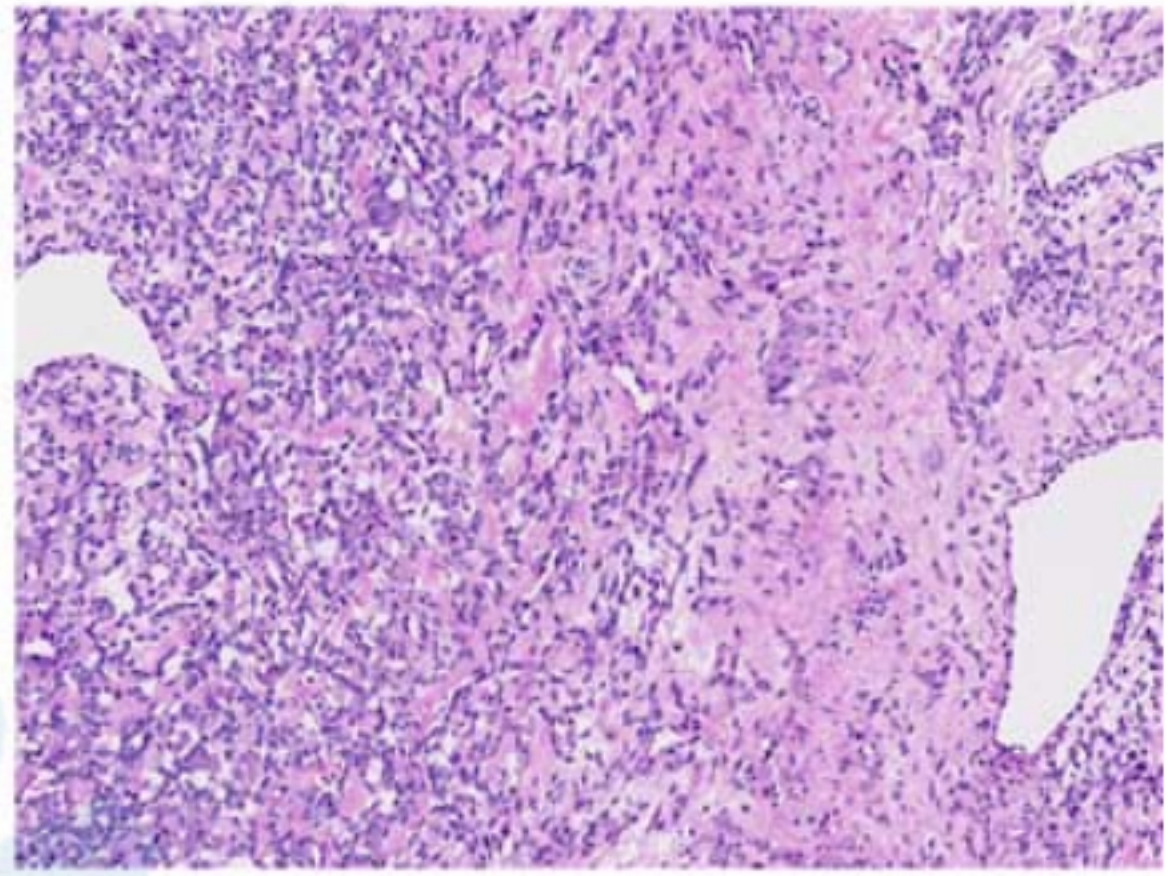

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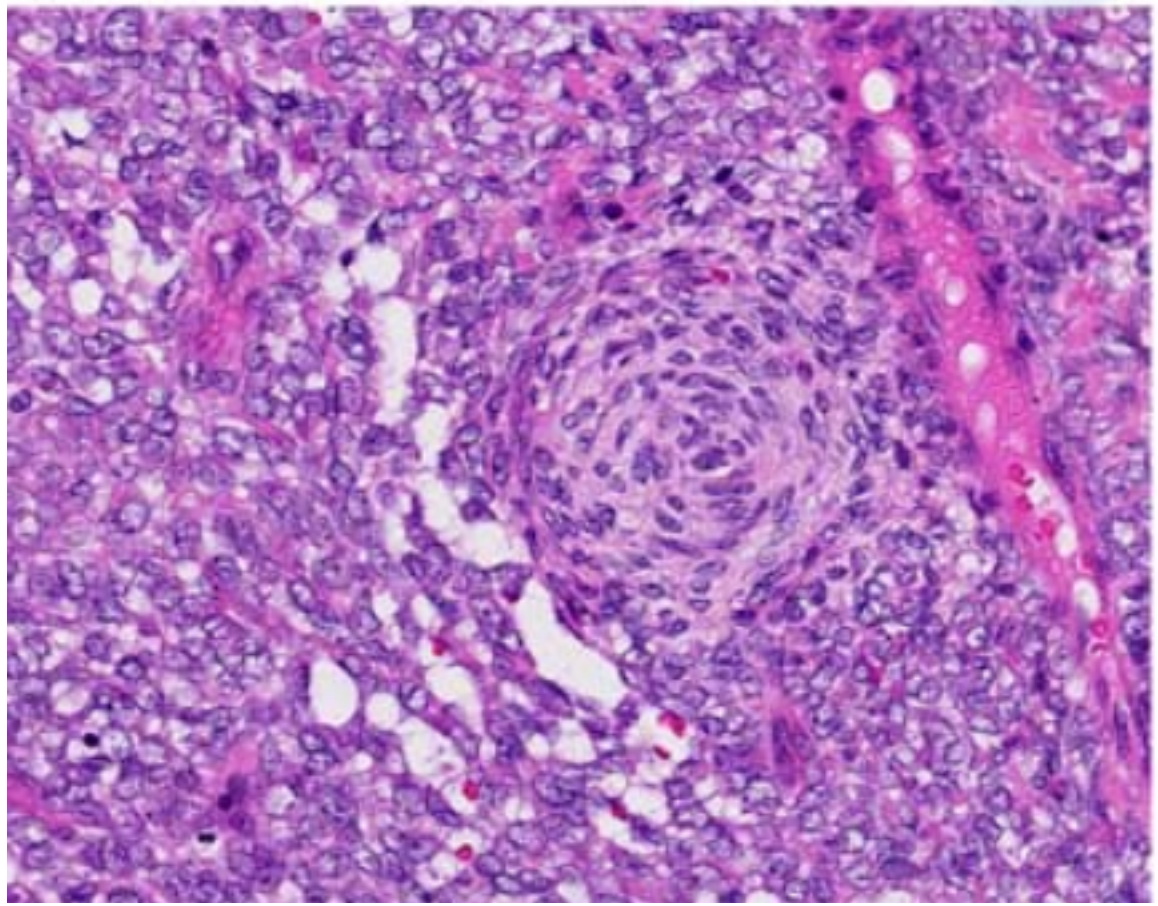

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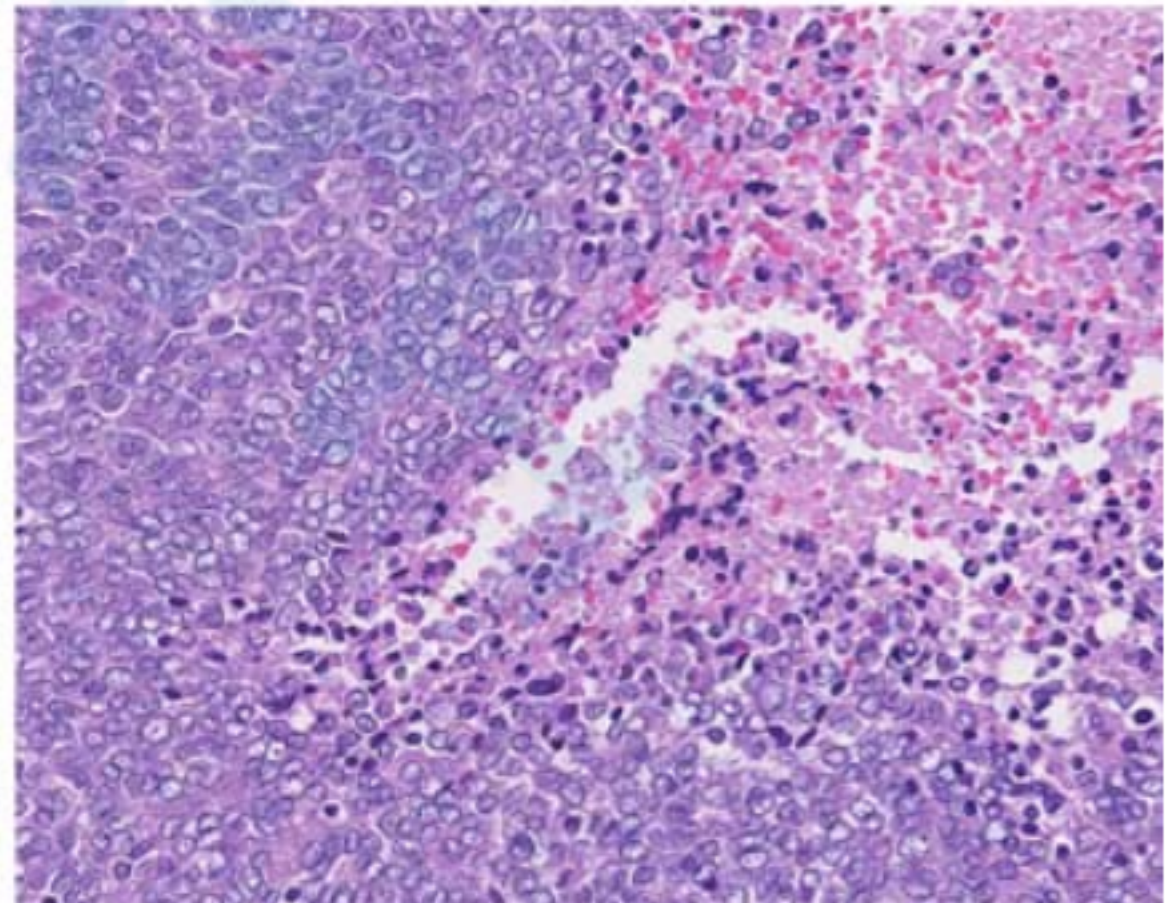

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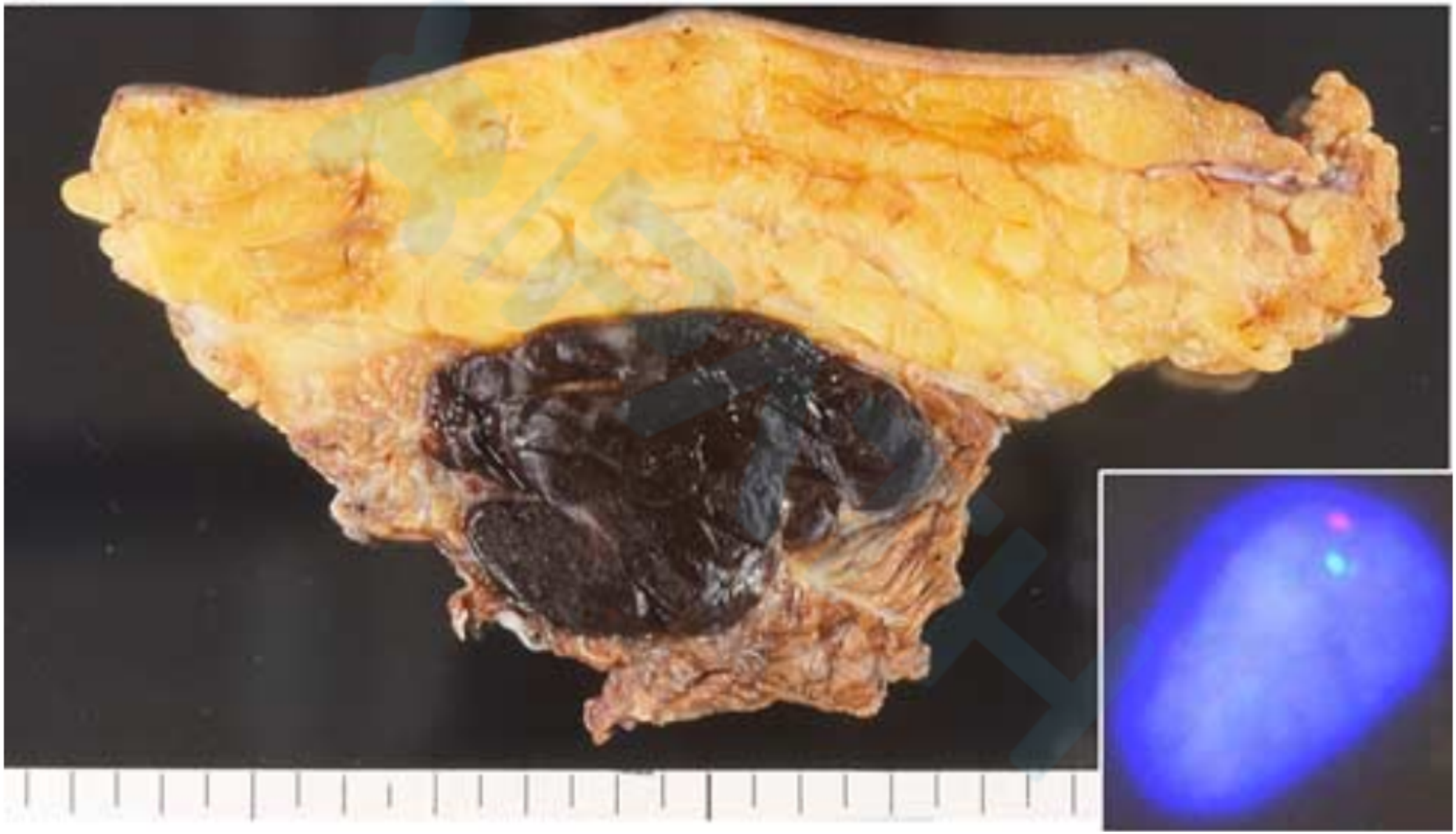

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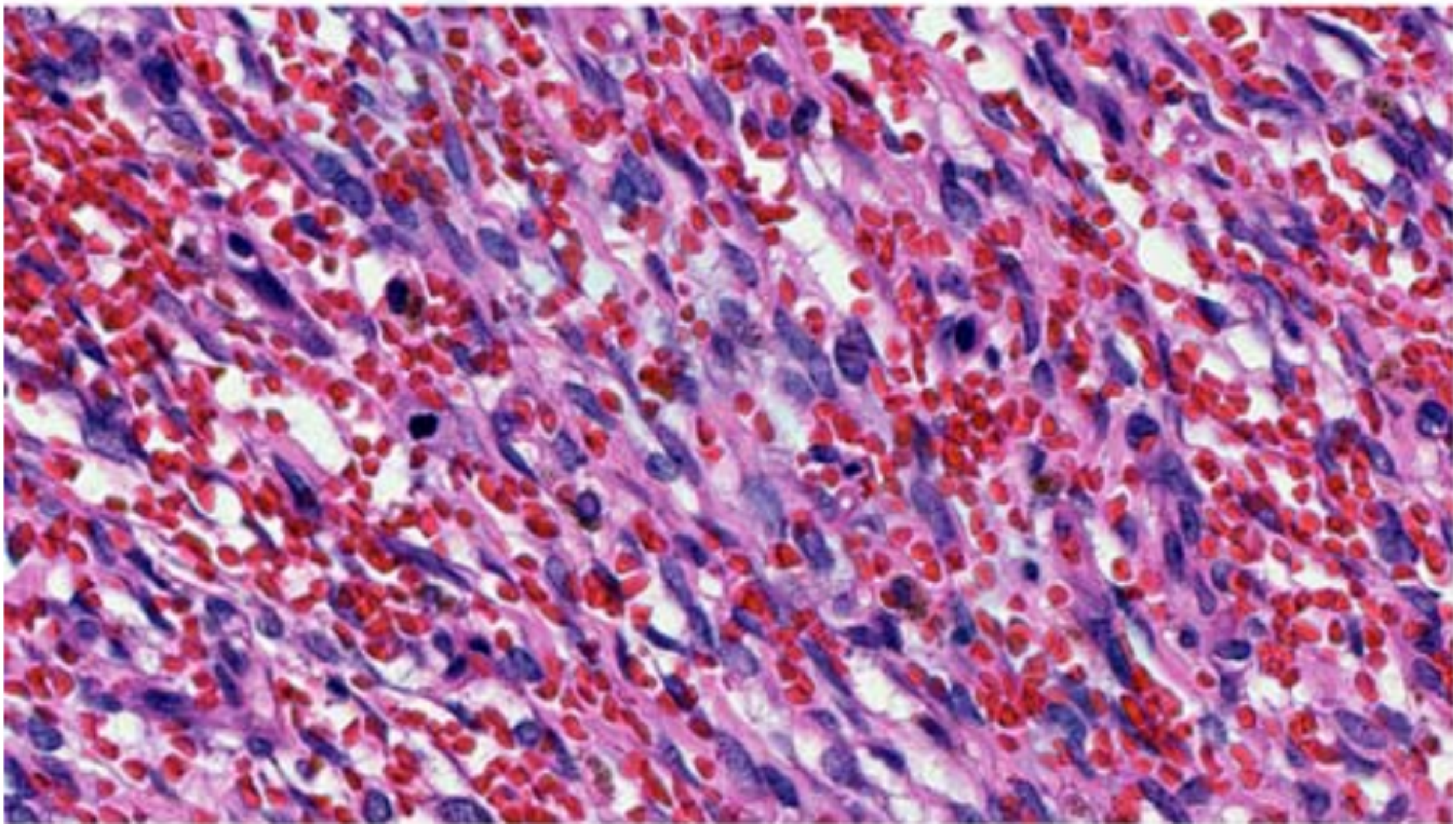
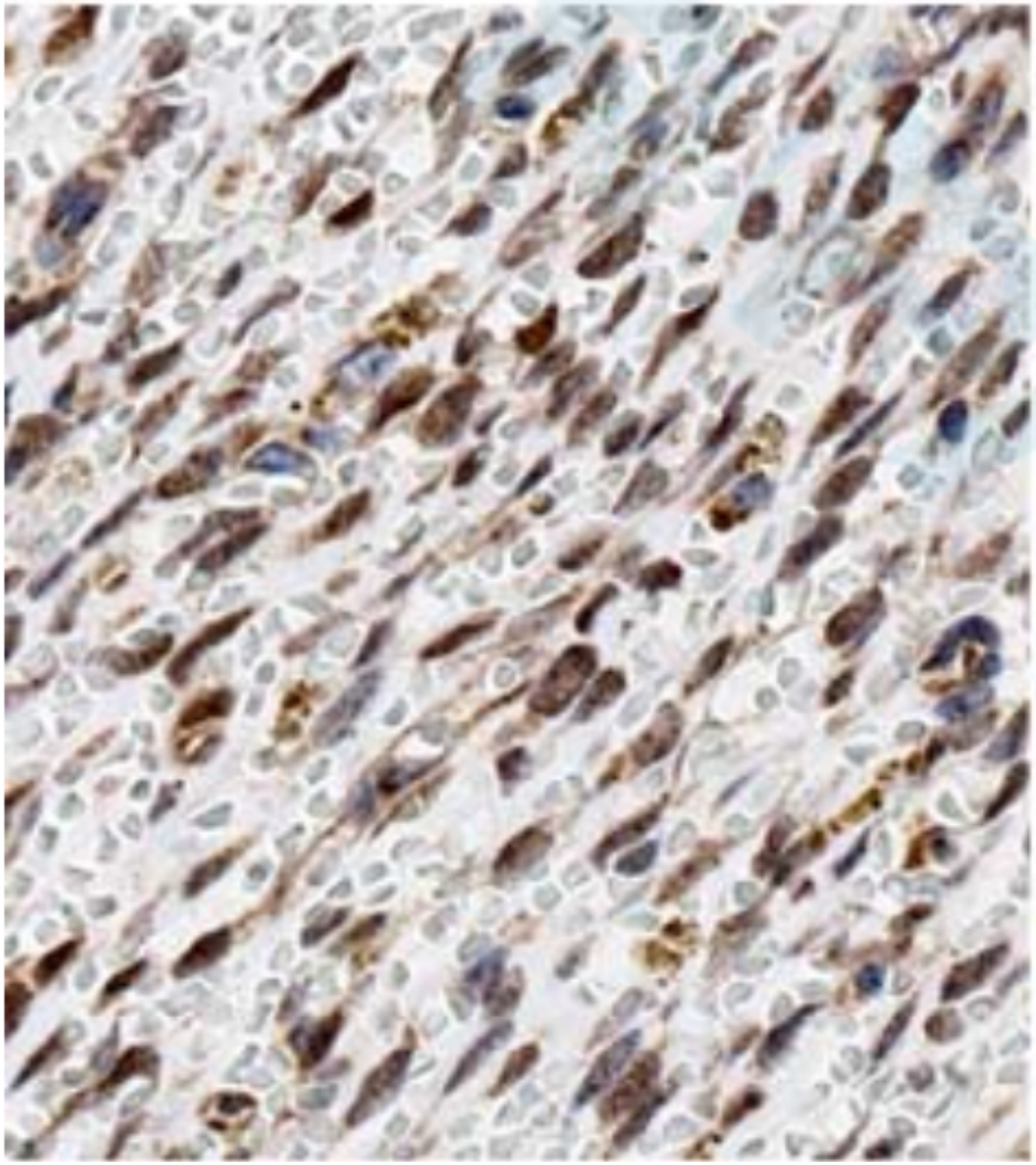


CCNB3

BCOR

C



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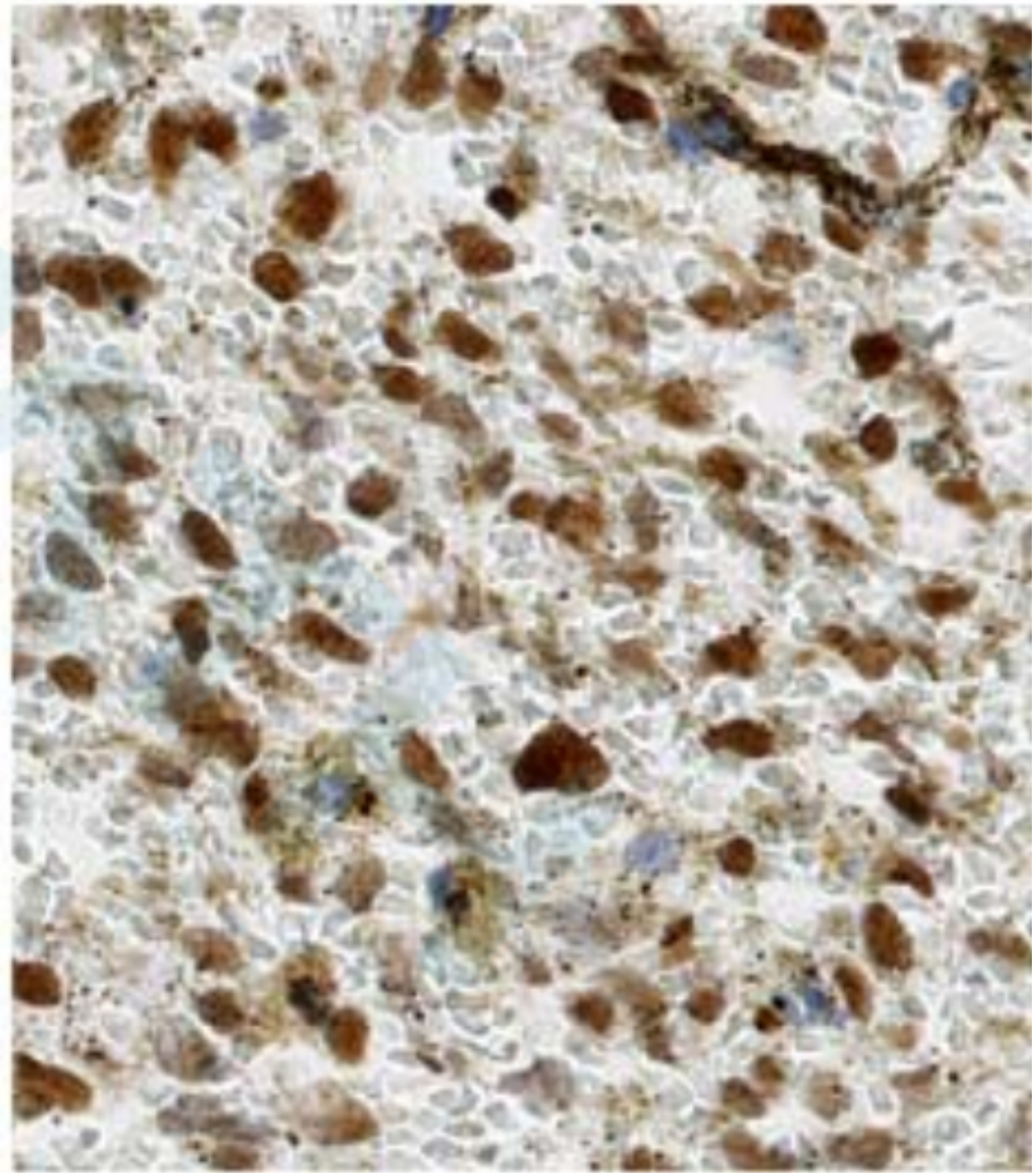
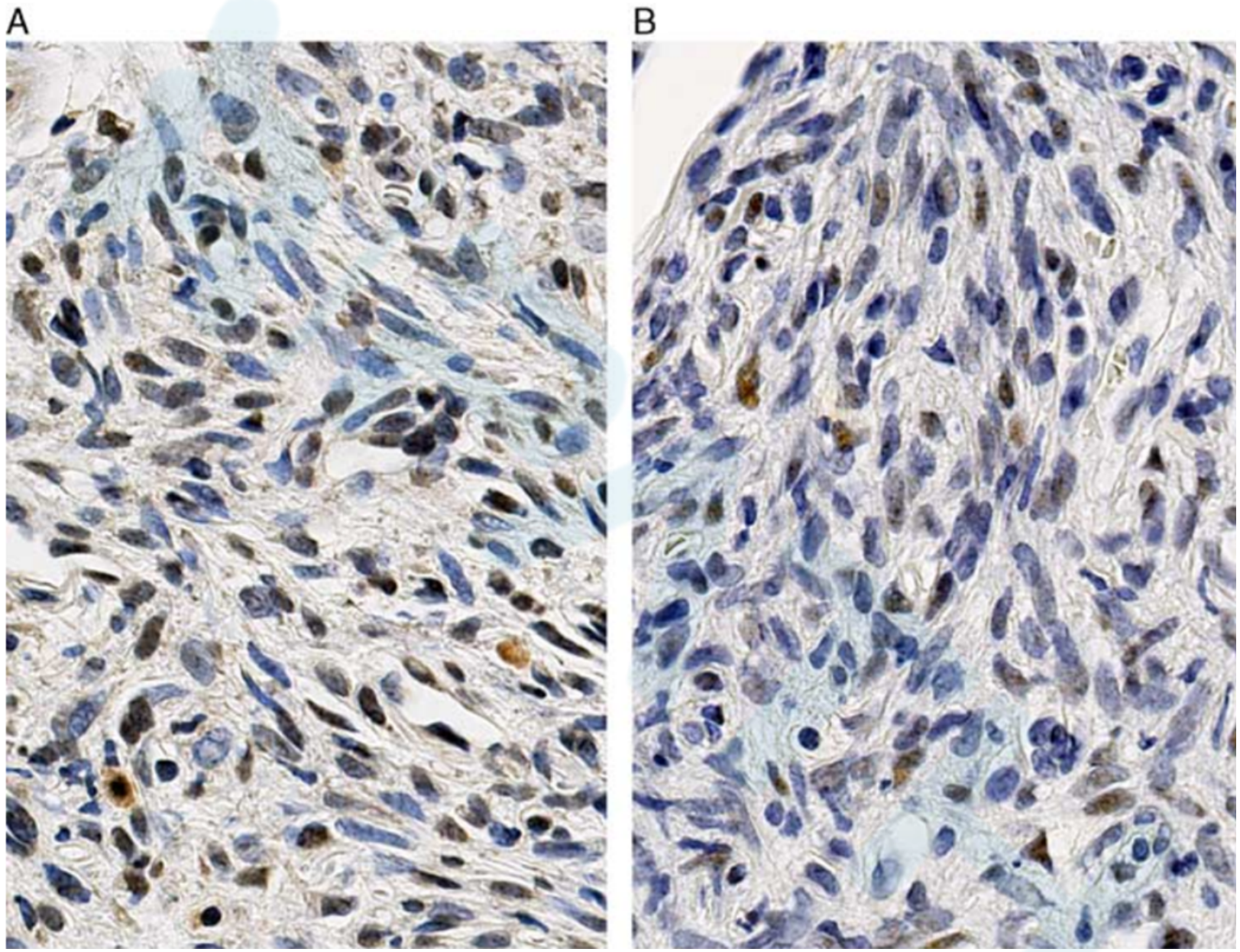


TABLE 2. Immmunohistochemical Expression of CCNB3 and BCOR in Small Round or Spindle Cell Tumors

	CCNB3	BCOR
Adipocytic tumors		
Spindle cell lipoma	0/22	0/22
Well-differentiated liposarcoma	0/23	0/23
Dedifferentiated liposarcoma	0/14	0/14
Myxoid/round cell liposarcoma	0/23	0/23
Fibroblastic/myofibroblastic tumors		
Nodular fasciitis	0/23	0/23
Myositis ossificans	0/4	0/4
Desmoid-type fibromatosis	0/23	0/23
Superficial fibromatosis	0/10	0/10
Dermatofibrosarcoma protuberans	0/19	0/19
Solitary fibrous tumor	3/19	5/19
Inflammatory myofibroblastic tumor	0/4	0/4
Myxoinflammatory fibroblastic sarcoma	0/2	0/2
Fibrosarcoma	1/11	0/11
Myxofibrosarcoma	0/24	0/24
Low grade fibromyxoid sarcoma	0/6	0/6
Smooth muscle and skeletal muscle tumors		
Leiomyosarcoma	0/20	0/20
Rhabdomyosarcoma	1/12	0/12
Vascular tumors		
Kaposi sarcoma	0/3	0/3
Kaposiform hemangioendothelioma	0/1	0/1
Angiosarcoma	0/6	0/6
Tumors of uncertain differentiation		
Myoepithelioma of soft tissue	0/3	0/3
Synovial sarcoma	0/17	3/17
Clear cell sarcoma	0/6	0/6
Desmoplastic small round cell tumor	0/1	0/1
Extraskeletal myxoid chondrosarcoma	0/8	0/8
Undifferentiated/unclassified sarcoma		
Undifferentiated pleomorphic sarcoma	0/22	0/22
Unclassified small round cell sarcoma	0/2	0/2
Unclassified spindle cell sarcoma	0/4	0/4
Chondrogenic, osteogenic, and Ewing tumors		
Dedifferentiated chondrosarcoma	0/3	0/3
Mesenchymal chondrosarcoma	0/2	0/2
Osteosarcoma	0/8	1/8
Ewing sarcoma	1/18	2/18
Other tumors		
Malignant peripheral nerve sheath tumor	0/17	0/17
Gastrointestinal stromal tumor	0/9	0/9
Malignant lymphoma	0/13	4/13
Small cell carcinoma	0/10	3/10
Total	6/412	18/412

CCNB3

BCOR

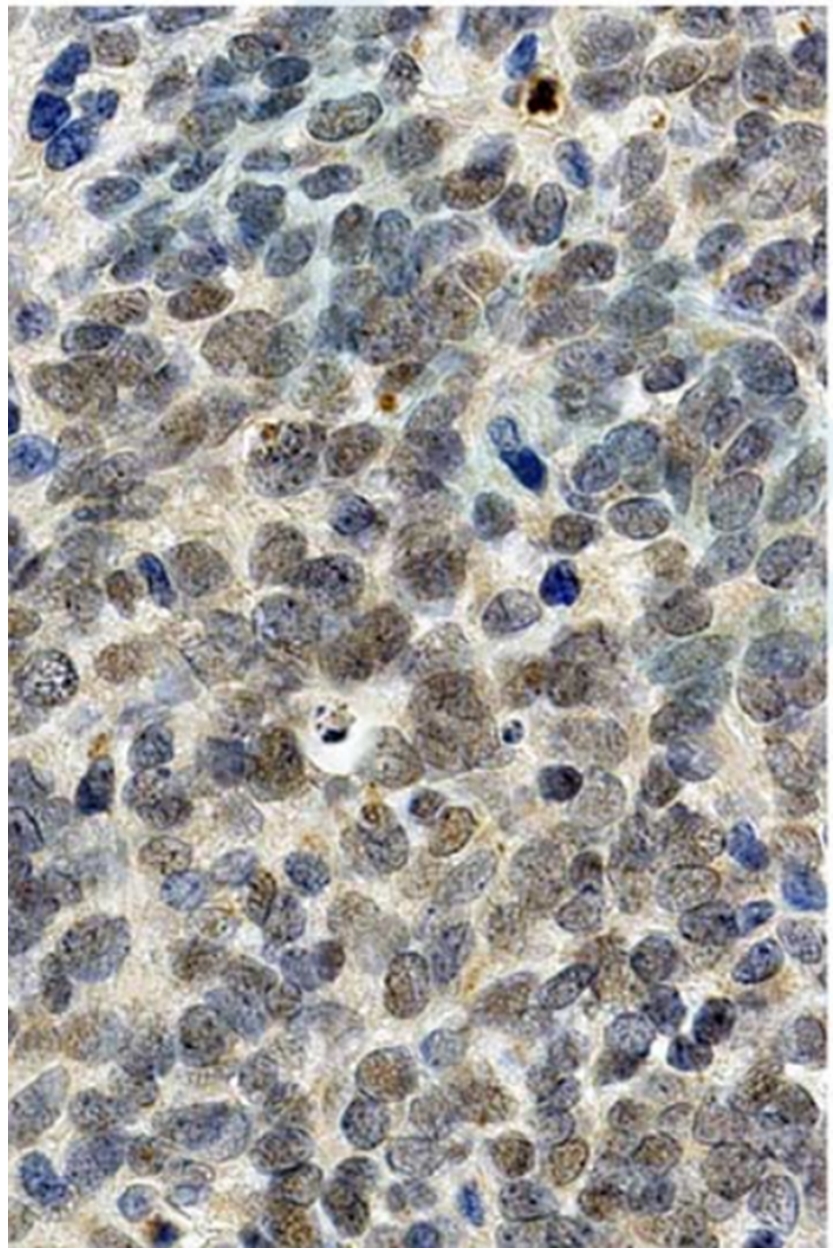


孤立性纤维性肿瘤

CCNB3

BCOR

C



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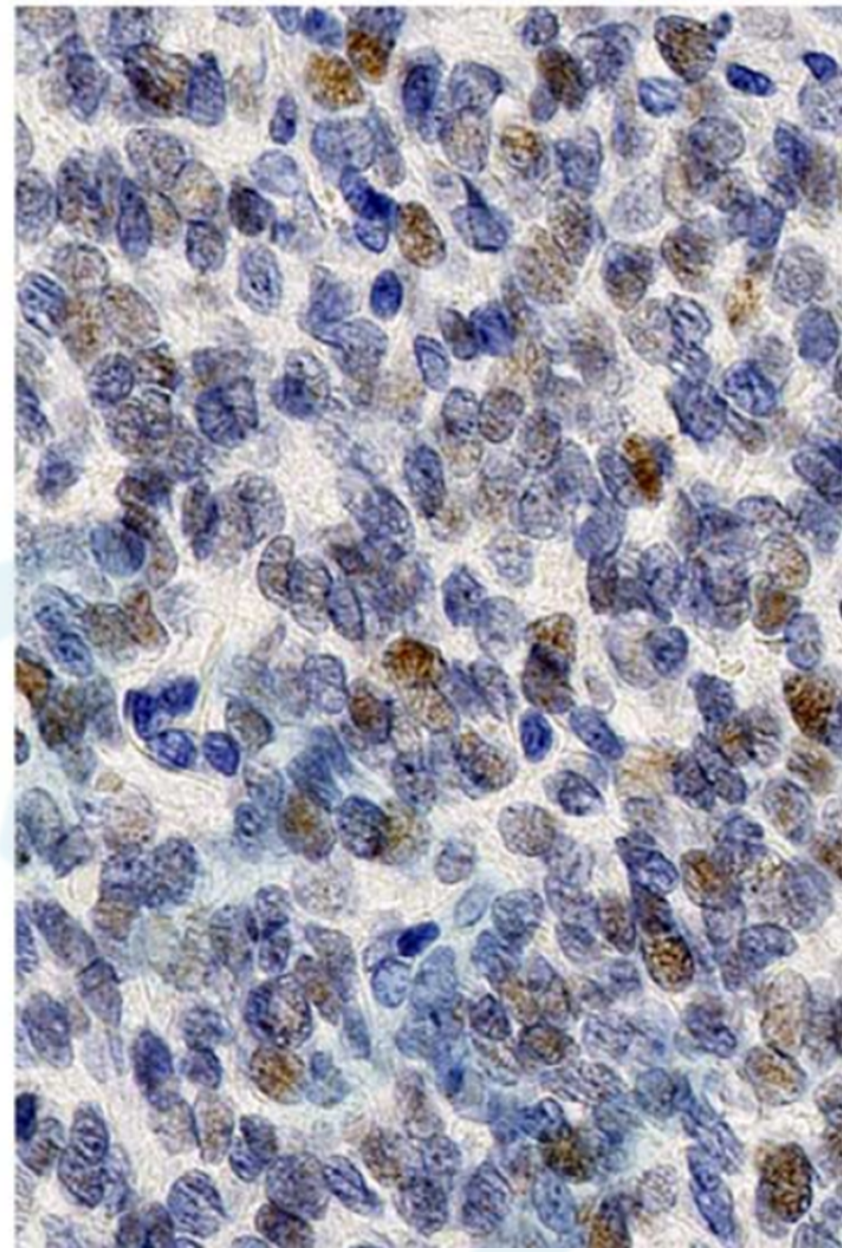

Ewing肉瘤

DISCUSSION

- Histologic variation in undifferentiated sarcomas with the BCOR-CCNB3 fusion

DISCUSSION

- More anatomic locations

  The present cases included 5 soft tissue and 4 skeletal tumors, as well as 1 each of a pulmonary and paranasal tumor

DISCUSSION

- Immunoreactivity to CCNB3 is not fully specific for BCOR-CCNB3 sarcomas ; BCOR is a sensitive marker, but is less specific than CCNB3 for BCOR-CCNB3 sarcomas

CONCLUSION

- A wider range of clinicopathologic features of undifferentiated sarcoma with BCOR-CCNB3 fusion than those described previously
- Many features may overlap partially not only with Ewing sarcoma, but also with other small round or spindle cell tumors, such as synovial sarcoma, SFTs, and vascular tumors

CONCLUSION

- Because immunohistochemistry for either CCNB3 or BCOR is not completely sensitive and specific, a molecular genetic approach, in addition to CCNB3 immunohistochemistry, is essential for diagnosis

Thanks