

**Original contribution****Synovial sarcoma of nerve**

**Bernd W. Scheithauer MD<sup>a,\*</sup>, Kimberly K. Amrami MD<sup>c</sup>, Andrew L. Folpe MD<sup>a</sup>,  
Ana I. Silva MD<sup>a,d</sup>, Mark A. Edgar MD<sup>e</sup>, James M. Woodruff MD<sup>e</sup>,  
Allan D. Levi MD, PhD<sup>f</sup>, Robert J. Spinner MD<sup>b</sup>**

<sup>a</sup>Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, MN 55905, USA

<sup>b</sup>Department of Neurosurgery, Mayo Clinic, Rochester, MN 55905, USA

<sup>c</sup>Department of Radiology, Mayo Clinic, Rochester, MN 55905, USA

<sup>d</sup>Department of Pathology, Hospital Sao Marcos, Braga, Portugal

<sup>e</sup>Department of Pathology, Memorial Sloan-Kettering Cancer Center (JMW, Emeritus), New York, NY 10021, USA

<sup>f</sup>Department of Neurosurgery, University of Miami, Miami, FL 33133, USA

Received 21 June 2010; revised 11 August 2010; accepted 20 August 2010

**Keywords:**

Nerve;  
Sarcoma;  
Synovial sarcoma;  
Immunohistochemistry

**Summary** Tumors of peripheral nerve are largely neuroectodermal in nature and derived from 2 elements of nerve, Schwann or perineurial cells. In contrast, mesenchymal tumors affecting peripheral nerve are rare and are derived mainly from epineurial connective tissue. The spectrum of the latter is broad and includes lipoma, vascular neoplasms, hematopoietic tumors, and even meningioma. Of malignant peripheral nerve neoplasms, the vast majority are primary peripheral nerve sheath tumors. Malignancies of mesenchymal type are much less common. To date, only 12 cases of synovial sarcoma of nerve have been described. Whereas in the past, parallels were drawn between synovial sarcoma and malignant glandular schwannoma, an uncommon form of malignant peripheral nerve sheath tumor, molecular genetics have since clarified the distinction. Herein, we report 10 additional examples of molecularly confirmed synovial sarcoma, all arising within minor or major nerves. Affecting 7 female and 3 male patients, 4 tumors occurred in pediatric patients. Clinically and radiologically, most lesions were initially thought to be benign nerve sheath tumors. On reinterpretation of imaging, they were considered indeterminate in nature with some features suspicious for malignancy. Synovial sarcoma of nerve, albeit rare, seems to behave in a manner similar to its more common, soft tissue counterpart. Those affecting nerve have a variable prognosis. Definitive recommendations regarding surgery and adjuvant therapies await additional reports and long-term follow-up. The literature is reviewed and a meta-analysis is performed with respect to clinicopathologic features versus outcome.

© 2011 Published by Elsevier Inc.

**1. Introduction**

The vast majority of peripheral nerve tumors are neuroectodermal in nature. Derived mainly from Schwann

cells, most are represented by schwannoma and neurofibroma. Only in recent years have the 2 variants of perineurioma come to be recognized, a soft tissue form unassociated with nerve [1] and subsequently the intraneural variety involving multiple fascicles and exhibiting pseudo-onion bulb formation, a highly distinctive histologic feature [2]. Mesenchymal tumors and tumor-like lesions are rare and comprise a wide variety of benign and malignant soft tissue tumors [3,4].

\* Corresponding author. Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, MN 55905, USA.

E-mail address: [scheithauer.bernd@mayo.edu](mailto:scheithauer.bernd@mayo.edu) (B. W. Scheithauer).

Synovial sarcoma is a distinctly rare primary tumor of nerve. Only 12 examples have been described to date [5-15]. This may not only reflect its true rarity in this anatomical location but may also reflect the natural tendency of pathologists to diagnose as “malignant peripheral nerve sheath tumor” (MPNST) all monomorphous, spindle cell sarcomas arising in nerve. Alternative diagnoses are infrequently considered. Herein, we report the clinicopathologic features of 10 primary synovial sarcomas of nerve, all with molecular genetic confirmation of the synovial sarcoma-specific translocation t(X;18) [16].

## 2. Materials and methods

### 2.1. Case selection

The consultation archives of 2 of the authors (B. W. S., A. L. F.) were searched for cases coded as “synovial sarcoma” occurring as primary tumors of nerve. All lesions were limited to nerve; no tumors with features of secondary neural involvement were included in this study. The tumor of case 3 was encountered in practice at another institution by one of the authors (M. A. E.). The diagnosis of synovial sarcoma was based largely on its characteristic histology, as well as on clinicopathologic features dissimilar to MPNST, fully half of which occur in association with NF1 and arise in transition from neurofibroma, are far more often high grade (85%), and show far greater histologic diversity [3]. All tumors were found to be positive for either the *SS18-SSX1* (4 cases) or *SS18-SSX2* (6 cases) gene fusions by reverse transcriptase–polymerase chain reaction (RT-PCR).

### 2.2. Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue sections were immunostained for vimentin (Dako, Carpinteria, CA; 1:500, V9), epithelial membrane antigen (EMA) (Dako, 1:50, E29), S-100 protein (Dako, 1:1600, polyclonal), CD57 (Becton Dickinson, 1:20; HNK-1), neurofilament protein (Dako, 1:800, 2F11), collagen IV (Dako, 1:25, CIV22), TLE1 (Santa Cruz Biotechnology, Inc, Santa Cruz, CA; dilution 1:100, polyclonal), Fli1 (BD Pharmingen, San Jose, CA; 1:50, BRD, G146-254), and Ki-67 (Dako, 1:30, MIB-1) using heat-induced epitope retrieval and the Dako Envision detection system. Appropriate positive and negative controls were used.

### 2.3. Molecular genetics

Methods for the characterization of synovial sarcoma including RT-PCR (10 cases) and fluorescence in situ hybridization (FISH) (1 case) have been previously published elsewhere [17].

## 3. Results

### 3.1. Clinicopathologic features

Essential clinical and therapeutic data regarding our 10 cases are summarized in Table 1. The tumors occurred in 7 female and 3 male patients ranging in age from 11 to 68 years (mean, 40 years), inclusive of 4 pediatric cases.

### 3.2. Imaging

Imaging was available for review in 4 patients (cases 2, 3, 5, 8). All had MRI examinations (3 with gadolinium enhancement) performed at 1.5 T or lower. A positron emission tomography (PET) scan was available in a single patient (case 2). The nerves involved were the distal tibial nerve, peroneal division of the sciatic nerve, median nerve in the distal arm, and the middle trunk of the brachial plexus. All lesions arose from the affected nerve and extended proximally and distally along its length (“tail sign”) (Figs. 1 and 2A). In the case of the tibial nerve lesion (case 3), the mass extended from the common tibial nerve into the medial and lateral plantar branches. All lesions were isointense to muscle on T1-weighted imaging, hyperintense on T2-weighted sequences, and showed avid enhancement in the 3 cases wherein post-contrast images were available (Figs. 1 and 2A). Smaller lesions showed homogeneous enhancement. The large, complex sciatic lesion (case 2) showed a more heterogeneous signal and enhancement in addition to hemorrhage within the largest portion of the tumor. Of the 4 tumors (cases 1, 2, 3, 8), 3 were oval in shape and ranged from slightly less than 1 cm to 3 cm in maximum dimension with irregular margins in each case. The sciatic lesion (case 2) was multinodular, the 4 distinct, ovoid nodules collectively measuring 19 cm in length and 4 cm in maximal axial dimension (Fig. 2A). The PET scan in this case showed avid uptake of the fluorodeoxyglucose (FDG) in all the nodules (Fig. 2B). On reinterpretation of imaging, the 4 tumors, based on the presence of irregular margins, were considered indeterminate in nature and suspicious for malignancy.

### 3.3. Operative findings

The tumors ranged in size from 1.5 to 19.5 cm (mean, 3.25 cm; median, 10.7 cm). At surgery, all involved the substance of a nerve, the 4 smaller examples being described as intraneural (cases 1, 3, 6, 7). In the majority of cases, operative reports indicated that a clear resection plane was not evident. Only one small (3.5 × 1.5 × 1.0 cm) tumor (case 5) was stated to involve a single fascicle seen to both enter and exit the lesion. With one exception (case 2; Fig. 3), all tumors were uninodular.

**Table 1** Synovial sarcoma of nerve

Present series									
Case	Age/ sex	Presentation	Nerves involved	Imaging	Operative features	Tumor size	Resection (ST/GT)	Radio-/ chemotherapy	Follow-up
1	47/F	Ankle mass	Deep peroneal	N/A	Intraneural, ovoid	2.4 × 1.3 × 1.0	GT	No/yes	No recurrence at 8 y
2	11/M	Idiopathic, isolated right peroneal n. palsy at age 6 mo. Painful R posterior thigh mass at age 10 y	Sciatic nerve thigh and common peroneal nerve	Avid, irregular enhancement Irregular margins Parent nerve seen FDG PET strongly positive	Intraneural, multinodular	19.5 × 5.0 × 4.5 cm	ST; focal margin involvement	No/unstated	N/A
3	42/M	Pain medial to L ankle × 2 y. Mass at site recent	Tibial nerve	Irregular, localized enlargement of the nerve with extension into the medial and lateral plantar branches	Intraneural, ovoid, noninfiltrative	1.5 × 0.8 cm	GT	Unstated	N/A
4	64/M	Sudden onset L leg weakness and bladder incontinence	L4 nerve root	Enhancing intraspinal and foraminal mass	Intra- and extraspinal unencapsulated and hemorrhagic	Tumor 3.0 × 2.0 × 0.4 cm and 1.0 × 1.0 × 0.4)	ST	Unstated	N/A
5	68/F	Pain above L elbow and numbness in hand. Previous failed carpal tunnel release	Median nerve distal arm	Avid, irregular enhancement Irregular margins Mildly heterogeneous T2 signal Parent nerve seen	Uninodular. Nerve-attached; one entering/ exiting fascicle	3.5 × 1.5 × 1.0 cm	ST	No/no	Wide resection and reconstruction 2 mo after diagnosis; no recurrence at 4.5 y
6	15/F	N/A	Brachial plexus (C7, middle trunk)	N/A	Intraneural, plexiform	5.3 × 0.9 × 0.9 cm	ST	Yes/yes	Metastasis to spine (4 mo postop then brain; died 1.5 y postop)
7	13/F	Painful popliteal fossa mass	Tibial nerve	MRI consistent with nerve sheath tumor	Uninodular, encapsulated nerve fascicles attached	4.5 × 3.5 × 1.7 cm	GT	Unstated	N/A
8	52/F	Left shoulder, arm and chest wall pain × 3 y	Brachial plexus— middle trunk	Avid, slightly irregular enhancement Irregular margin distally Parent nerve seen	Ovoid, encapsulated but adherent to surrounding fascicles—more than a single fascicle	2.1 × 1.7 × 1.9 cm	GT	Yes/no	No recurrence at 2.5 y postop. Full body PET scan negative
9	17/F	N/A	R peroneal	N/A	N/A	3.5 × 3 × 2.5 cm	N/A	N/A	N/A
10	28/F	N/A	R ulnar	N/A	N/A	N/A	N/A	N/A	N/A

**Table 1** (continued)

Literature review									
Published cases, author(s) (reference)	Age/sex	Presentation	Nerve(s) involved	Imaging	Operative finding	Size (cm)	Resection (ST/GT)	Radio-/chemotherapy	Follow-up
Cugola and Pisa [7]	16/F	Mass and palsy	Radial	No lesion on x-ray	Encapsulated intraneural tumor. Sural graft	2.0	GT	No/no	Well at 5 y; functional recovery
Rinehart et al [10]	23/F	2 y pain, palpable mass	Median	CT and MRI showed tumor	Intraepineural tumor	2.5	GT	No/no	Sural nerve graft; partial functional recovery; well at 7 mo
O'Connell et al [9]	16/M	1 y enlarging palm "lump"	Radial, common digital branch	–	Intraneural tumor	2.5	GT/ray resection middle finger	No	Unstated
Tacconi et al [12]	44/F	Supraclav mass; C5-C6 sensory symptoms	Brachial plexus	CT: heterogeneous mass with calcifications	Nerve (perifascicular)	2 × 1.5 cm	ST	Yes (55 Gy)/yes	Immediate GT reexcision. ChemoRx
Spielmann et al [11]	43/M	3 wk enlarging, tender, mass popliteal fossa; pain/numbness in foot, Tinel sign	Tibial nerve, popliteal fossa	X-ray: delicate calcifications; MRI: mass in tibial nerve	Tumor within nerve sheath	3.5	Biopsy; AK amputation. Tumor in tibial and common peroneal nerve	No/no	Tumor-free at 8 mo
Chesser et al [5]	16/M	1 y mass of flexor R wrist	Median	Unstated	Tumor within epineurium	2.0	Unstated	Yes/no	No recurrence at 1 y
Zenmyo et al [15]	58/F	Sciatica; S1 sensory deficit	S1 root	X-ray: calcifications; CT and MRI: mass anterior to S1 foramen	Intraneural tumor in foramen and retroperitoneum	5.5 cm	ST	No/no	Dead of pulmonary adenocarcinoma at 6 mo
Lestou et al [8]	54/M	Palsy	Peroneal n.	Thickened nerve	Intraneural tumor	Unstated	Biopsy	Unstated	Unstated
Chu et al [6], case 1	46/F	Infra-auricular mass × several months	Facial	Lemon shape	Local excision; + margin	0.8	ST and wide excision	Yes/no	No recurrence at 5 y
Chu et al [6], case 2	11/F	Pain in C and T distribution; triceps/biceps atrophy	C6-C7	MRI: expansile lesion at foramen	Schwannoma-like lesion	0.4	GT	Postoperative proton beam/yes	One recurrence at 1.5 y; re-excision. Reexcision of tumor (histologically biphasic). Chemotherapy. Hemiplegia 22 mo thereafter due to intraspinal spread (C4-C6). DOD 6 y after initial diagnosis

(continued on next page)

**Table 1** (continued)

Present series									
Case	Age/ sex	Presentation	Nerves involved	Imaging	Operative features	Tumor size	Resection (ST/GT)	Radio-/ chemotherapy	Follow-up
Weimeb et al [14]	48/F	Intermittent shooting pain L leg, big toe	Tibial	MRI: heterogeneous mass posterior compartment of L calf	Debulking	8.7	ST	Unstated	Recurrences 3 mo postop. AK amputation. Recurrence-free at 14 mo Local recurrence at 14 mo requiring additional resection
Uehara et al [13]	3/F	Radiating pain R palm. Decreased grasp strength. Atrophy of thenar muscles	Median	MRI: enhancing spindle-shaped tumor	Subcapsular removal	1.5 × 1.2	GT on immediate reexcision	Yes/no	

Abbreviations: ST, subtotal; GT, gross total; N/A, not available; AK, above knee.

### 3.4. Pathology

Of the 10 tumors, 9 showed classic histologic features of monophasic synovial sarcoma, including a fascicular proliferation of monomorphic, hyperchromatic spindled cells in association with wiry collagen and a branching, “staghorn” vascular pattern (Fig. 4). In one instance (case 2), a biphasic variant, epithelial differentiation, took the form of small glands lined by cuboidal to slightly columnar cells (Fig. 5). Mitotic activity ranged from 1 to 13/10 high-powered fields (HPF) (mean, 4/10 HPF). No tumor showed calcification. Round cell areas or necrosis, that is, poorly differentiated histology, was not encountered.

### 3.5. Immunohistochemical findings

The immunohistochemical results are summarized in Table 3 and illustrated in Fig. 6. All tumors were diffusely positive for vimentin. Patchy expression of EMA, pan-cytokeratin, and cytokeratin 7 was seen in the spindled cells of 90%, 80%, and 100% of studied cases, respectively. S100 protein and CD57 were positive in a variable number of cells in 50% and 100% of cases. Immunostains for neurofilament protein showed single or grouped and aligned axons within 6 of 8 tumors studied (cases 1, 3, 4, 5, 7, 8), suggesting either intrafascicular origin or extension of the tumor (Fig. 6F). Diffuse nuclear expression of TLE1 protein was present in all cases. No case expressed FLI-1 protein.

### 3.6. Molecular genetic findings

As noted previously, 6 cases were known to carry the *SS18-SSX2* fusion and 4, the *SS18-SSX1* fusion.

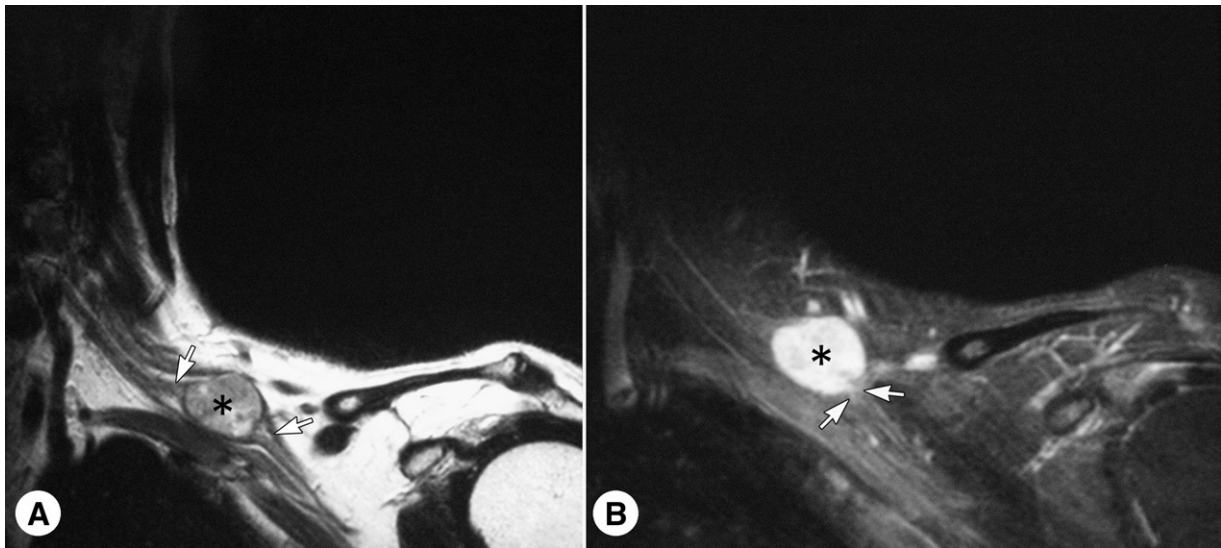
### 3.7. Literature review

Comparable data regarding the 12 previously published cases are summarized in Tables 1 and 2.

## 4. Discussion

Synovial sarcoma is a relatively common malignant soft tissue neoplasm, comprising approximately 10% of soft tissue sarcomas. Despite its name, synovial sarcoma rarely involves synovium or joints. It is now abundantly clear that this tumor bears no relationship to synovium. Synovial sarcomas most often involve the extremities of adolescents and young adults but may occur in patients of any age and in any soft tissue or even visceral location. Indeed, with the discovery that synovial sarcomas carry a variety of specific translocations, including t(X;18)(p11.23;q11)(SS18-SSX1) (~65% of cases), t(X;18)(p11.21;q11) (SS18-SSX2) (~35% of cases), t(X;18)(p11;q11) (SS18-SSX4) (<1% of cases), and t(X;20)(p11;q13.3) (SS181-SSX1) (<1% of cases), the





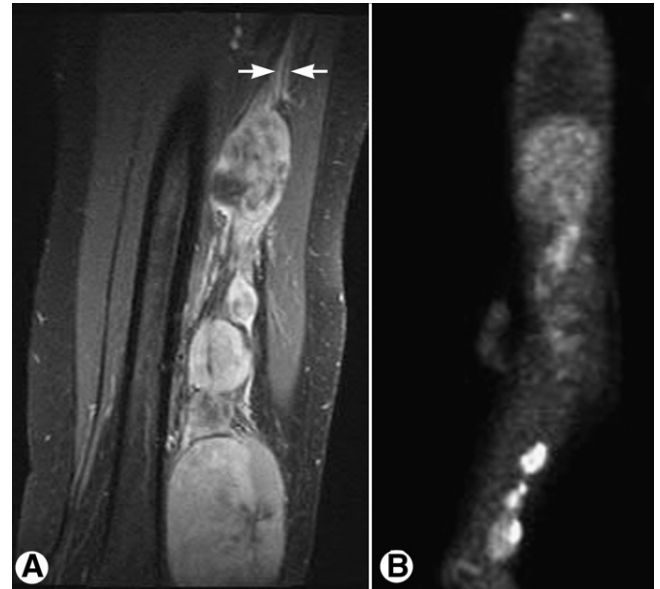
**Fig. 1** A, Case 8. Coronal T2-weighted MR image without fat suppression showing a relatively well-margined mass in the middle trunk of the supraclavicular brachial plexus (asterisk). The mass is bright on T2 with mild signal heterogeneity. The normal nerve proximal and distal to the lesion is clearly seen. B, Case 8. Post-contrast T1-weighted image with fat suppression at the same level as A. This image shows the irregular margins of the tumor, especially at its distal aspect (arrows) and avid contrast enhancement.

diagnostic application of molecular techniques (RT-PCR, FISH) has made it increasingly apparent that many synovial sarcomas occur in unusual locations [18,19].

Primary synovial sarcomas of nerve are very rare, there being only 22 reported cases, inclusive of those in the present series (Tables 1 and 2) [5-12,14,15]. Extremely rare cases of intraneural metastases from synovial sarcoma have also been reported [20]. As noted in the present study, the morphologic and immunohistochemical features of intraneural synovial sarcomas are essentially identical to those of their more common soft tissue counterparts. However, 9 (90%) of 10 cases in the present series were of monophasic type, as compared with 70% of soft tissue cases, and 6 (60%) of 10 carried *SS18-SSX2* fusions, versus the 35% frequency seen in synovial sarcomas at nonneural sites. This suggests that synovial sarcomas of nerve have some unique features. Given the relatively small sample size, however, it is entirely possible that these findings represent a statistical aberration.

The radiographic features of primary intraneural synovial sarcoma have not been previously described in depth. Imaging studies were available for 4 of cases in the present series. The lesions had similar imaging characteristics: all had irregular margins and clearly were associated with individual nerves. None had imaging features suggestive of a benign nerve sheath tumor. Indeed, 3 of the 4 cases had MR imaging characteristics consistent with MPNST. One tumor affecting the tibial nerve (case 7) was not as characteristic, presenting with less prominent localized enlargement of the nerve, an appearance indeterminate by imaging criteria; contrast enhancement, which might have improved sensitivity and narrowed the differential diagnosis, was unavailable in this case. The one instance wherein PET imaging was available (case 2) showed avid uptake of the tracer FDG. Although this

is occasionally seen in cellular, benign nerve sheath tumors, the appearance in this case was more consistent with a malignant process. Soft tissue synovial sarcomas are usually heterogeneously isointense on T1, bright on T2-weighted



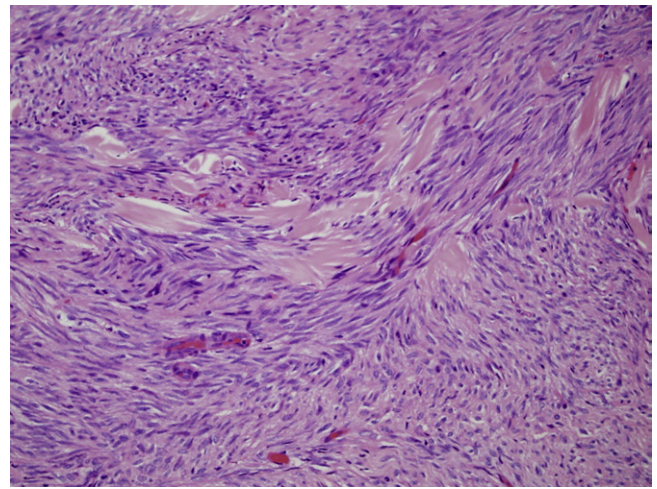
**Fig. 2** A, Case 2. Sagittal T1-weighted image after gadolinium enhancement in the thigh shows heterogeneous contrast enhancement within the nodules of the mass extending along the peroneal division of the sciatic nerve. The margins are irregular and the most proximal nodule has nonenhancing areas consistent with necrosis (asterisk). At least 4 dominant nodules are seen. The nerve proximal to the mass is seen and is normal. The distal extent of the mass is not included on this image. B, Case 2. Sagittal FDG-PET image of the trunk and thigh shows avid uptake in the multinodular mass within the thigh.



**Fig. 3** Case 2. Gross photo of the specimen showed this unusual tumor of the peroneal division of the sciatic nerve to be multilobed.

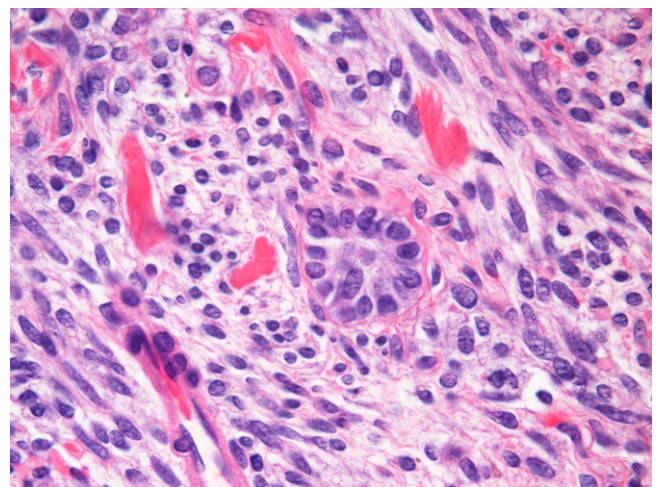
imaging, and homogeneously enhancing in most cases. Approximately one third of tumors will have associated calcifications, a feature lacking in our 4 cases. On imaging, soft tissue synovial sarcomas are often mistaken for benign nerve sheath tumors given their oval shape and frequent longitudinal orientation relative to surrounding soft tissue. Nonetheless, close inspection shows slight irregularity of their margins and no association with an individual nerve. This is in sharp distinction to the cases reviewed herein, where the parent nerve was always visualized.

The differential diagnosis for primary intraneural synovial sarcoma is mainly with conventional, spindle cell MPNST. The morphologic features of monophasic synovial sarcomas and conventional, spindle cell MPNST are remarkably similar. The only features offering significant discriminatory assistance being tumor occurrence in a patient with documented neurofibromatosis type 1 and/or an origin from a preexisting plexiform neurofibroma. Additional morphologies include the presence of wiry collagen and stromal calcifications in synovial sarcoma and the often greater pleomorphism of MPNST. Even glandular differentiation may be seen in both synovial sarcoma and MPNST, although the glands of biphasic synovial sarcoma tend to be small, lined by cuboidal cells, and filled with eosinophilic debris, in contrast to the enteric-type glands seen in those extremely



**Fig. 4** Case 5. Histologically, most of the lesions were monophasic, consisting of sheaves of spindle cells associated with collagen bundles (original magnification  $\times 400$ ).

rare MPNST with glandular differentiation [21]. Similarly, the immunophenotypes of monophasic synovial sarcoma and MPNST show considerable overlap, with frequent expression of putative nerve sheath markers such as S100 protein and CD57 in synovial sarcoma [22], expression of EMA both in synovial sarcoma and in MPNST with perineurial differentiation, rare reported cytokeratin-positive MPNST [23], and very focal or even absent expression of epithelial markers in some monophasic synovial sarcomas. CD34 expression, frequently present in MPNST, particularly low-grade examples [24] but essentially unheard of in synovial sarcoma, may be helpful in this differential diagnosis. TLE1, a WNT pathway-associated transcription factor, has recently been shown to be a highly sensitive marker of synovial sarcomas, typically showing expression in nearly 100% of nuclei in a given tumor [25]. TLE1 is not, however, a perfectly specific marker, as it may be positive in a significant number of benign and malignant peripheral nerve sheath tumors, albeit typically



**Fig. 5** Case 3. A single tumor of the biphasic subtype, featuring well-formed glands (original magnification  $\times 600$ ).



**Table 2** Synovial sarcoma of nerve: histology, immunohistochemistry, genetics

Present cases										
Case	Histologic type	Mitoses/10 HPF	EMA	AE1-AE3	S-100 protein	CD57	TLE-1	Fli1	NFP showing nerve association	PCR
1	Monophasic	13	+	1+	+	1+	4+	–	Axons	SYT-SSX2
2	Monophasic	10	–	1+	–	1+	2+	–	–	SYT-SSX1
3	Biphasic	3	2	2+	–	2+	4+	–	Axons	SYT-SSX1
4	Monophasic	2	1	2+	1+	2+	3+	–	Axons	SYT-SSX1
5	Monophasic	4	2	–	1+	1+	1+	–	–	SYT-SSX2
6	Monophasic	3	1+	1+	–	3+	4+	–	Axons	SYT-SSX2
7	Monophasic	2	2+	1+	1+	1+	4+	–	Axons	SYT-SSX2
8	Monophasic	3	2+	1+	ND	3+	1+	–	Axons	SYT-SSX2
9	Monophasic	1	1+	2+/no	1+	ND	ND	ND	Axons	SYT-SSX2
10	Monophasic	2	scant	1+/NA	1+	ND	2+	ND	–	SYT-SSX1
Literature review										
Published cases, author(s) (reference)	Histologic type	EMA	KERATIN	S100 protein	NFP showing nerve association	Miscellaneous	Genetics/PCR			
Cugola and Pisa [7]	Biphasic	NA	NA	NA	NA	–	SYT-SSX1			
Rinehart [10]	Monophasic	Focal+	Focal+	Focal+	Axons	Desmin—focal	SYT-SSX2			
O’Connell [9]	Biphasic	+ <5%	15%-20%+	Neg	Axons	SMA, CD34-	x;18			
Tacconi et al [12]	Monophasic	+	+	Focal+	NA	–	NA			
Spielmann et al [11]	Biphasic	Focal	Neg	Neg	Axons	CD99+; MSA, Desmin–	SYT-SSX2			
Chesser et al [5]	Biphasic	NA	+	NA	NA	–	SYT-SSX1			
Zenmyo et al [15]	Monophasic	+	+	NA	NA	bcl-2+	t(x;18) (p11;q11) SYT-SSX - ?later			
Lestou et al [8]	Monophasic	Minor+	Minor+	Minor+	NA	Vimentin and CD99+	Cryptic t(x;18), ins (6;18) and SYT-SSX2 gene fusion			
Chu et al [6], case 1	Biphasic	+ Tumor and perineurium	+	Neg	Axons	–	t(x;18) (SYT-SSX)			
Chu et al [6], case 2	Monophasic	Neg	Neg	Neg	Axons	–	t(x;18) (SYT-SSX)			
Weinreb et al [14]	Biphasic	+	+	Neg	Neg	Desmin, actin, and CD34–; BCL-2+	SYT-SSX1			
Uehara et al [13]	Monophasic	+	+	+	+	–	SYT-SSX1			

Abbreviations: NFP, neurofilament protein; NA, not assessed; ND, not done.  
 NOTE. Scant = less than 5%; 1+ = 5% to 25%; 2+ = 25% to 50%; 3+ = more than 50%.  
 1+ = 1% to 10%; 2+ = 11% to 25%; 3+ = 26% to 50%; 4+ = 51% to 100%.

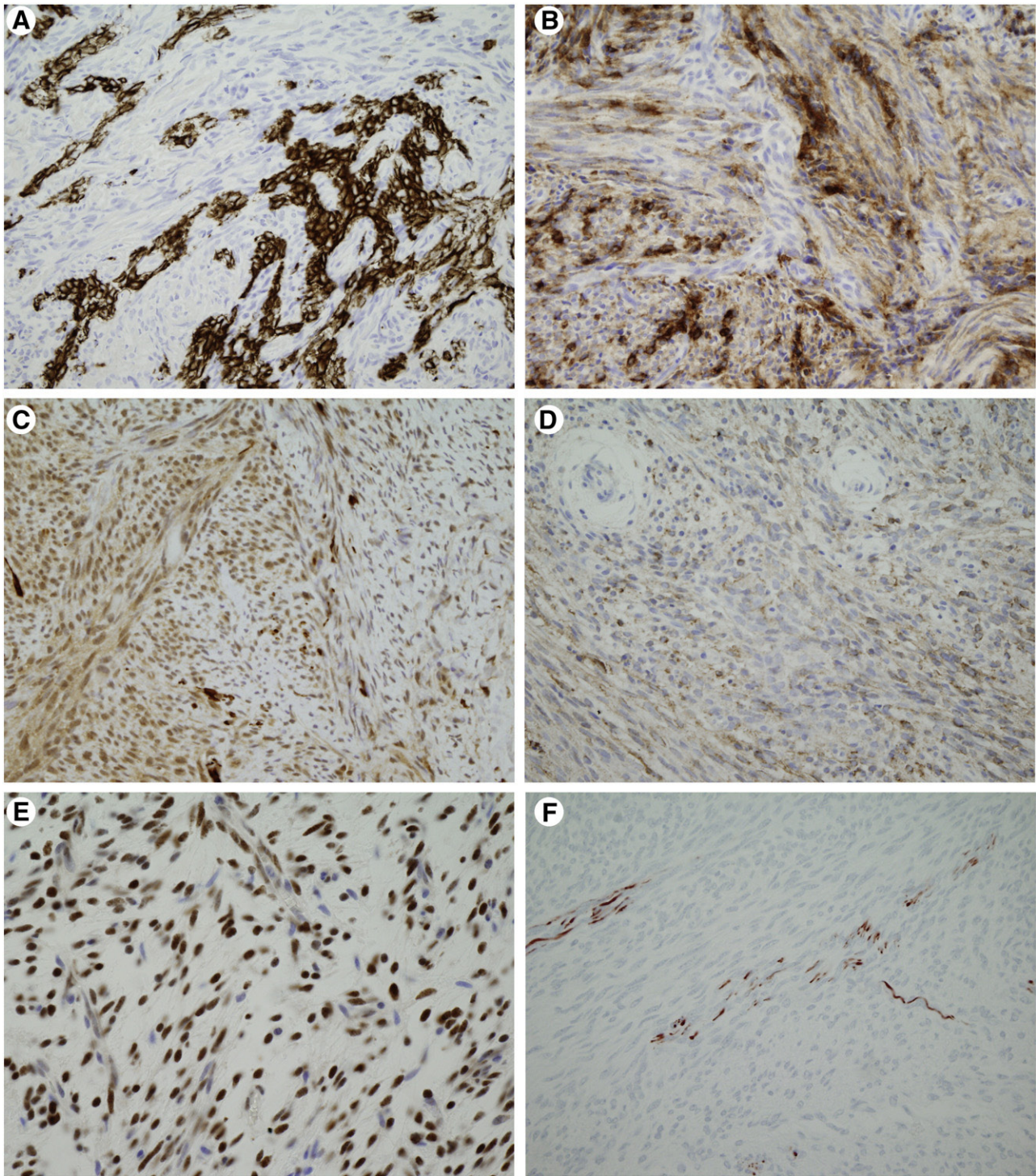
in a smaller percentage of tumor nuclei [26]. A large number of other markers, including BCL-2, SYT protein, CD56, p75NTR, nestin, and HMGA2 protein, have been suggested to be of some value in this differential diagnosis but either lack specificity (BCL-2, CD56) or have been studied only in a very small number of cases (nestin, HMGA2).

Given some morphologic and considerable immunophenotypic overlap between synovial sarcoma and MPNST, demonstration of one of the synovial sarcoma-associated fusion genes has come to be regarded as the “gold standard” for this differential diagnosis. Although it was initially asserted that MPNST and other types of nerve sheath tumors could contain the (X;18) translocation [27], this has

subsequently been disproved by a number of large, carefully performed studies [28-30]. Positive molecular markers of MPNST, which may also be of value in this differential diagnosis, include NF1 and p16 deletions as well as epidermal growth factor receptor amplification and polysomies for either chromosome 7 or 22 as demonstrated by FISH [31].

In conclusion, we have described the clinical, radiographic, pathologic, and molecular genetic findings in 10 cases of primary intraneural synovial sarcoma, the largest series to date. In general, primary intraneural synovial sarcomas are similar to their more common soft tissue counterparts, although there may be a relative intraneural predominance of monophasic tumors and tumors containing *SS18-SSX2* fusions. Based on





**Fig. 6** The immunophenotype of the tumors included keratin (A; case 3), epithelial membrane antigen (B; case 3), S-100 protein reactivity (C; case 5), CD57 (D; case 6), and TLE1 (E; case 6). Axons immunoreactive for neurofilament protein were identified within some tumors and indicated endoneurial involvement (F; case 7) (A-F, original magnification  $\times 400$ ).

relatively limited follow-up, we see no reason to believe that the behavior of intraneural synovial sarcomas is any different from that of synovial sarcomas at other locations, particularly in extremities. Definitive recommendations regarding possible roles for adjuvant radiation and chemotherapy await the study of additional cases.

The present series, even combined with our literature review, has limitations with regard to assessing recurrence/survival data. Nonetheless, several clinicopathologic factors appear to affect outcome. Comparing our data with that of Lewis et al [32], a multivariate analysis of prognostic factors in 112 patients with primary localized synovial sarcomas of



the extremities, we believe that small tumor size may affect the prognosis. Of the combined 22 patients in our report and review study, 16 (73%) had small (<5 cm) tumors, a meaningful prognostic factor according to Lewis et al [32]. An early presentation with neurologic symptoms may be the basis of their small size. Indeed, 15 (75%) of 20 patients experienced sensorimotor loss and/or pain, a not surprising presentation for a nerve-based tumor. Thus, synovial sarcomas of nerve may be associated with a more favorable prognosis than nonneural examples. Relative to MPNST of the extremities, particularly lower extremity examples, which have a poor prognosis [33], synovial sarcomas at this site appear to have a more favorable prognosis.

## References

- [1] Lazarus SS, Trombetta LD. Ultrastructural identification of a benign perineurial cell tumor. *Cancer* 1978;41:1823-9.
- [2] Emory TS, Scheithauer BW, Hirose T, Wood M, Onofrio BM, Jenkins RB. Intraneural perineurioma. A clonal neoplasm associated with abnormalities of chromosome 22. *Am J Clin Pathol* 1995;103:696-704.
- [3] Scheithauer BW, Woodruff JM, Erlandson RA. Benign and malignant non-neurogenic tumors (chapter 10). In: Rosai J, Sobin LH, editors. *Atlas of tumor pathology—tumors of peripheral nervous system*. Washington, D.C.: Third Series, Fascicle 24. Armed Forces Institute of Pathology; 1999. p. 283-302.
- [4] Scheithauer BW, Woodruff JM, Erlandson RA. Primary malignant tumors of peripheral nerve (chapter 11). In: Rosai J, Sobin LH, editors. *Atlas of tumor pathology—tumors of peripheral nervous system*. Washington, D.C.: Third Series, Fascicle 24. Armed Forces Institute of Pathology; 1999. p. 303-72.
- [5] Chesser TJ, Geraghty JM, Clarke AM. Intraneural synovial sarcoma of the median nerve. *J Hand Surg [Br]* 1999;24:373-5.
- [6] Chu PG, Benhattar J, Weiss LM, Meagher-Villemure K. Intraneural synovial sarcoma: two cases. *Mod Pathol* 2004;17:258-63.
- [7] Cugola L, Pisa R. Synovial sarcoma: with radial nerve involvement. *J Hand Surg [Br]* 1985;10:243-4.
- [8] Lestou VS, O'Connell JX, Robichaud M, et al. Cryptic t(X;18), ins (6;18), and SYT-SSX2 gene fusion in a case of intraneural monophasic synovial sarcoma. *Cancer Genet Cytogenet* 2002;138:153-6.
- [9] O'Connell JX, Browne WL, Gropper PT, Berean KW. Intraneural biphasic synovial sarcoma: an alternative "glandular" tumor of peripheral nerve. *Mod Pathol* 1996;9:738-41.
- [10] Rinehart GC, Mustoe TA, Weeks PM. Management of synovial sarcoma of the median nerve at the elbow. *Plast Reconstr Surg* 1989;83:528-32.
- [11] Spielmann A, Janzen DL, O'Connell JX, Munk PL. Intraneural synovial sarcoma. *Skeletal Radiol* 1997;26:677-81.
- [12] Tacconi L, Thom M, Thomas DG. Primary monophasic synovial sarcoma of the brachial plexus: report of a case and review of the literature. *Clin Neurol Neurosurg* 1996;98:249-52.
- [13] Uehara H, Yamasaki K, Fukushima T, et al. Intraneural synovial sarcoma originating from the median nerve. *Neurol Med Chir* 2008;48:77-82.
- [14] Weinreb I, Perez-Ordóñez B, Guha A, Kiehl TR. Mucinous, gland predominant synovial sarcoma of a large peripheral nerve: a rare case closely mimicking metastatic mucinous carcinoma. *J Clin Pathol* 2008;61:672-6.
- [15] Zenmyo M, Komiya S, Hamada T, et al. Intraneural monophasic synovial sarcoma: a case report. *Spine* 2001;26:310-3.
- [16] Sandberg AA, Bridge JA. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors. Synovial sarcoma. *Cancer Genet Cytogenet* 2002;133:1-23.
- [17] Weinbreck N, Vignaud JM, Begueret H, et al. SYT-SSX fusion is absent in sarcomatoid mesothelioma allowing its distinction from synovial sarcoma of the pleura. *Mod Pathol* 2007;20:617-21.
- [18] Billings SD, Meisner LF, Cummings OW, Tejada E. Synovial sarcoma of the upper digestive tract: a report of two cases with demonstration of the X;18 translocation by fluorescence in situ hybridization. *Mod Pathol* 2000;13:68-76.
- [19] Pan CC, Chang YH. Primary synovial sarcoma of the prostate. *Histopathology* 2006;48:321-3.
- [20] Matsumine A, Kusuzaki K, Hirata H, Fukutome K, Maeda M, Uchida A. Intraneural metastasis of a synovial sarcoma to a peripheral nerve. *J Bone Joint Surg Br* 2005;87:1553-5.
- [21] Woodruff JM, Christensen WN. Glandular peripheral nerve sheath tumors. *Cancer* 1993;72:3618-28.
- [22] Guillou L, Wadden C, Kraus MD, Dei Tos AP, Fletcher CDM. S-100 protein reactivity in synovial sarcomas—a potentially frequent diagnostic pitfall: immunohistochemical analysis of 100 cases. *Appl Immunohistochem* 1996;4:167-75.
- [23] Smith TA, Machen SK, Fisher C, Goldblum JR. Usefulness of cytokeratin subsets for distinguishing monophasic synovial sarcoma from malignant peripheral nerve sheath tumor. *Am J Clin Pathol* 1999;112:641-8.
- [24] Zhou H, Coffin CM, Perkins SL, Tripp SR, Liew M, Viskochil DH. Malignant peripheral nerve sheath tumor: a comparison of grade, immunophenotype, and cell cycle/growth activation marker expression in sporadic and neurofibromatosis 1-related lesions. *Am J Surg Pathol* 2003;27:1337-45.
- [25] Jagdis A, Rubin BP, Tubbs RR, Pacheco M, Nielsen TO. Prospective evaluation of TLE1 as a diagnostic immunohistochemical marker in synovial sarcoma. *Am J Surg Pathol* 2009;33:1743-51.
- [26] Kosemehmetoglu K, Vrana JA, Folpe AL. TLE1 expression is not specific for synovial sarcoma: a whole section study of 163 soft tissue and bone neoplasms. *Mod Pathol* 2009;22:872-8.
- [27] O'Sullivan MJ, Kyriakos M, Zhu X, et al. Malignant peripheral nerve sheath tumors with t(X;18). A pathologic and molecular genetic study. *Mod Pathol* 2000;13:1253-63.
- [28] Coindre JM, Hostein I, Benhattar J, Lussan C, Rivel J, Guillou L. Malignant peripheral nerve sheath tumors are t(X;18)-negative sarcomas. Molecular analysis of 25 cases occurring in neurofibromatosis type 1 patients, using two different RT-PCR-based methods of detection. *Mod Pathol* 2002;15:589-92.
- [29] Ladanyi M, Woodruff JM, Scheithauer BW, et al. Re: O'Sullivan MJ, Kyriakos M, Zhu X, Wick MR, Swanson PE, Dehner LP, Humphrey PA, Pfeifer JD: malignant peripheral nerve sheath tumors with t(X;18). A pathologic and molecular genetic study. *Mod Pathol* 2000;13:1336-46. *Mod Pathol* 2001;14:733-7.
- [30] Tamborini E, Agus V, Perrone F, et al. Lack of SYT-SSX fusion transcripts in malignant peripheral nerve sheath tumors on RT-PCR analysis of 34 archival cases. *Lab Invest* 2002;82:609-18.
- [31] Perry A, Kunz SN, Fuller CE, et al. Differential NF1, p16, and EGFR patterns by interphase cytogenetics (FISH) in malignant peripheral nerve sheath tumor (MPNST) and morphologically similar spindle cell neoplasms. *J Neuropathol Exp Neurol* 2002;61:702-9.
- [32] Lewis JJ, Antonescu CR, Leung DH, et al. Synovial sarcoma: a multivariate analysis of prognostic factors in 112 patients with primary localized tumors of the extremity. *J Clin Oncol* 2000;18:2087-94.
- [33] Hruban RH, Shiu MH, Senie RT, Woodruff JM. Malignant peripheral nerve sheath tumors of the buttock and lower extremity. A study of 43 cases. *Cancer* 1990;66:1253-65.