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Case Report

Intraneural Synovial Sarcoma of Femoral Nerve: A Case Study with Review of Literature

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ABSTRACT

Synovial sarcoma is a soft tissue malignancy commonly originating from skeletal muscle and supporting connective tissues of the extremities but they have also been reported in various other anatomical locations but rarely peripheral nerves. An unusual case of a patient affected with intraneural synovial sarcoma of femoral nerve was studied and the case study presented here with a review of literature.

Key words: Synovial sarcoma, Intraneural, femoral nerve

INTRODUCTION

Synovial sarcomas are belligerent soft-tissue malignancies with a tendency for distant metastases. They represent approximately 5-10% of soft tissue sarcomas. [1] Although they have been described in people of all ages; SS most commonly occurs in adolescents and young adults 15–40 years of age with a male preponderance. [1, 2] Despite being treated by radical surgical resection, local irradiation and displaying a fairly high response rate to chemotherapy; their prognosis is bad with only a 50–60% five-year survival rate. [1]

Regardless of their name, they are unusual in joint cavities and encountered in areas with no apparent relation to synovial structures. [2] The predominant site of origin of synovial sarcomas is skeletal muscle and supporting connective tissues of the extremities, most often the leg, but they have also been reported in other anatomical locations including the head, neck, mediastinum, heart, esophagus, pleura, small intestine, and lung. [1]

Synovial sarcoma of peripheral nerve (SSPN) is rare with less than 50 cases reported in literature and none reported from India.

CASE REPORT

A 15 year old male presented with swelling over the right upper thigh since 1 year which was initially small and gradually progressing in size. Since 3 months the swelling increased rapidly and was associated with moderate pain and tenderness. On clinical examination the swelling was 10X8 X4cms located in the upper 1/3rd of the anterior aspect of right thigh; firm in consistency; non-mobile and tender. There was no other lesion elsewhere in the body. The mass was excised along with overlying subcutaneous tissue and skin. On intraoperative examination the mass appeared to arise from femoral nerve as a fusiform swelling, so a clinical diagnosis of peripheral nerve sheath tumor was given.

Gross examination (figure1) revealed a mass with attached subcutaneous tissue and skin measuring 9x7x4 cms. It was seen to arise from the central part of a large nerve 8.5 cm in length. External surface of the mass was smooth with areas of bosselation. Cut surface was

multinodular, variegated with solid, grey white to yellow brown areas. It had pushing margins. Microscopic examination (figure 2, 3) revealed a partially circumscribed tumour seen arising from the nerve. The tumor exhibited nodules composed of ovoid cells separated by fibrous septa. The cells were monomorphic with moderate to scant cytoplasm, centrally placed round to ovoid nuclei and vesicular chromatin with conspicuous nucleoli. Areas of spindling noted. Mitotic activity was15-18/10hpf. Areas of necrosis present (>50%). Areas of haemorrhage also seen. Areas of bone formation noted. The tumor cells were infiltrating adjacent subcutaneous adipose tissue. A tentative diagnosis of high grade sarcoma, FNCLCC Grade 3 was rendered and IHC was advised. The differential diagnosis considered were epithelioid MPNST, poorly differentiated synovial sarcoma and epithelioid leiomyosarcoma. IHC (figure 4) was done and tumor cells expressed pan CK, EMA, Bcl2 and were negative for S100, SMA and CD34. Molecular studies were done for confirmation and revealed t(X; 18)(SYT-SSX 2) by RT-PCR assay using formalin-fixed, paraffin embedded tissue blocks confirming the diagnosis of intraneural synovial sarcoma(poorly differentiated SS with focal spindling). The patient was further given radiotherapy +chemotherapy. The patient was subsequently lost to follow up.

Figures legends:

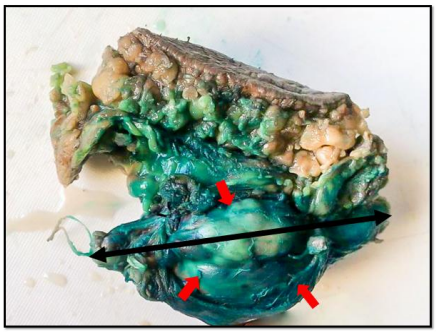

Figure 1: Gross examination revealed a mass(marked by red arrows) with attached subcutaneous tissue and skin measuring 9x7x4 cms. It was seen to arise from the central part of a large nerve 8.5 cm in length(black arrow) as a fusiform swelling. External surface of the mass was smooth with areas of bosselation.

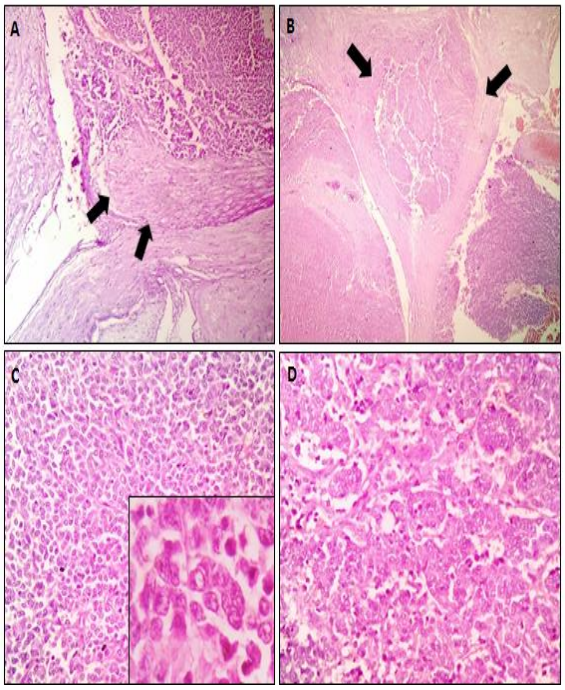

Figure2: A:photomicrograph showing tumor which is seen to arise from a nerve(marked by arrows); H&E,100X.
B:photomicrograph showing tumorcells arranged in a nodular pattern,(nodule marked by arrows);H&E,40X.
C:photomicrograph showing tumor with predominant cell population being ovoid with moderate to scant cytoplasm, centrally placed round to ovoid nuclei and vesicular chromatin with conspicuous nucleoli. The cells were arranged in diffuse sheets;H&E,400X(inset-high power view-1000X).
D:photomicrograph showing tumor with focal nesting pattern,H&E,400X.

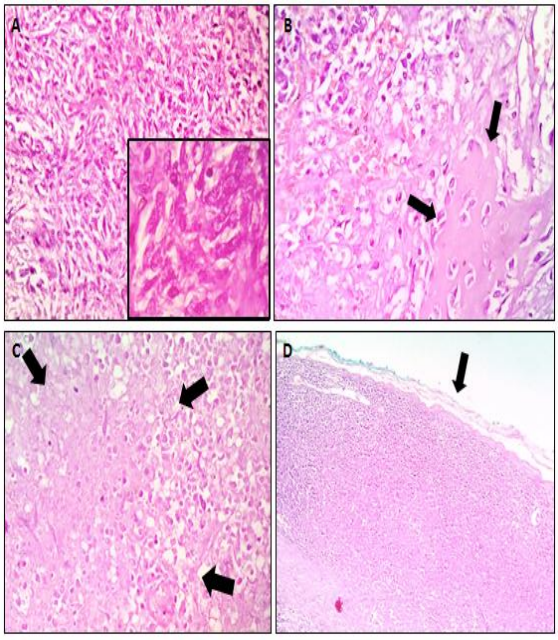

Figure3:A: photomicrograph showing tumor with focal spindle cell element;H&E,400X(inset-high power view,1000X).
B:photomicrograph showing tumor with heterologous elements in the form of bone (marked by arrows);H&E,400X.
C:photomicrograph showing areas of necrosis (marked by arrows);H&E,400X.
D:photomicrograph showing tumor with partial encapsulation (margins inked green);H&E,40X.

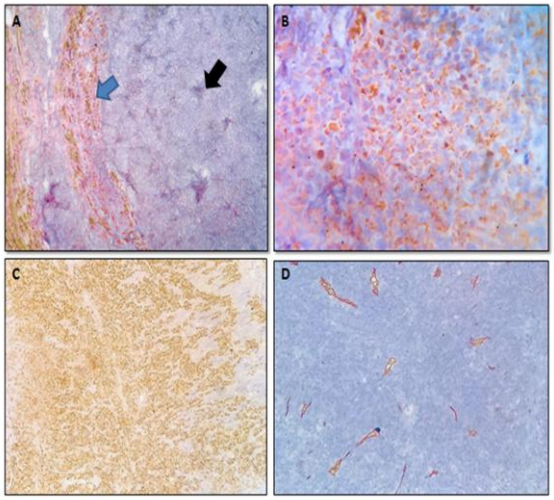

Figure 4: A: photomicrograph showing S100-negativity in tumorcells(black arrow)and positivity in adjacent nerve(blue arrow)S100 IHC,100X
B:photomicrograph showing tumor cells expressing cytokeratin(cytoplasmic granular),CK IHC,400X.
C: photomicrograph showing tumor cells expressing BCL2 (nuclear),BCL2 IHC,100X.
D:photomicrograph showing CD34 negativity in tumor cells and positivity in vessels,CD34 IHC,100X.

DISCUSSION

Peripheral nerve tumors are predominantly of neuroectodermal origin and developed from two components of nerve, Schwann or perineurial cells. Schwannoma and neurofibroma represent the benign tumors and malignant peripheral nerve sheath tumor represents the malignant counterpart of tumors with schwannian origin. Contrarily, mesenchymal tumors involving peripheral nerve are infrequent and are derived mainly from epineurial connective tissue. [3] Synovial sarcoma is a class of mesenchymal tumors with no apparent relation to synovial tissue and their likely origin is from primitive undifferentiated mesenchymal cells present at any site. [1] The intraneural type of SS is a rare entity often misdiagnosed as peripheral nerve sheath tumor.

Among the previously reported cases of intraneural SS; age group was wide ranging from 3-68 years; and females were predominantly affected with a ratio of 3:1.Neuropathic symptoms like pain, numbness and paraesthesia were the most common presenting features. The nerves of origin were diverse-radial, ulnar, median, brachial plexus, peroneal, posterior tibialis, common digital, facial, sciatic nerve, or the C7, L4, L5, S1 or T1 nerve root. [3,4,5] The size of the tumors was variable ranging from 1.5 cm to 19.5 cm. [3,4,5] The present case was a 15 year old male with involvement of femoral nerve and presenting with pain and swelling 9cm in size.

The uncommon location of an SS within a nerve root poses diagnostic difficulties without the use of specific ancillary techniques. The radiological pattern is nonspecific and hence non-diagnostic. They may have variable intensity and enhancement on MRI. They are comparatively isointense or hypointense to muscle and isointense or faintly hyperintense to fat and have a tendency to besharply marginated tumors with oval outline. [3]

As noted in literature, the morphologic and immunohistochemical features of intraneural SS are basically indistinguishable from those of their soft tissue counterparts. Three distinct histopathological patterns of synovial sarcoma are recognized. The first is the biphasic type, comprising of epithelial cells in glandular arrangements along with spindle cell components in varying proportions. Monophasic type morphologically consists of spindle cells only. A third, lesser common histopathological pattern of synovial sarcomas, the poorly differentiated subtype, is also acknowledged; which can exist alone or in combination with biphasic/monophasic spindled component; as in our case. [1] Literature review revealed that monophasic SS outnumbered biphasic subtype in intraneural category, with poorly differentiated foci in only 4 previous cases. [1,3,4] There is no major histologic feature to confirm the diagnosis of an SS arising from a nerve unless a biphasic component is identified. [6]

Though immunohistochemistry is not diagnostic, useful markers for SS include cytokeratin 7, 8 / 18, 19 (both components), AE1 / AE3 (70% of

monophasic, 46% of poorly differentiated), EMA (epithelial areas, 100% of monophasic, 92% of poorly differentiated), CD99 (90-100% of monophasic or poorly differentiated), BCL2 (both components, 90% of monophasic fibrous or poorly differentiated) and TLE1. [7,8] Literature review for INSS revealed that in one series of 10 cases, all tumors were diffusely positive for vimentin and patchily positive for EMA, pan cytokeratin, and cytokeratin 7. Diffuse nuclear expression of TLE1 protein was present in all cases. [3]

INSS and peripheral nerve sheath tumor may have similar histologic features, in that both tumors may have spindled or epithelioid cell morphology. Immunohistochemistry can be useful in the differential diagnosis of biphasic SS vs. PNST by demonstrating cytokeratin 7 and 19 positivity in biphasic SS and S-100 protein positivity in PNST. Even PNST may rarely exhibit glandular elements that may mimic SS. But, these glandular elements often show mucinous features and commonly express neuroendocrine markers such as chromogranin and serotonin, whereas the epithelial elements in INSS are negative for these neuroendocrine markers. [6] Another helpful observation is the frequent expression of CD34 in MPNST, particularly low-grade tumors, which is essentially absent in synovial sarcoma; thus aiding in the correct diagnosis. [3] The present case demonstrated expression of CK, EMA, BCL2 with negativity for SMA, desmin, S100 and CD34.

Like INSS, intraneural perineurioma is a rare clinical entity, which also tends to affect major nerve trunks and may be confused with intraneural monophasic SS. However, morphologically the spindle cells in perineurioma are generally more thin and elongated than seen in SS, and form pseudo-onion bulb structures with a clear central zone. Immunohistochemistry is not very helpful to delineate INSS and intraneural perineurioma as both tumors express EMA and are negative for S-100 protein. Molecular studies however reveal that intraneural perineurioma often carry t(X; 18) translocation. [6]

Cytogenetic testing is the most conclusive way to establish the diagnosis of synovial sarcoma. A gene translocation between chromosomes 18 and X; t(x; 18)(p11.2;q11.2) is seen to occur in over 90% of synovial sarcomas which leads to fusion of one of two variants of the SSX gene with the SYT gene, culminating in either the SYT/SSX1 or SYT/SSX2 chimeric fusion proteins. Practically all biphasic tumors express SYT/SSX1, while monophasic tumors express SYT/SSX1 in roughly half of the cases and SYT/SSX2 in the remainder.[4]Minority of cases demonstrate t(X;18)(p11;q11) (SS18-SSX4) (<1% of cases), and t(X;20)(p11;q13.3) (SS181-SSX1) (<1% of cases). [3] Literature review of the INSS cases with existing data revealed that most of the biphasic tumors expressed SYT/SSX1 and most of the monophasic tumors expressed SYT/SSX2. [3] No molecular evidence was available for the poorly differentiated cases of INSS.

As per literature review; INSS was mostly treated by surgery supplemented with radiation therapy in majority cases (45%), surgery + chemotherapy in 25% cases, surgery alone in 20% cases and surgery+ chemotherapy+ radiotherapy in 10% cases [1,3] The prognosis of synovial sarcoma has been attributed to several factors: body site (axial or extremities), sex, age, extent of primary surgery, tumor size (larger or smaller than 5 cm), invasiveness, areas of necrosis, bone or neurovascular invasion, poor differentiation, mitotic rate and type of translocation [1,3] According to Scheithauer et al., even in children; the overall prognosis of intraneural synovial sarcoma is superior to that of classic synovial sarcoma which can be ascribed to an earlier diagnosis, due to the neurological deficits consequent to intraneural growth. [3] Patients with SYT/SSX2 expressing tumors are also supposed to have a considerably better prognosis to those with SYT/SSX1

tumors considering the rates of metastasis and overall survival. [1]

To put it briefly, synovial sarcoma is an aggressive tumor that can occur anywhere in the body, including peripheral nerves; as illustrated in our case. Due to its origin within a nerve it can be erroneously reported as a peripheral nerve sheath tumor with radically diverse treatment strategy and patient outcome. Even its histological appearance is deceptive and only immunohistochemistry supplemented by molecular studies are diagnostic.

In conclusion, I report a case of poorly differentiated intraneural synovial sarcoma; a common tumor in an unusual site and wish to highlight the fact that they should be considered in the differential diagnosis of all intraneural lesions because a prompt, multidisciplinary approach may achieve a good long-term outcome.

ABBREVIATIONS

SS: Synovial
Sarcoma FNCLCC: Federation Nationale des Centres de Lutte Contre le Cancer
IHC: Immunohistochemistry
MPNST: Malignant peripheral nerve sheath tumor CK: Cytokeratin
EMA: Epithelial membrane antigen
Bcl2: B-cell lymphoma 2S100: Soluble in 100%, i.e. saturated, ammonium sulfate at neutral pH
SMA: Smooth muscle actin
CD: Cluster of differentiation-PCR: Reverse transcriptase polymerase chain reaction
H&E: Haematoxylin and eosin
MRI: Magnetic resonance imagingTLE1: Transducin-Like Enhancer of split 1

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