Primary intracranial dural-based synovial sarcoma with an unusual SYT fluorescence in situ hybridization pattern

Case report

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The authors present the case of an elderly man with a primary dural-based intracranial synovial sarcoma. Histological and immunohistochemical profiles of the lesion were diagnostic for a synovial sarcoma, and molecular studies using fluorescence in situ hybridization were compatible with a synovial sarcoma. A wide array of spindle cell neoplasms has been described as originating in the dura. To the authors’ knowledge, however, this is only the second primary dural-based intracranial synovial sarcoma ever reported, emphasizing the importance of a broad differential diagnosis when encountering spindle cell lesions of the meninges. (DOI: 10.3171/JNS/2008/109/11/0897)

KEY WORDS • dura • spindle cell neoplasm • synovial sarcoma • translocation

Dural-based neoplasms are among the most common central nervous system tumors encountered by neurosurgeons. Although most are low-grade meningiomas, a multitude of tumors can arise from the dura mater and leptomeninges. Such tumors include rhabdomyosarcomas, dendritic cell sarcomas, primitive neuroectodermal tumors/Ewing sarcomas, melanocytic tumors, hemangioblastomas, lipomas, leiomomas, chondrosarcomas, hemangiopericytomas/solitary fibrous tumors, MPNSTs, and undifferentiated sarcomas, among others.1,2,4,6–8,17,20,21,26,29,36,37 Moreover, even within the class of meningiomas there are 15 subtypes encompassing 3 grades of severity.24 If metastatic and hematopoietic tumors are included as well, the possible differential diagnosis for meningeal tumors grows even larger. Thus, both neurosurgeons and neuropathologists must be wary when encountering such tumors because therapeutic regimens and prognoses frequently differ based on the tumor classification. The authors recently encountered an example of this difficulty in an elderly man with a left parietal lesion that ultimately proved to be a synovial sarcoma, most likely originating in the dura. The clinical, surgical, histological, and molecular aspects of this tumor are discussed.

Abbreviations used in this paper: EMA = epithelial membrane antigen; FISH = fluorescence in situ hybridization; GFAP = glial fibrillary acidic protein; MPNST = malignant peripheral nerve sheath tumor; SMA = smooth muscle actin.
ventilation-associated respiratory alkalosis. After the procedure, no other masses were detected on CT scans of the chest, abdomen, or pelvis (not shown). The patient refused to undergo a bone scan. After a 10-day hospital stay the patient was stable enough to be discharged to a rehabilitation center. The patient was treated with multiple cycles of postoperative radiation therapy that ended 2 months after surgery. As of 5 months after the initial tumor resection, his right-sided numbness had subsided, his speech had improved, and he had switched from using a wheelchair to using a walker. Follow-up MR imaging has yet to demonstrate tumor regrowth or dissemination.

**Immunohistochemical Analysis**

Immunohistochemical studies of the tumor were performed on 4–μm-thick sections obtained from paraffin-embedded material. The primary antibodies, including manufacturer, clone, and dilution, were as follows: CD56 (Cell Marque, 123.C3.D5, prediluted); CD99 (Dako, 12E7, 1:75); Bcl-2 (Cell Marque, 124, prediluted); p53 (Dako, DO-7, 1:100); vimentin (Ventana, V9, prediluted); SMA (Cell Marque, 1A4, prediluted); GFAP (Dako, polyclonal, 1:1000); S100 protein (Dako, polyclonal, 1:500); CD34 (Ventana, QBend10, prediluted); and cytokeratin AE1/3 (Dako, AE1/3, 1:100). The antibody labeling was performed using the avidin–biotin complex method and visualized using a horseradish peroxidase enzyme label and 2′-diaminobenzamide (Dako) as the substrate chromogen (brown) for all antibodies, with the exception of S100, which was visualized using an alkaline phosphatase enzyme label with Fast Red (Dako) as the substrate chromogen.

**Fluorescence In Situ Hybridization**

Formalin-fixed paraffin-embedded sections were mounted and serially sectioned at 5-mm intervals. Sections stained with H & E were used by the pathologist to determine the area of the tissue to be targeted for analysis. The FISH slides were deparaffinized in xylene twice for 10 minutes, dehydrated twice with 100% ethanol, and then pretreated using the Vysis Paraffin Pretreatment Kit. Slides were digested for 18 minutes in protease solution (0.5 mg/ml) at 37°C. Fluorescence in situ hybridization was performed using the SYT dual-color break-apart probe (Vysis,
Inc.). The target slide and probe were codenatured at 95°C for 8 minutes and incubated overnight at 37°C in a humidified chamber. Posthybridization washes were performed using 2X standard saline citrate/0.3% Igepal (Sigma) at 72°C for 2 minutes. Slides were air-dried in the dark and counterstained with 4',6'-diamidino-2-phenylindole (Vysis, Inc.). Analysis was performed using a Nikon Optiphot-2 microscope (Nikon, Inc.) and Quips Genetic Workstation equipped with a Chroma Technology filter fitted with single-band excitors for SpectrumOrange, fluorescein isothiocyanate, and 4',6'-diamidino-2-phenylindole (uv 360 nm; Vysis, Inc). Only individual and well-delineated cells were

Fig. 3. Photomicrographs from the immunohistochemical analysis. The tumor cells stained strongly positive for CD56 (A), CD99 (B), Bcl-2 (C), p53 (D), and vimentin (E), and MIB-1 was positive in > 80% of the cells (F). Smooth muscle actin was weakly and focally positive (G). The tumor was negative for EMA (H), GFAP, S100, CD34, and cytokeratin AE1/3 (GFAP, S100, CD34, and cytokeratin stains not shown). Original magnification × 100.
scored. Overlapping cells were excluded from the analysis. Approximately 60 cells were analyzed in the targeted region.

The specimen was soft and tan–gray with focal hemorrhage. Microscopically the tumor was hypercellular and composed of plump spindle cells with numerous mitoses (about 6 per 10 hpf), many of them atypical (Fig. 2). The cells were mostly arranged in large compact sheets, as well as in fascicles. No epithelioid areas were seen.

The tumor cells were strongly positive for CD56, CD99, Bcl-2, p53, and vimentin (Fig. 3A–E). The proliferation marker MIB-1 was positive in > 80% of the cells (Fig. 3F). Smooth muscle actin was only weakly and focally positive (Fig. 3G), whereas EMA (Fig. 3H) was negative. Glial fibrillary acidic protein, S100, CD34, and cytokeratin AE1/3 were also negative (not shown).

The FISH analysis using a dual-color break-apart probe within the SYT gene on 18q11.2 showed a complex pattern in 100% of the cells, consisting of 1–3 fusion signals along with 1–3 orange signals (Fig. 4).

Reverse transcription–polymerase chain reaction on both the SYT-SSX1 and SYT-SSX2 fusion gene products was unsuccessful due to inadequate RNA quality from the formalin-fixed, paraffin-embedded tissue.

**Discussion**

Synovial sarcoma is a well-characterized high-grade mesenchymal neoplasm most commonly arising in the extremities of younger adults. It was originally believed to arise from the synovial tissues of joints, but now it is believed to arise from (currently) undefined multipotent stem cells, which would explain why a synovial sarcoma is so often biphasic with epithelioid and mesenchymal components. As in this case, however, the majority of synovial sarcomas are monophasic spindle-cell neoplasms that can easily be confused with MPNSTs, high-grade hemangiopericytomas, leiomyosarcomas, or fibrosarcomas. The differential diagnosis for dural-associated tumors also includes anaplastic meningiomas (Table 1).

**Immunohistochemical and Molecular Characteristics**

Fortunately, the immunohistochemical profile of synovial sarcomas is fairly distinct, with coexpression of vimentin, CD99, Bcl-2, and CD56 essentially ruling out all other tumors. A positive stain for cytokeratin and/or EMA is often observed, especially in the epithelioid component, but is not mandatory for diagnosis when encountering the monophasic spindle-cell variant. Weak SMA is often seen, as in this case, but should not be confused with a leiomyosarcoma, which is usually more strongly reactive.

Synovial sarcomas are one of the relatively few neoplasms known to have a characteristic molecular signature. In this case, the SYT gene on 18q and either the SSX1 or SSX2 gene on Xp undergo a reciprocal translocation, forming a fusion SYT-SSX gene and subsequent fusion protein. The specific actions of this protein have not yet been fully elucidated, but it does localize to the nucleus, has both transcriptional promoter and suppressor capabilities, and appears to act on DCC, a tumor suppressor gene originally described in colorectal carcinomas. Additionally, the fusion protein has been shown to promote tumorigenesis and proliferation by upregulating cyclins A and D1, downregulating the proliferation inhibitor COM1, and initiating β-catenin/Wnt signaling. More than 90% of synovial sarcomas have this highly specific t(X;18) signature. The SSX2 variant of the fusion gene appears to be more common in monophasic than in biphasic synovial sarcoma, but whether the SSX1 or SSX2 translocation produces a more aggressive tumor is controversial. Regardless, aggressive behavior does appear to correlate well with a high MIB-1 proliferation index and nuclear p53 accumulation, both of which were observed in this case.

The molecular analysis of synovial sarcoma can be performed using classic karyotyping or polymerase chain reaction, but the technique most often used in routine clinical diagnostics is FISH because it can be performed on formalin-fixed, paraffin-embedded tissues, requires few cells, and is technically simple. The most widely used set of FISH probes labels a 1044 kb DNA sequence proximal to the SYT gene with a green fluorophore, while a second probe with an orange fluorophore binds to a 650 kb segment of DNA that includes the distal end of the SYT gene. Thus, the normal unbroken 18q11.2 region will have a close apposition of the green and orange fluorophores, producing a single optically yellow signal. When the 18q11.2 region is broken at the critical junction between the probes, as in the classic t(X;18) signature, the signal will split into separate green and orange signals.

The “break apart” approach to FISH in synovial sarcoma has the advantage of detecting any translocation involving the SYT gene, but does not identify the translocation partner. In most cases it does not matter, because the classic positive result is 1 yellow fusion signal, 1 green signal, and 1 orange signal. Our case, however, produced a complex pattern wherein 1–3 yellow fusion signals were observed per tumor cell, along with 1–3 orange signals without a green counterpart (Fig. 4). This finding sug-
Primary intracranial dura-based synovial sarcoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Synovial Sarcoma</th>
<th>Anaplastic Meningioma</th>
<th>Hemangiopericytoma</th>
<th>MPNST</th>
<th>Leiomyosarcoma</th>
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<tr>
<td><strong>histological</strong></td>
<td>sheets &amp; fascicles of spindle cells ± epithelioid component</td>
<td>sarcomatous or carcinomatous appearance, may see whorls</td>
<td>lobules of spindle cells, staghornlike vascular spaces</td>
<td>tightly packed fascicles of spindle cells, abundant cytoplasm</td>
<td>plump spindle cells w/ cigar-shaped nuclei in fascicles</td>
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<td><strong>immunohistochemical</strong></td>
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<td>vimentin</td>
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<td>CD99</td>
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<td>Bcl-2</td>
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<tr>
<td><strong>cytokeratin &amp; other findings</strong></td>
<td>+ or − in spindle cells</td>
<td>deletion of 22q; NF2 mutation; SYT-SSX1 or SYT-SSX2 fusion gene</td>
<td>17q amplification, deletion of 6q, 9p, 10, 14q</td>
<td>no consistent pattern; some have rearrangement of 12q13</td>
<td>NF1 &amp; TP53 mutations; CDKN2A/p16 deletion</td>
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<td>(X;18) can produce either an SYT-SSX1 or SYT-SSX2 fusion gene</td>
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<td><strong>genetic &amp; other findings</strong></td>
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<td>association w/ immunosuppression, EBV</td>
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* Data compiled from references 7, 15, 24, and 39. + = stains positive; − = stains negative; EBV = Epstein–Barr virus.

gests that there was variable aneuploidy of chromosome 18, or at least 18q, along with an interstitial deletion of at least the 1044 kb sequence labeled by the green probe in 18q11.2. That all tumor cells carried at least 1 independent orange signal suggests disruption or translocation in the SYT gene region. Synovial sarcomas with chromosomal aberrations in addition to t(X;18) have been well documented and sometimes involve monosomy or trisomy of the chromosome 18 copy that is uninvolved in the translocation.44 Such extensive chromosomal abnormalities are often noted in more aggressive synovial sarcomas, as this case would appear to be, judging by the mitotic index, MIB-1 proliferation index, and nuclear p53 accumulation (Figs. 2 and 3).

Clinical and Biological Characteristics

Although synovial sarcomas are far more common in the distal extremities of younger adults, primary tumors have been described in such unusual locations as the lung, head and neck, mediastinum, abdominal wall, and paraspinous region.5,6,10,19,35,38,40 Only 2 primary intradural synovial sarcomas have been reported within the spine, and only 1 in the brain.12,21,33 Although the dura most commonly produces meningiomas, it is quite capable of giving rise to other spindle cell neoplasms like hemangiopericytomas, solitary fibrous tumors, dendritic cell sarcomas, rhabdomyosarcomas, primitive neuroectodermal tumors/Ewing sarcomas, MPNSTs, and undifferentiated sarcomas, among others.1,2,4,6,8,17,20,21,26,29,36,37 Even though primary dura-based synovial sarcomas are rare, they do exist.

To date, our patient has refused a bone scan, which would of course be essential to unequivocally rule out a primary tumor site in the extremities. However, if this large dural mass were only a metastatic lesion, the primary site would almost certainly be of such a size as to have already manifested itself clinically. Such was the case in an elderly woman who presented with a hemorrhagic cerebellar synovial sarcoma that was found to have metastasized from a 20–cm right popliteal mass originally misdiagnosed as a large Baker cyst.45 Furthermore, a synovial sarcoma of the extremities that metastasized to the brain would be expected to have metastasized to other sites in the body, and CT scans of the chest, abdomen, and pelvis in this patient were negative. Thus, it is reasonable to conclude that this mass most likely is the primary site in this patient.

Surgical Management, Adjuvant Therapy, and Prognosis

Much has been learned about the genetic makeup of synovial sarcomas, but it has yet to translate into targeted therapy. When the tumor arises in a typical site in the extremities, the most critical part of treatment continues to be complete excision with negative margins and sparing of the limb when possible. If the lesion is small and superficial, and is not associated with bone or neurovascular structures, no adjuvant treatment is indicated. If, however, the tumor is in the deep soft tissue and/or is close to bone or neurovascular structures, adjuvant radiation therapy is usually administered.46 This combined modality has proven highly effective at reducing the local recurrence risk to < 10% for many soft-tissue sarcomas.47 Unfortunately, a synovial sarcoma is a high-grade tumor; even with combined surgery and radiation almost half of all patients will either have a local recurrence or distant metastases within 10 years, with risk of the latter increasing sharply when the tumor size exceeds 5 cm. Chemotherapy (commonly doxorubicin-based) is usually only administered at the discretion of the oncologist, and only if the primary tumor is > 5 cm. Whether chemotherapy reduces the risk of metastases or enhances survival is controversial.48

Synovial sarcomas of the extremities are rare enough, but synovial sarcomas of the dura are even rarer. Thus, no studies exist that systematically evaluate optimal treatment. The most reasonable approach is therefore similar to the treatment of anaplastic meningioma; namely, striving for total resection and following up with radiotherapy.
or stereotactic radiosurgery but not chemotherapy. Fractionated radiotherapy at a dose of 50–60 Gy is the most widely accepted treatment for anaplastic meningioma and is similar to treatment for synovial sarcomas of the extremities.

Regarding the prognosis of synovial sarcoma, the 5-year survival rate is ~ 65%. This rate includes those patients with tumors in the extremities, which tend to have a better prognosis. As mentioned above, other variables contributing to the survival rate include the size of the tumor and the presence of metastases. An intracranial, dura-based synovial sarcoma with particularly aggressive features and the presence of metastases. An intracranial, dura-based synovial sarcoma as an unusual cause of exophthalmos: case report.

Conclusions

We report a case of primary intradural synovial sarcoma in the cranium. To our knowledge, this is only the second such case described in the literature. Although the molecular signature of the tumor was complex, the histological appearance and immunohistochemical profile were diagnostic and ruled out all other spindle cell tumors. Thus, a wide differential diagnosis is necessary when confronted with such neoplasms in the dura.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Primary intracranial dura-based synovial sarcoma


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