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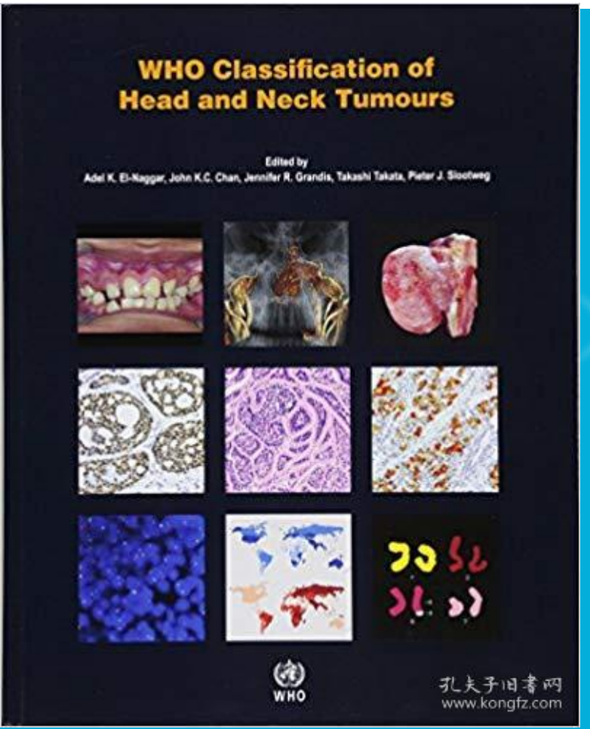
Expression of PAX3 Distinguishes Biphenotypic Sinonasal Sarcoma From Histologic Mimics

Vickie Y. Jo, MD, Adrián Mariño-Enríquez, MD, PhD, Christopher D.M. Fletcher, MD, FRCPath, and Jason L. Hornick, MD, PhD



汇 报 人：徐梦微
指导老师：刘坦坦

Journal Club

WHO classification of tumours of the nasal cavity, paranasal sinuses and skull base

Carcinomas	
Keratinizing squamous cell carcinoma	8071/3
Non-keratinizing squamous cell carcinoma	8072/3
Spindle cell squamous cell carcinoma	8074/3
Lymphoepithelial carcinoma	8082/3
Sinonasal undifferentiated carcinoma	8020/3
NUT carcinoma	8023/3*
Neuroendocrine carcinomas	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Adenocarcinomas	
Intestinal-type adenocarcinoma	8144/3
Non–intestinal-type adenocarcinoma	8140/3
Teratocarcinosarcoma	9081/3
Sinonasal papillomas	
Sinonasal papilloma, inverted type	8121/1
Sinonasal papilloma, oncocytic type	8121/1
Sinonasal papilloma, exophytic type	8121/0
Respiratory epithelial lesions	
Respiratory epithelial adenomatoid hamartoma	
Seromucinous hamartoma	
Salivary gland tumours	
Pleomorphic adenoma	8940/0
Malignant soft tissue tumours	
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma	8802/3
Leiomyosarcoma	8890/3
Rhabdomyosarcoma, NOS	8900/3
Embryonal rhabdomyosarcoma	8910/3
Alveolar rhabdomyosarcoma	8920/3
Pleomorphic rhabdomyosarcoma, adult type	8901/3
Spindle cell rhabdomyosarcoma	8912/3
Angiosarcoma	9120/3
Malignant peripheral nerve sheath tumour	9540/3
Biphenotypic sinonasal sarcoma	9045/3*
Synovial sarcoma	9040/3
Borderline/low-grade malignant soft tissue tumours	
Desmoid-type fibromatosis	8821/1
Sinonasal glomangiopericytoma	9150/1
Solitary fibrous tumour	8815/1
Epithelioid haemangioendothelioma	9133/3
Benign soft tissue tumours	
Leiomyoma	8890/0
Haemangioma	9120/0
Schwannoma	9560/0
Neurofibroma	9540/0
Other tumours	
Meningioma	9530/0
Sinonasal ameloblastoma	9310/0
Chondromesenchymal hamartoma	
Haematolymphoid tumours	
Extranodal NK/T-cell lymphoma	9719/3
Extraosseous plasmacytoma	9734/3
Neuroectodermal/melanocytic tumours	
Ewing sarcoma/primitive neuroectodermal tumour	9364/3
Olfactory neuroblastoma	9522/3
Mucosal melanoma	8720/3

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [776A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.

KEY WORDS

- ✓ **biphenotypic sinonasal sarcoma**
- ✓ **malignant peripheral nerve sheath tumor**
- ✓ **monophasic synovial sarcoma**
- ✓ **spindle cell rhabdomyosarcoma (RMS)**
- ✓ **solitary fibrous tumor**
- ✓ **sinonasal hemangiopericytoma**
- ✓ **cellular schwannoma**
- ✓ **alveolar RMS**

INTRODUCTION

双表型鼻腔鼻窦肉瘤（Biphenotypic Sinonasal Sarcoma）

- ICD-O编码：9045-3
- 男：女=1:2；发病中位年龄：52岁；好发于鼻腔和筛窦的上方，也可延伸至眼眶或筛板。
- 肿瘤境界不清，由密集的梭形细胞组成，呈长束状或交错束状排列，常见血管外皮瘤样结构，瘤细胞核形态温和，核分裂象罕见，未见坏死。
- IHC：S100(+)、SMA(+)

  CD34 、desmin 、MYOD1、myogenin、EMA

- Lewis JT, Oliveira AM, Nascimento AG, et al. Low-grade sinonasal sarcoma with neural and myogenic features: a clinicopathologic analysis of 28 cases. Am J Surg Pathol. 2012;36:517–525.
- 赵明,刘绮颖,赵丹珲,王哲,王坚.双表型鼻腔鼻窦肉瘤临床病理和分子遗传学特征分析[J].中华病理学杂　志,2017,46(12):841-846.

INTRODUCTION

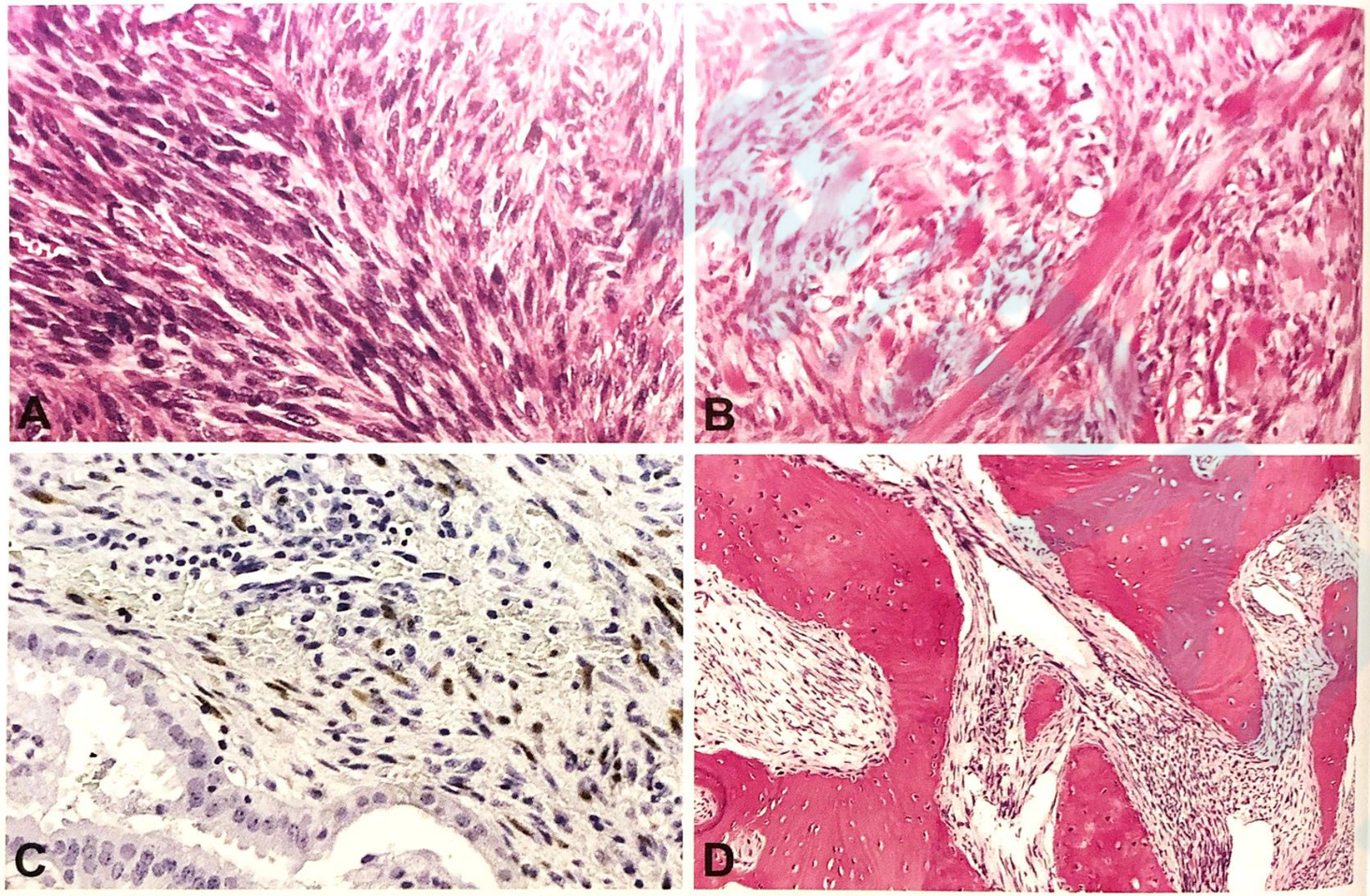


Fig. 1.33 Biphenotypic sinonasal sarcoma. **A** Uniform, elongate spindle cells arrayed in long intersecting fascicles; the nuclei show pale chromatin and punctate nucleoli without significant pleomorphism. **B** Focal rhabdomyoblastic differentiation is seen in a minority of biphenotypic sinonasal sarcomas. **C** S100 immunostaining often shows a spotty or patchy staining pattern. **D** Infiltration of sinonasal bones is a frequent finding.

Genetic profile

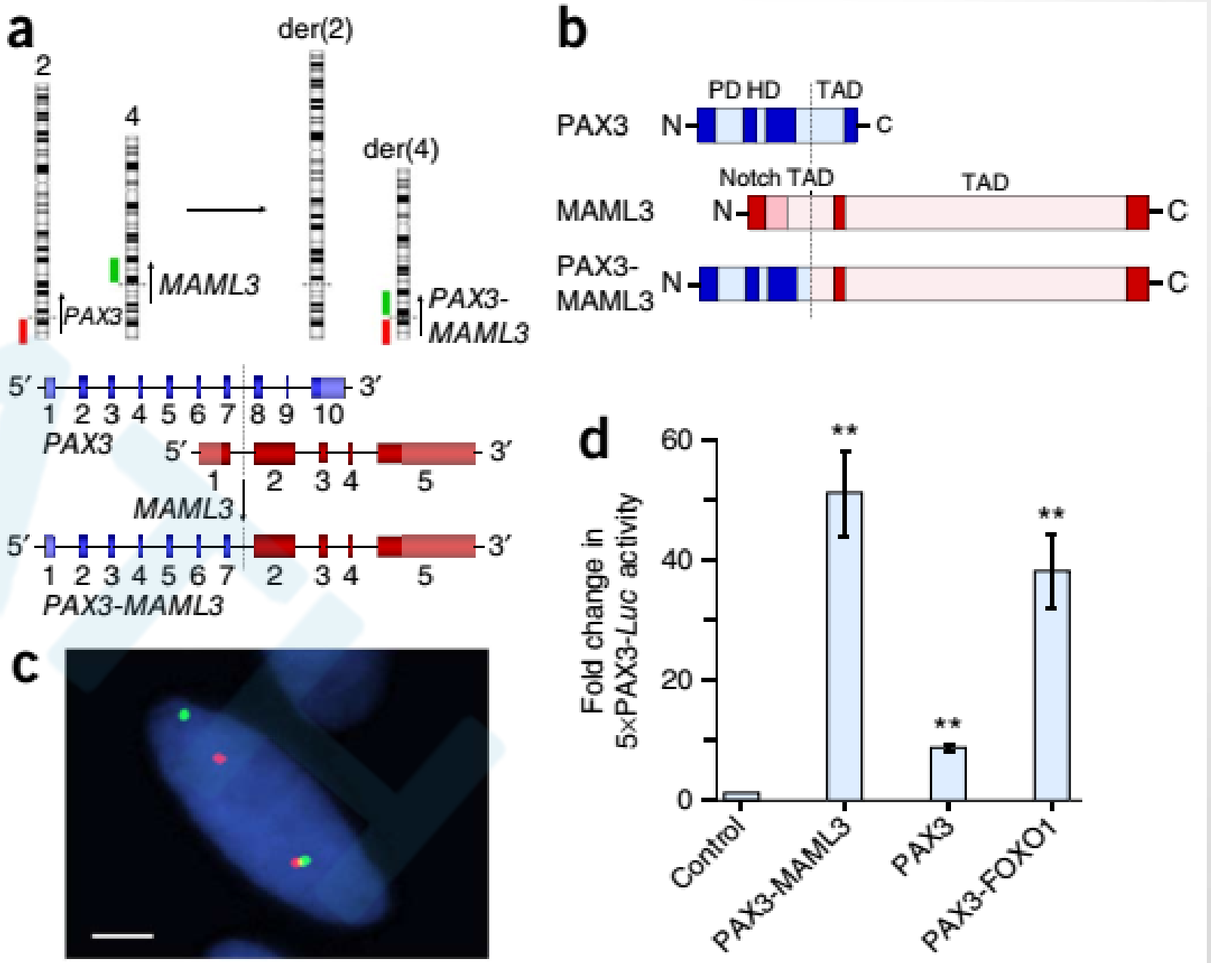
- ***PAX3 -MAML3*** gene fusion
- *PAX3 -FOXO1* gene fusion
- *PAX3 –NCOA1* gene fusion

INTRODUCTION

Recurrent *PAX3-MAML3* fusion in biphenotypic sinonasal sarcoma

Xiaoke Wang[1,7], Krista L Bledsoe[2,7], Rondell P Graham[1,7], Yan W Asmann[3], David S Viswanatha[1], Jean E Lewis[1], Jason T Lewis[1], Margaret M Chou[4], Michael J Yaszemski[5], Jin Jen[6], Jennifer J Westendorf[5] & André M Oliveira[1,5]

Biphenotypic sinonasal sarcoma (SNS) is a newly described tumor of the nasal and paranasal areas. Here we report a recurrent chromosomal translocation in SNS, t(2;4)(q35;q31.1), resulting in a PAX3-MAML3 fusion protein that is a potent transcriptional activator of PAX3 response elements. The SNS phenotype is characterized by aberrant expression of genes involved in neuroectodermal and myogenic differentiation, closely simulating the developmental roles of PAX3.



INTRODUCTION

低度恶性外周神经鞘瘤（malignant peripheral nerve sheath tumor）

- ICD-O编码：9540-3
- 起源于三叉神经的眼分支或上颌窦分支。肿块、疼痛、鼻出血、扁桃体易位和肿胀。
- 由细胞致密区和黏液样变的细胞疏松区相交互，可见局部坏死和血管周肿瘤细胞的聚集。瘤细胞胖梭形，紧密编织状排列，呈“鱼骨样”或波浪状排列。
- IHC：S100(+)、SOX10(+)
- 遗传学：NF1

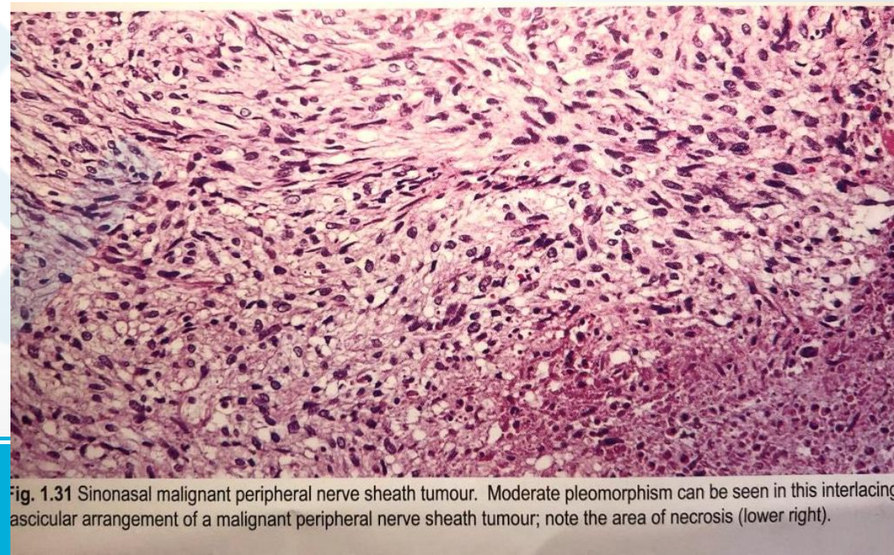


Fig. 1.31 Sinonasal malignant peripheral nerve sheath tumour. Moderate pleomorphism can be seen in this interlacing fascicular arrangement of a malignant peripheral nerve sheath tumour; note the area of necrosis (lower right).

滑膜肉瘤（Synovial sarcoma）

- ICD-O编码：9040-3
- 有单向性和双向性之分，双向性滑膜肉瘤具有上皮和梭形细胞成分，上皮细胞排列成腺样腔隙，腔内含上皮性黏液，细胞胞浆丰富，梭形细胞成分稀少；单向性滑膜肉瘤由一致性较小的椭圆形肿瘤细胞构成束状和片状，可含有大量的肥大细胞。
- IHC：CD99(+)、Bcl2(+)、CD56(+)
  S100(-)、WT1(-)
- 遗传学：*SS18* gene fusion

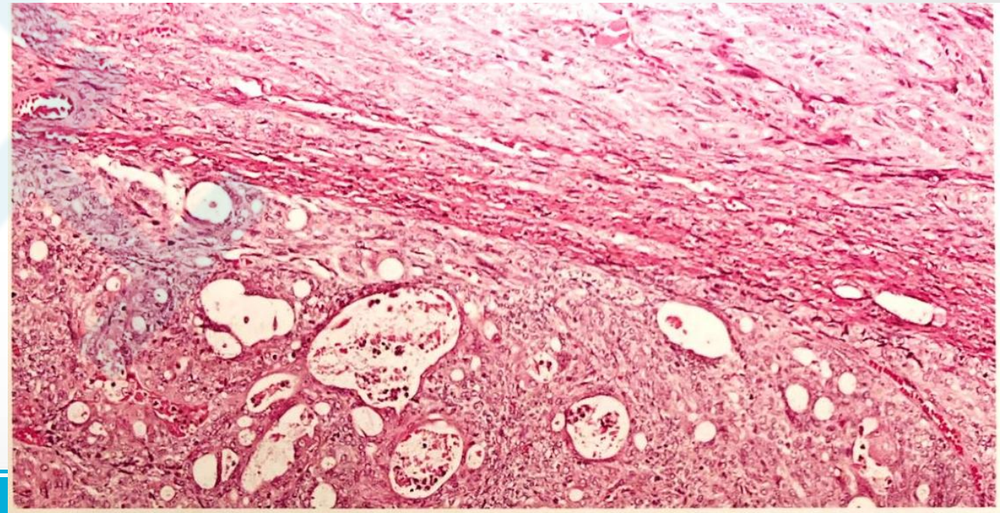
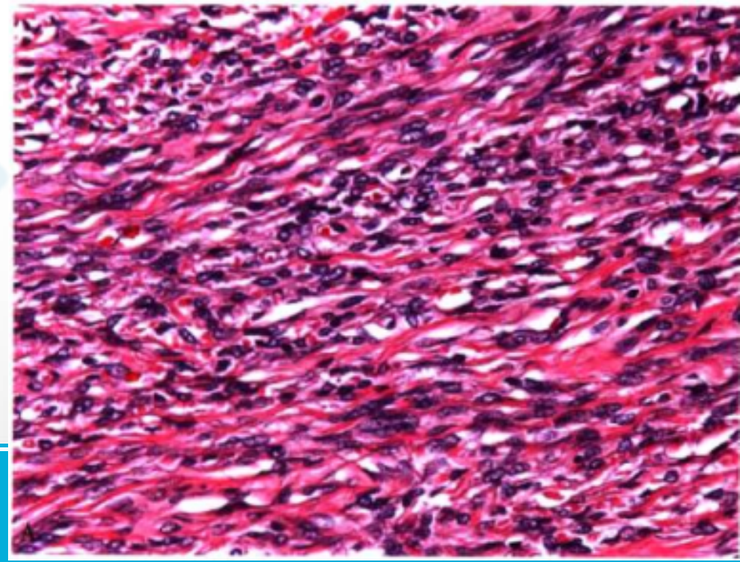


Fig. 1.35 Biphasic synovial sarcoma. High-power micrograph of a tumour of the skull base showing a biphasic appearance, with spindled and glandular cells.

孤立性纤维性肿瘤（solitary fibrous tumor）

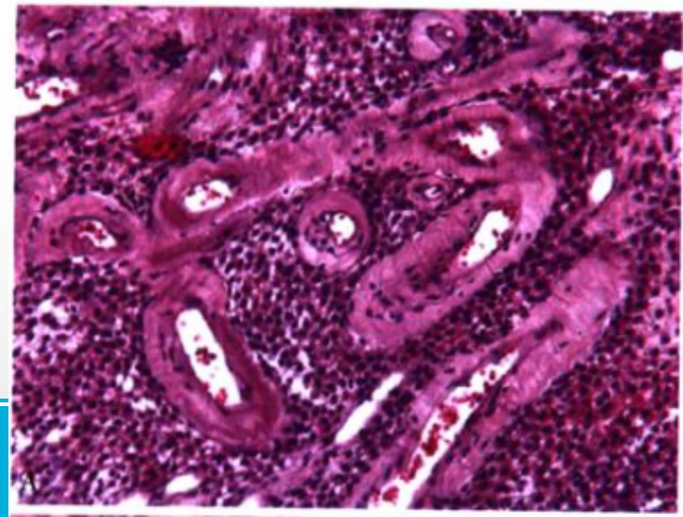
- ICD-O编码：8815-1
- 发生于任何年龄，无性别差异。鼻塞，鼻出血和其他非特异症状。肿瘤常为息肉状，质硬。
- 由不同程度增生的形态温和的卵圆形细胞，“绳索样”瘢痕胶原纤维及穿插于其中的薄壁血管构成。
- IHC：STAT6 (+)、CD34(+)、Bcl2(+)
- 遗传学：*NAB2-STAT6* gene fusion



INTRODUCTION

鼻腔鼻窦型血管外皮细胞瘤（sinonasal hemangiopericytoma）

- ICD-O编码：9150-1
- 发生于任何年龄，女性占优势。鼻塞，鼻出血和其他非特异症状。肿瘤常为息肉状，质软。
- 由密集的梭形细胞组成，呈短束状、席纹状、旋涡状排列，散在血管腔扩张伸展似珊瑚状或鹿角状，血管壁常伴有玻璃样变，核轻度异型。
- IHC：SMA(+)、β-catenin(+)、cyclin D1(+)、 XIIIa（+）、 Vimentin（+）
- 遗传学：β-catenin（*CCNB1*）



INTRODUCTION

PAX3

●PAX3基因是PAX家族转录因子的成员。PAX家族由九个人类基因（PAX1-PAX9）和九个小鼠基因（Pax1-Pax9）成员组成，分成四个亚族。

●PAX3可作为大多数靶基因的转录激活因子。在PAX3靶基因中，第一组与肌肉发育相关，第二组与神经和黑色素细胞发育相关。靶基因编码的蛋白质调节各种功能活性，包括分化，增殖，迁移，粘附和凋亡。

●在多种肿瘤中检测到表达：

- **腺泡状横纹肌肉瘤（ARMS）**
- **双表型鼻腔鼻窦肉瘤（BSNS）**
- **胶质母细胞瘤**
- **恶性黑色素瘤**
- **骨肉瘤**

INTRODUCTION

PAX8

- PAX转录因子家族的成员。参与甲状腺滤泡细胞的发育和甲状腺特异性基因的表达。
- PAX8（和PAX2）是泌尿生殖系统形态发生的重要调节因子之一。
- 主要表达于甲状腺、肾导管组织、副中肾管组织及相关肿瘤中，并在子宫内膜，卵巢，输卵管，精囊，附睾，胰岛细胞和淋巴样细胞中表达。

Pan-Trk Immunohistochemistry Is an Efficient and Reliable Screen for the Detection of *NTRK* Fusions

Jaclyn F. Hechtman, MD, Ryma Benayed, PhD,* David M. Hyman, MD,† Alexander Drilon, MD,† Ahmet Zehir, PhD,* Denise Frosina, BS,* Maria E. Arcila, MD,* Snjezana Dogan, MD,* David S. Klimstra, MD,* Marc Ladanyi, MD,* and Achim A. Jungbluth, MD**

Abstract: Activating neurotrophic tyrosine receptor kinase (*NTRK*) f… says, are … explore th… detect *NT*… prospectiv… eration s… arrangeme… assessed v… mAb EPR… and 20 cases negative for *NTRK* fusions on Archer. Of 23 cases with *NTRK* rearrangements, 15 had known activating fusions. Archer detected fusion transcripts in 6 of 8 novel *NTRK* rearrangements of uncertain functional significance. Pan-Trk IHC was positive in 20 of 21 cases with *NTRK* fusion transcripts confirmed by Archer. The discordant negative case was a mismatch repair- deficient colorectal carcinoma with an *ETV6-NTRK3* fusion. All 20 additional Archer-negative cases had concordant pan-TRK IHC results. Pan-Trk IHC sensitivity and specificity for transcribed *NTRK* fusions was 95.2% and 100%, respectively. All positive IHC cases had cytoplasmic staining while the following fusion partner-specific patterns were discovered: all 5 *LMNA-NTRK1* fusions displayed nuclear mem-

结直肠癌、膀胱癌、胶质瘤、肺癌、肉瘤、黑色素瘤、乳腺分泌性癌、腮腺分泌性癌共21例，均检测到NTRK基因融合。20/21Pan-Trk免疫组化染色阳性。

Neurotrophic tyrosine kinase receptor (*NTRK*) is a family of 3 proto-oncogenes including *NTRK1*, … Trk … bio- … tion, … In … inase … sent. … ingly … h re-

Screening *NTRK* fusions is usually done on a molecular level and can be achieved with next-generation sequencing (NGS) of DNA, or targeted RNA testing. However, molecular analyses are still expensive, comparable time-consuming and sampling error or nucleic acid degradation can pose a technical risk. Immunohistochemistry (IHC) is a well established method, usually less expensive and fast compared with current molecular tests. Here, we investigate pan-Trk IHC as a faster and more tissue-efficient method to identify *NTRK* fusions.

OBJECTIVE

➢评估PAX3和PAX8免疫组织化学在鉴别BSNS与组织学形态相类似肿瘤之间的诊断效用，并且评估了BSNS中pan-TRK抗体的免疫组化表达。

MATERIALS AND METHODS

肿瘤样本

- 15 BSNS
- malignant peripheral nerve sheath tumor(MPNST)
- monophasic synovial sarcoma
- spindle cell rhabdomyosarcoma (RMS)
- solitary fibrous tumor(SFT)
- sinonasal hemangiopericytoma(HPC)
- cellular schwannoma
- 10 alveolar RMS

10例

组织学，免疫组织化学和荧光原位杂交

MATERIALS AND METHODS

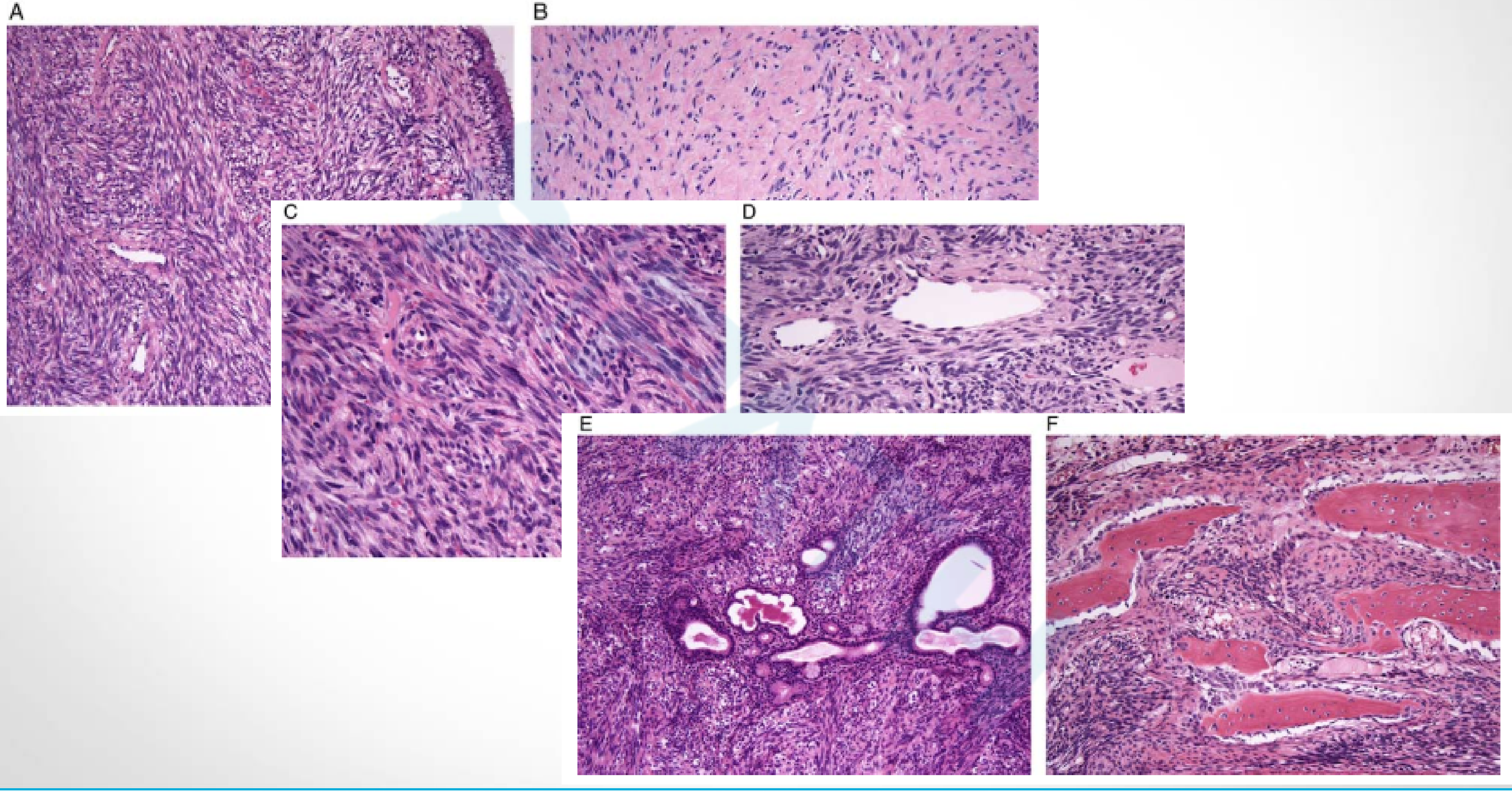
IHC

- PAX3 monoclonal antibody (clone 274212, Fisher Scientific, Pittsburgh, PA)
- PAX8 polyclonal antibody (Proteintech, Chicago, IL)
- pan-TRK monoclonal antibody (clone EPR17341, Abcam, Cambridge, MA)

FISH

- 样本：9例BSNS及1例梭形细胞RMS
- 具有> 30%核显示分离信号提示PAX3重排的阳性

Results

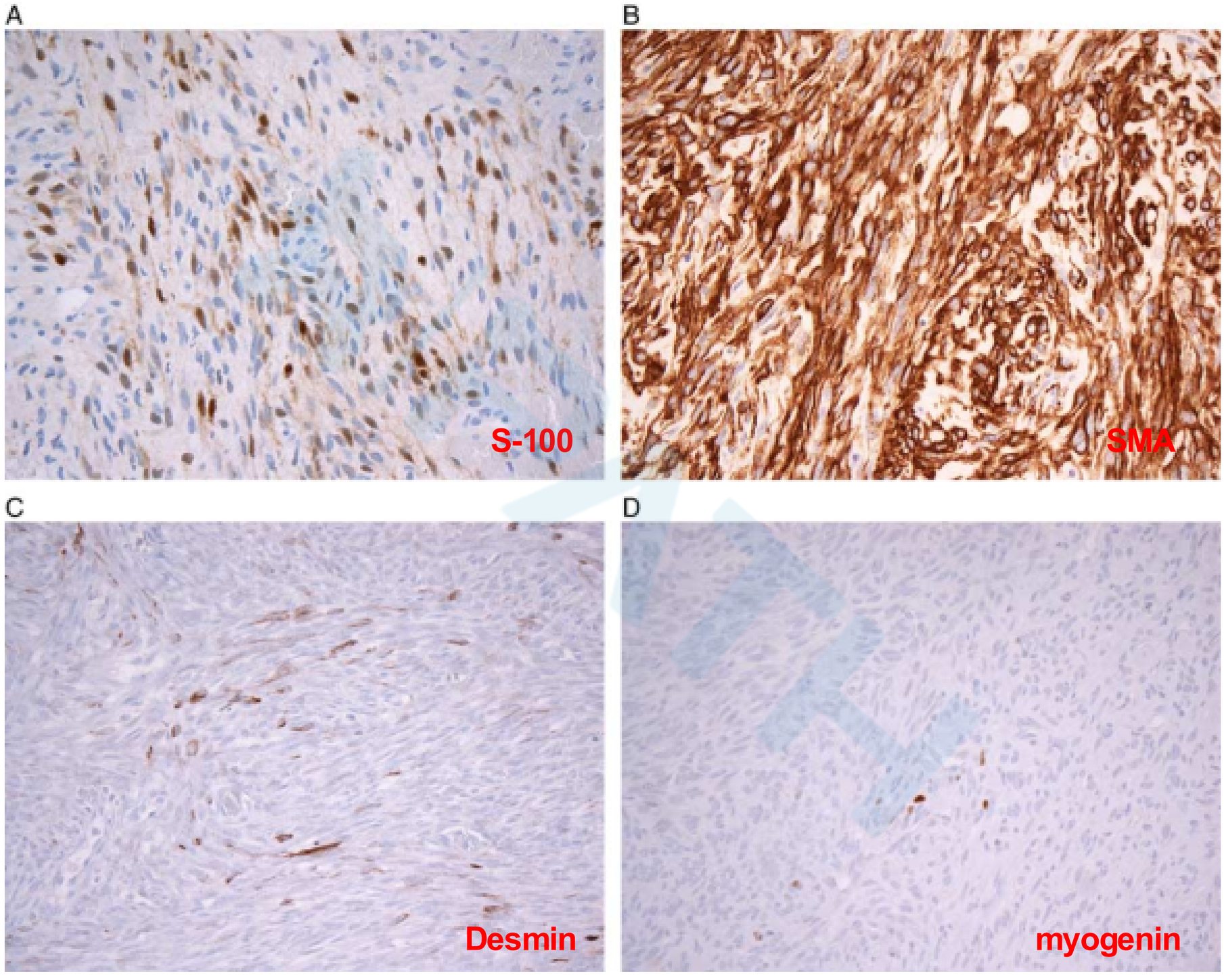

A
B
C
D
E
F

RESULTS

TABLE 1. PAX3 and Polyclonal PAX8 Staining in BSNS and its Histologic Mimics

	n/N (%)	
	PAX3	**PAX8**
BSNS	15/15 (100)	15/15 (100)
MPNST	0/10 (0)	7/10 (70)
Monophasic synovial sarcoma	0/10 (0)	1/10 (10)
SFT	0/10 (0)	1/10 (10)
Sinonasal HPC	0/10 (0)	2/10 (20)
Cellular schwannoma	0/10 (0)	3/10 (30)
Spindle cell RMS	1/10 (10)	1/10 (10)

RESUL



RESULTS

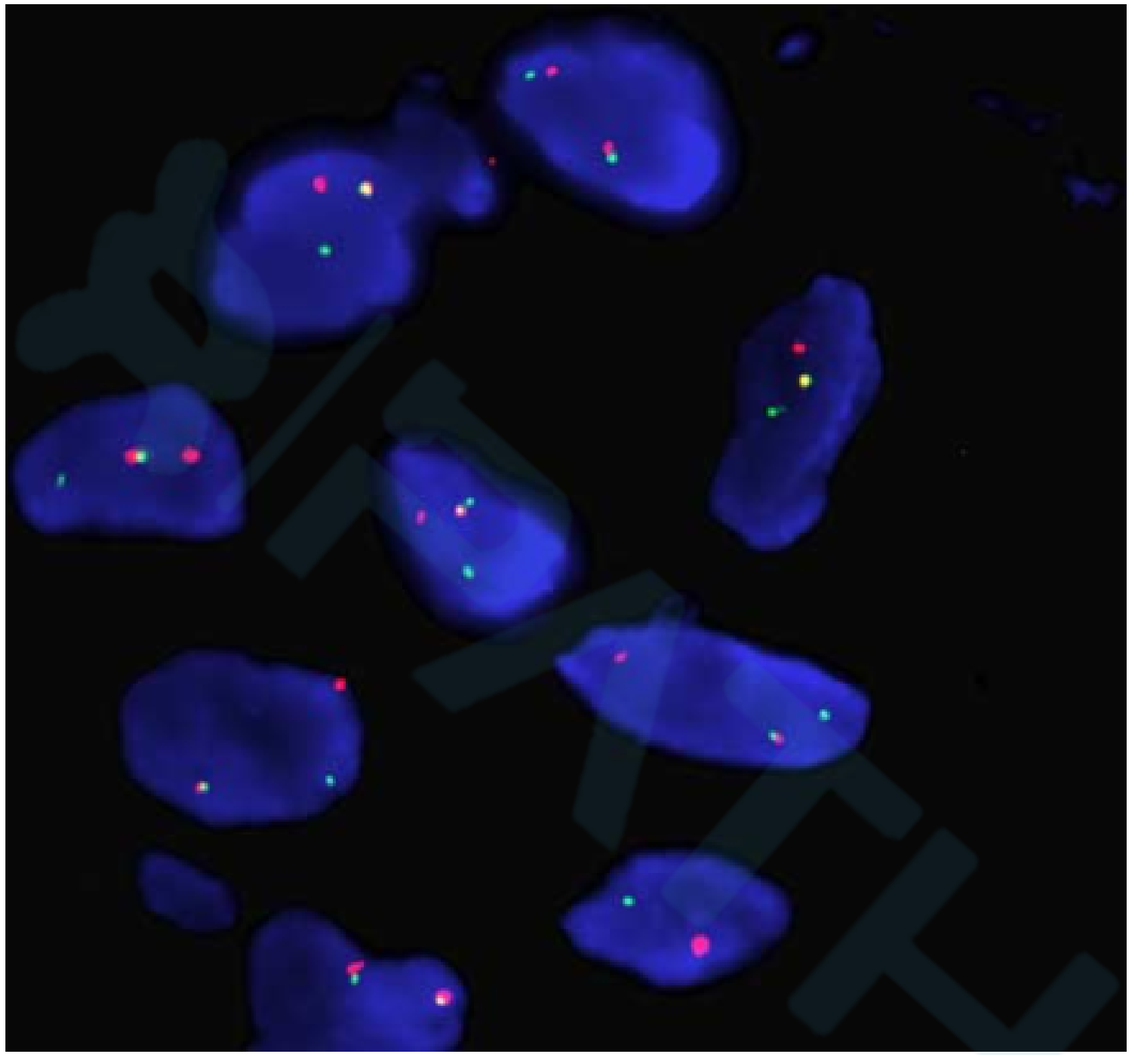
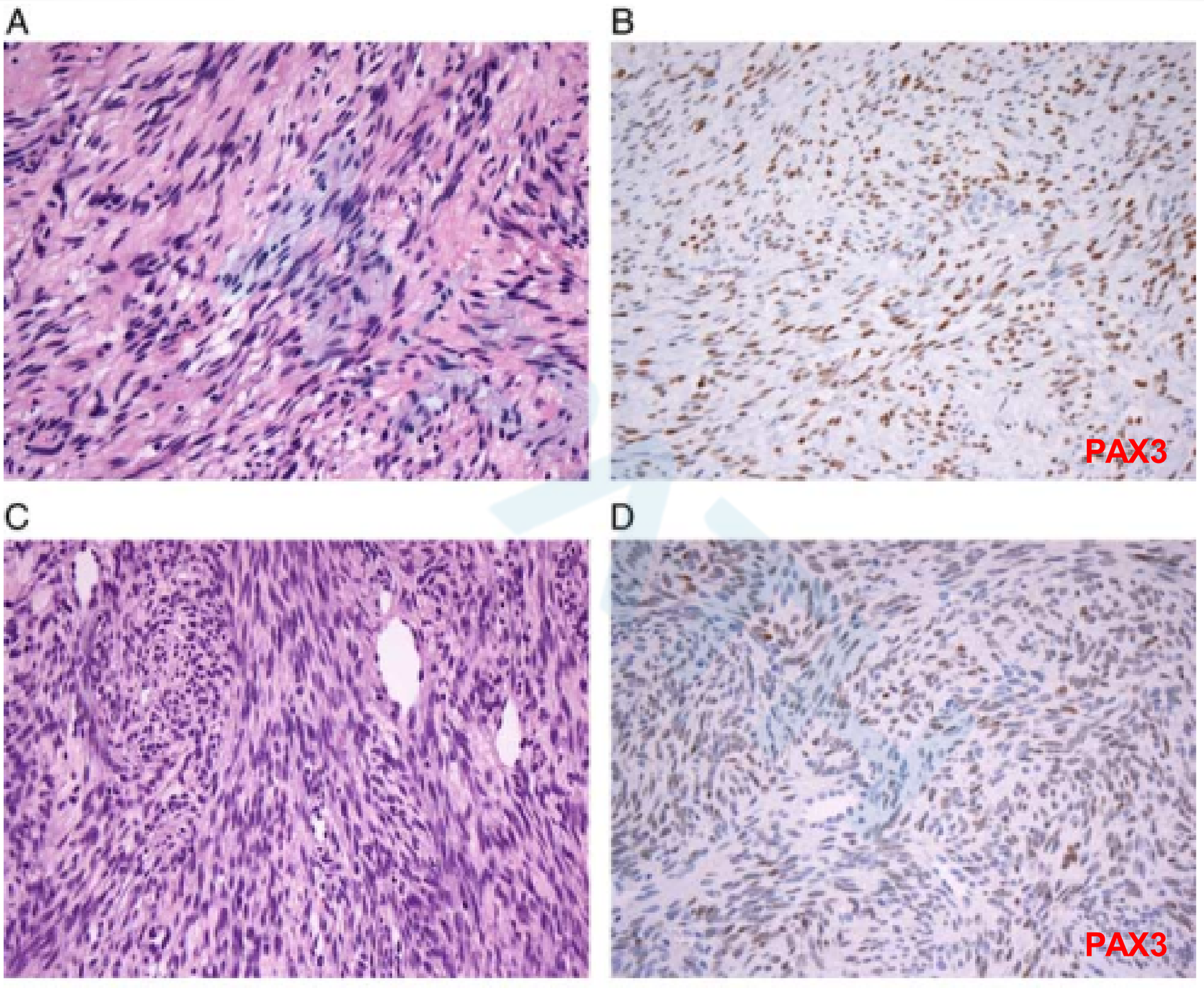


FIGURE 3. *PAX3* rearrangement was confirmed in all 9 BSNS cases tested. FISH analysis showing separate green, telomeric *PAX3* and red, centromeric *PAX3* signals.

RESULTS



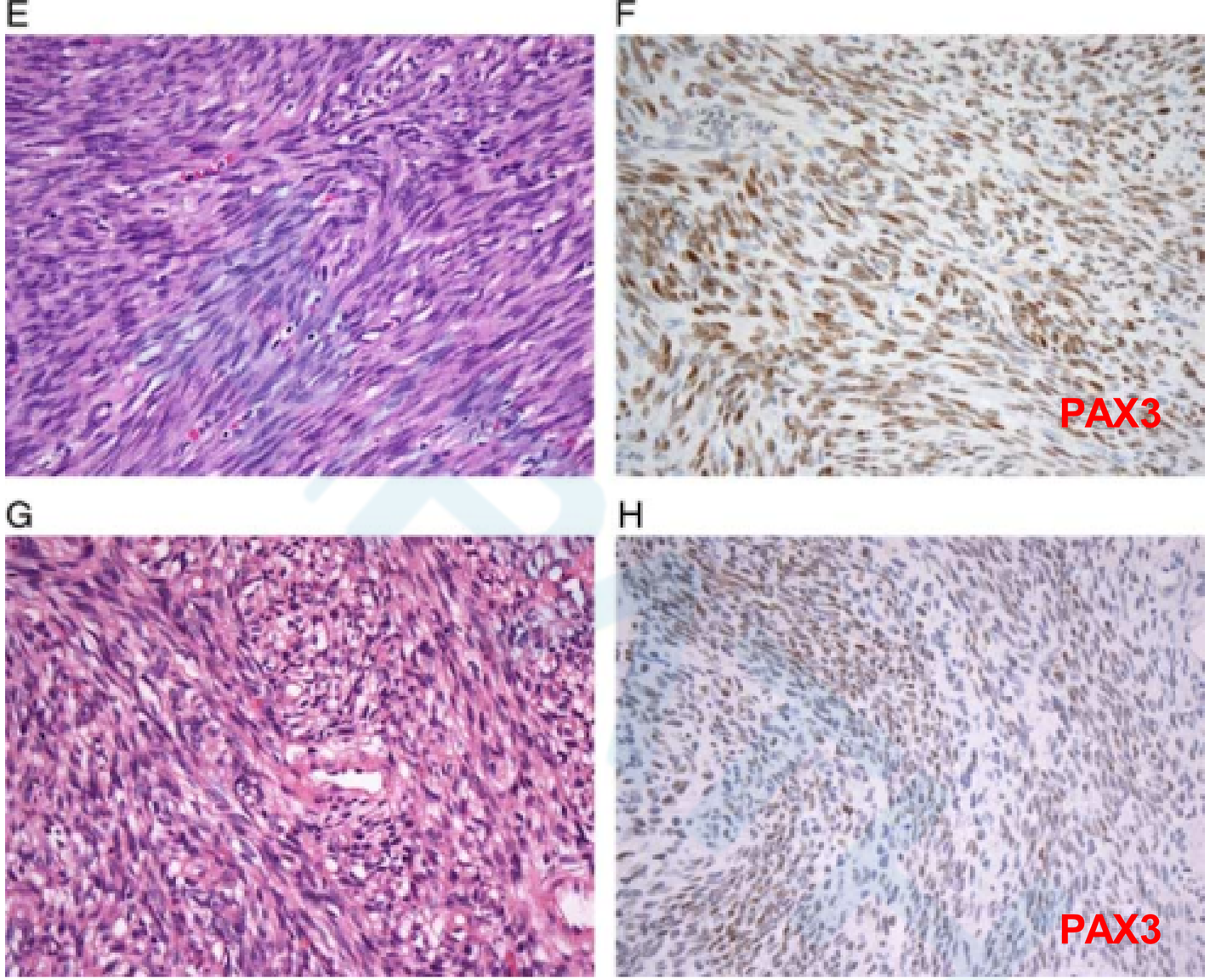


FIGURE 4. All 15 cases of BSNS showed nuclear expression of PAX3. BSNS from the nasal cavity mass of a 44-year-old woman (A, hematoxylin and eosin [H&E]), which had *PAX3* rearrangement and diffuse and strong nuclear PAX3 expression (B). A *PAX3*-rearranged BSNS from the nasal cavity of a 33-year-old woman (C, H&E) showing diffuse and moderate PAX3 expression (D). The *PAX3* status was unknown in this nasal cavity mass from a 37-year-old woman (E, H&E), which showed strong and diffuse PAX3 staining (F). This BSNS from the maxillary sinus of a 38-year-old woman was originally diagnosed as MPNST (G, H&E), and was confirmed to have both *PAX3* rearrangement and PAX3 expression (H).

RESULTS

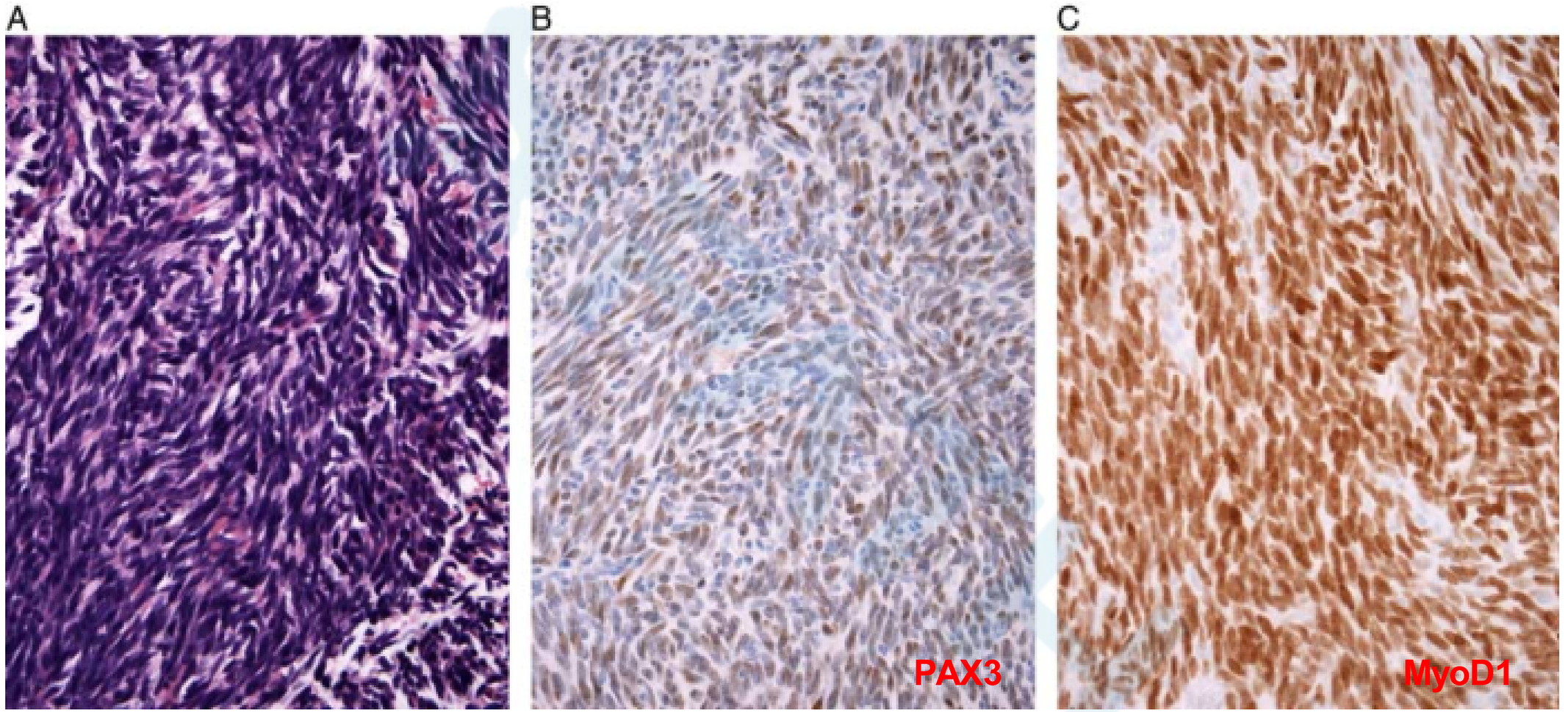


FIGURE 5. Among histologic mimics, PAX3 expression was seen in a single case of spindle cell RMS (A, hematoxylin and eosin; B, PAX3), which was confirmed to have strong diffuse MyoD1 expression (C).

RESULTS

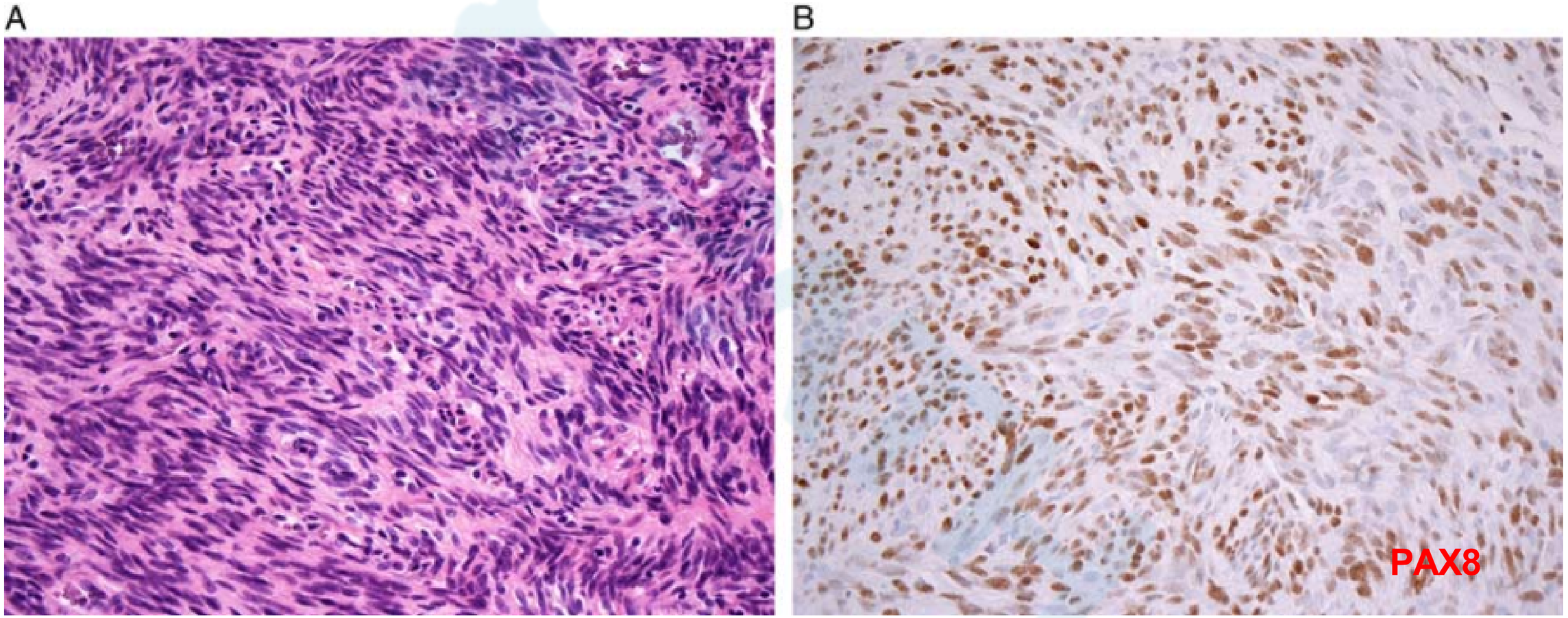


FIGURE 6. PAX8 expression was frequent in BSNS, as illustrated in this case from the nasal cavity of a 36-year-old man (A, hematoxylin and eosin; B, PAX8).

RESULTS

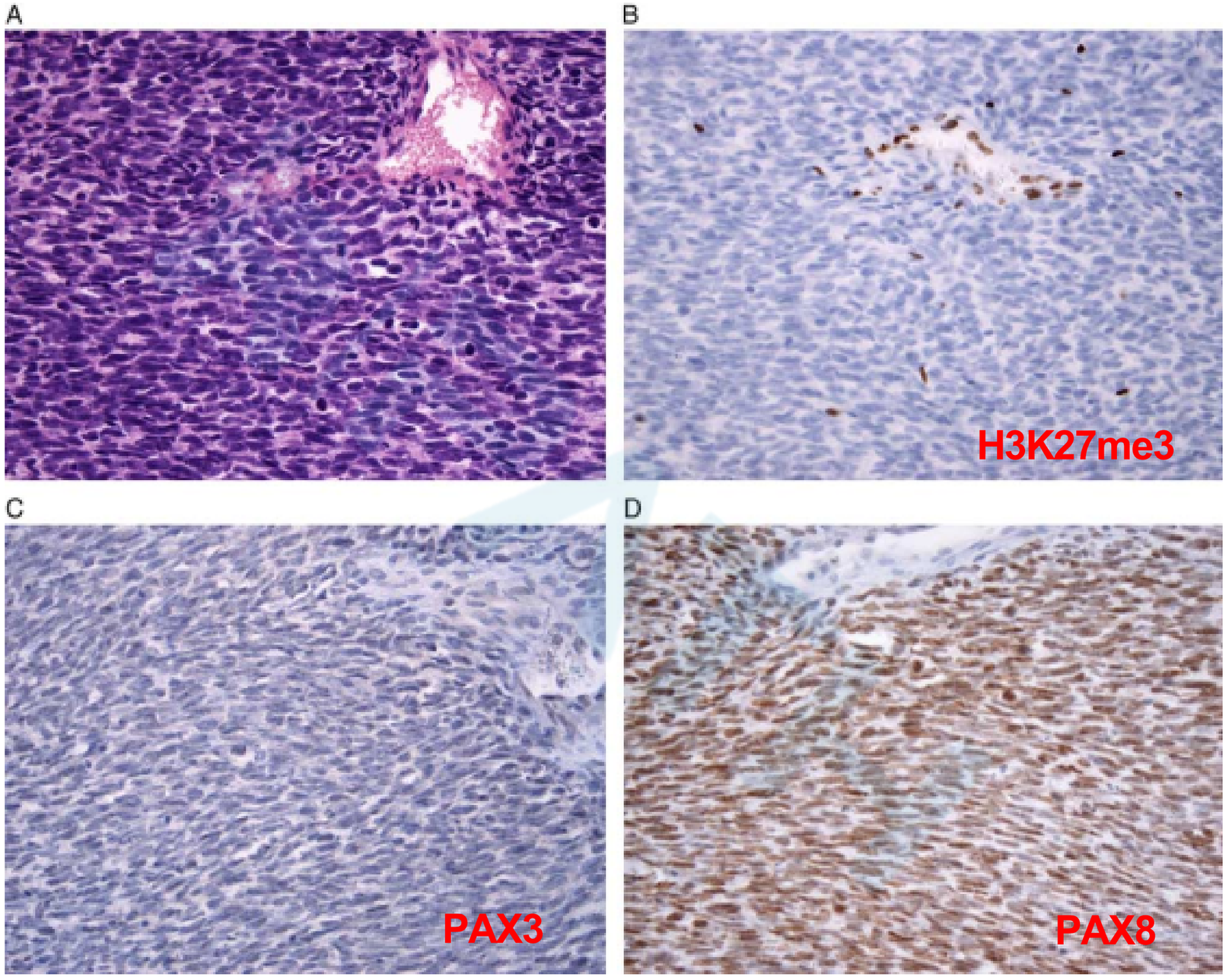
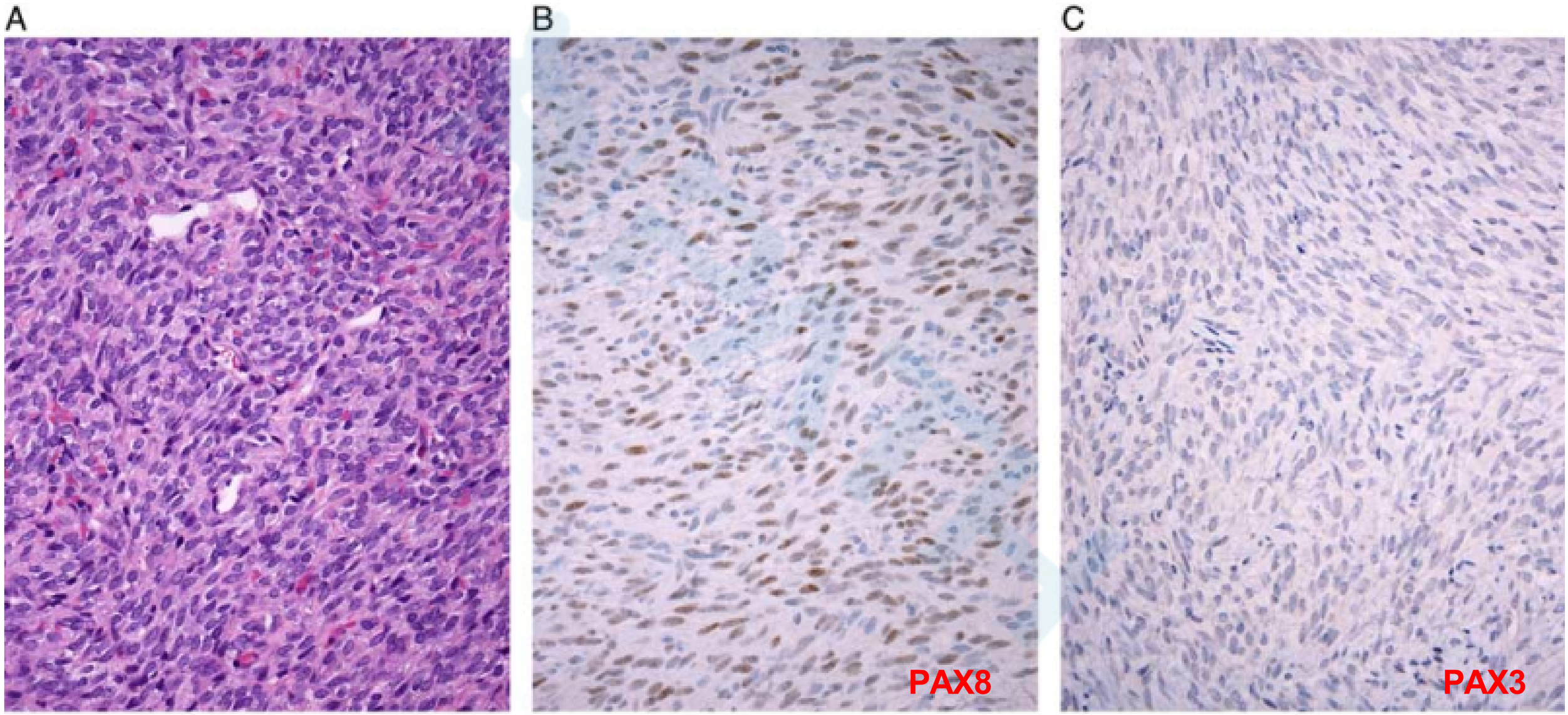
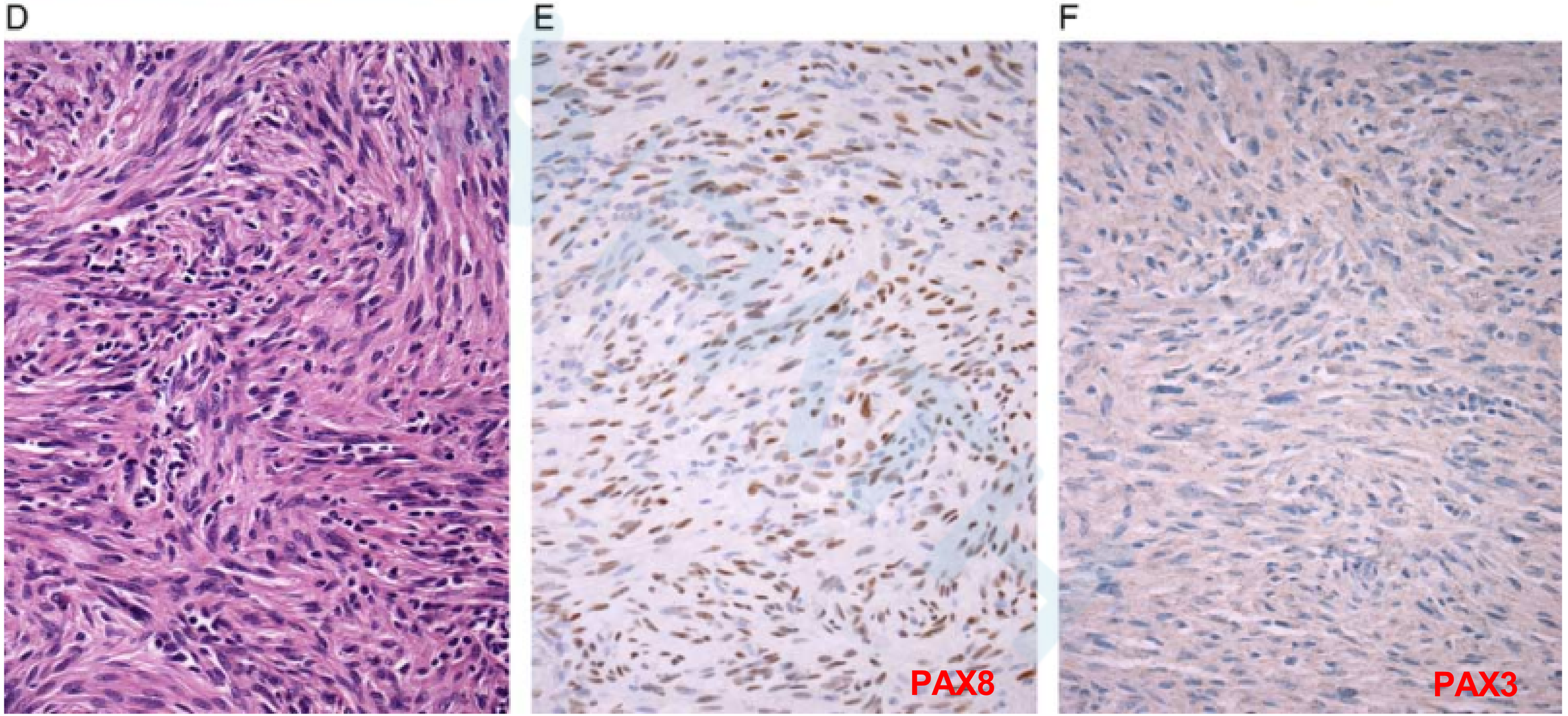


FIGURE 7. MPNST (A, hematoxylin and eosin; B, H3K27me3) was consistently negative for PAX3 (C), but showed frequent PAX8 expression (D).

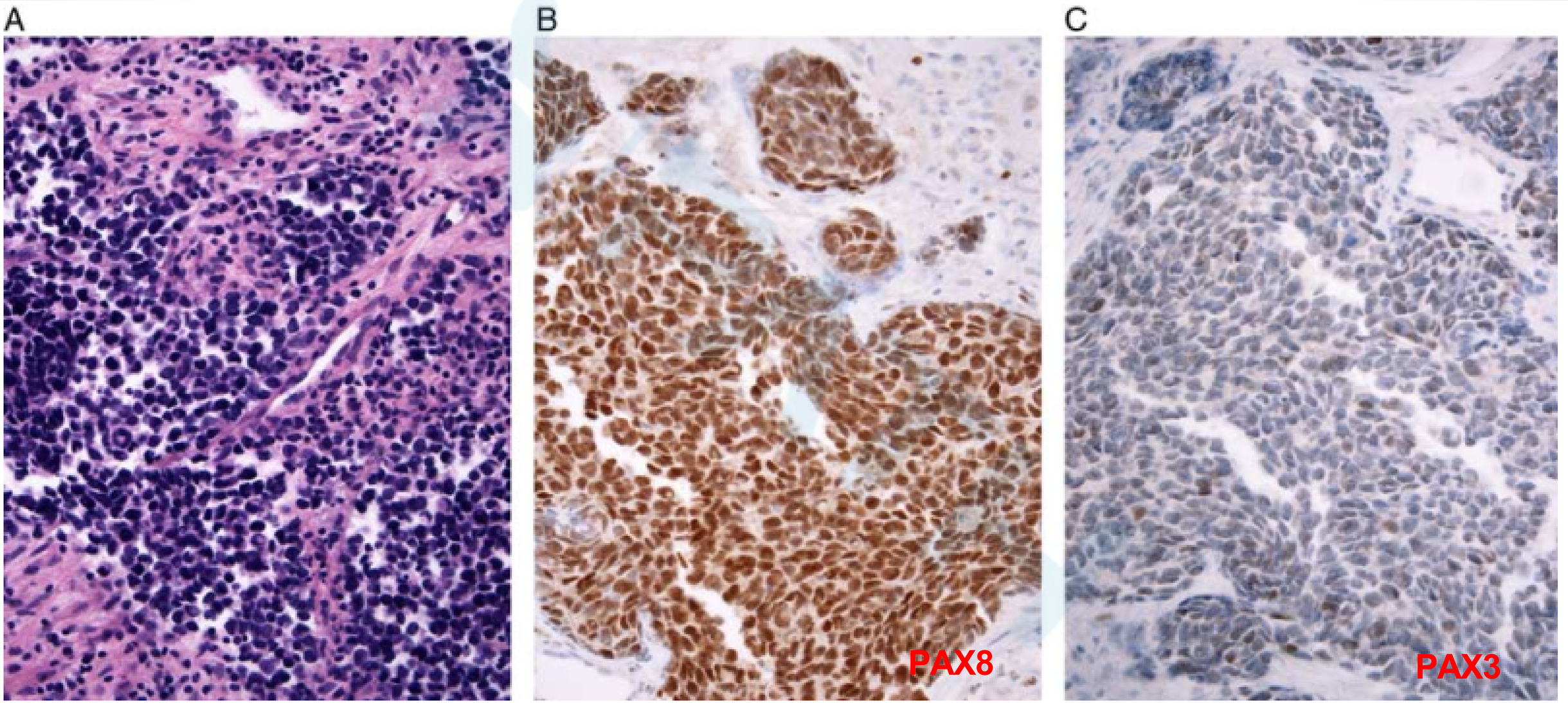
RESULTS



RESULTS



RESULTS



RESULTS

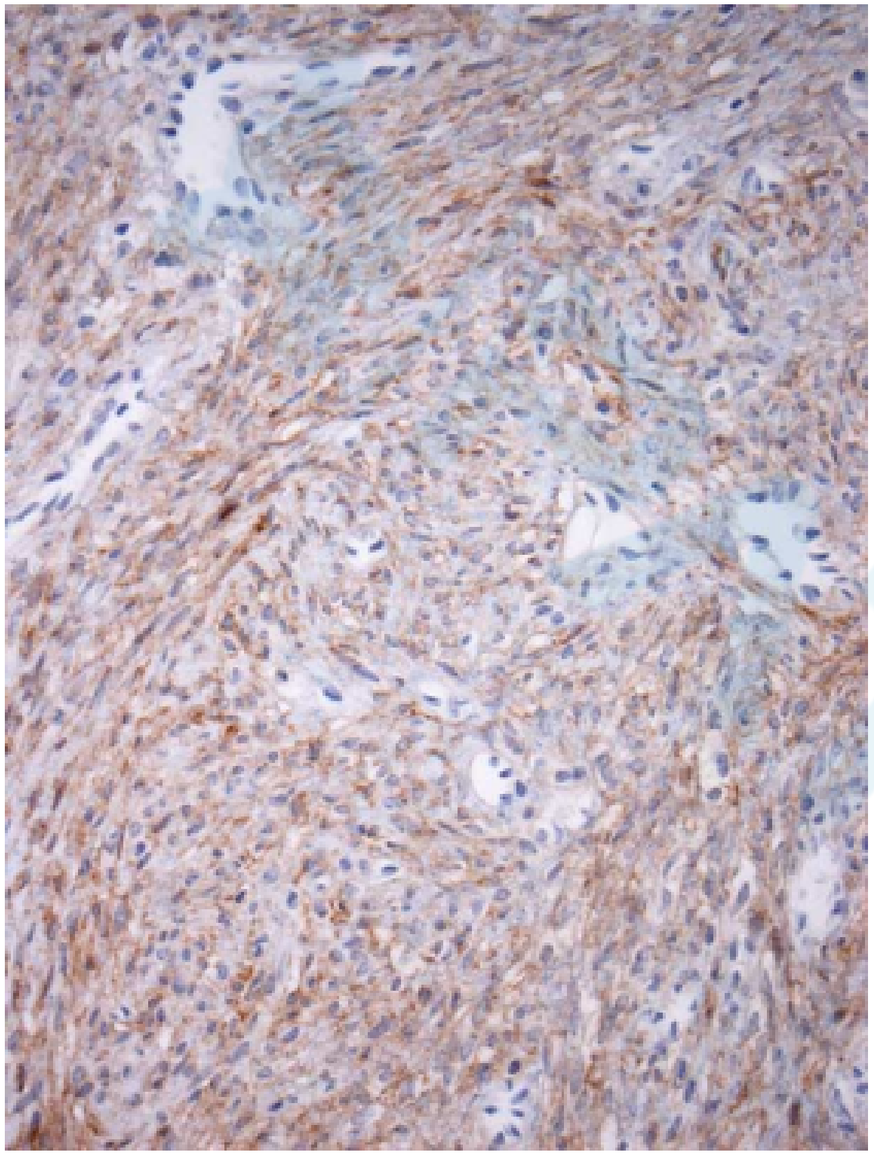


FIGURE 10. Cytoplasmic expression of pan-TRK was seen in most (12/14) cases of BSNS.

DISCUSSION

malignant peripheral nerve sheath tumor

- S-100、SOX10、H3K27me3
- **PAX3**

monophasic synovial sarcoma

- EMA、TLE1 /
- **SMA, desmin, and PAX3**
- **SS18 rearrangement**

spindle cell rhabdomyosarcoma (RMS)

- **PAX3、MyoD1**
- **molecular testing**

solitary fibrous tumor

- **characteristic “patternless pattern**
- **STAT6 and PAX3**

DISCUSSION

sinonasal hemangiopericytoma

- CTNNB1 mutations
- β-catenin

cellular schwannoma

- unencapsulated in the sinonasal tract
- not infiltrative
- SOX10 (+)
  PAX3 (-)

alveolar RMS

- PAX3 and PAX7 rearrangement
- *PAX3-FOXO1* and *PAX3-NCOA1* fusion
- PAX2 (100%),
  PAX5 (7.1–67%)
  PAX8 (35.4%)

.

Pan-TRK

tumors with NTRK fusion genes

CONCLUSION

- **PAX3** immunohistochemistry is a useful diagnostic marker for BSNS, and enables distinction from its morphologic mimics with high sensitivity and specificity.
- **PAX8** has much lower specificity (75%) for BSNS and should be interpreted with caution in the context of other immunohistochemical markers.
- evaluating a low grade spindle cell neoplasm in the sinonasal tract

  SMA, desmin,S-100, SOX10, and PAX3 .

Thanks for your attention