Malays J Pathol 2022; 44(1): 115 – 120

CASE SERIES

Sporadic malignant peripheral nerve sheath tumour (MPNST) in a 3-year-old girl: A diagnostic challenge

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Abstract

Introduction: Malignant peripheral nerve sheath tumour (MPNST) is an uncommon malignant neoplasm of childhood with unfavourable prognosis. Only a limited number of cases have been reported in children less than 12 years of age, and approximately one-half arise from a benign peripheral nerve sheath tumour, especially in the background of neurofibromatosis type 1 (NF1). Primary MPNST in children is even rarer. *Case report:* A 3-year-old Malay girl presented with painful right axillary swelling for six months, initially treated as axillary lymphadenitis and she defaulted follow up. She came back four months later with enlargement of the swelling. The previous biopsy was reported as Schwannoma, which correlates with a benign peripheral nerve sheath tumour's MRI findings. The final diagnosis after debulking surgery was consistent with MPNST. She succumbed to death 20 months after her initial diagnosis of advanced MPNST and lung metastasis. *Pathological findings:* Grossly, a huge partly circumscribed soft tissue mass was noted arising from a nerve with a solid greyish yellowish myxoid cut surface. Spindle-shaped cells arranged in a herringbone pattern alternated with areas of myxoid hypocellular areas exhibited marked pleomorphism, brisk mitosis, and extensive necrosis are seen microscopically. Immunohistochemistry shows patchy S100 protein staining with loss of expression of H3K27me3. *Conclusion:* Although MPNST is rare in the paediatric age group, the diagnosis should be considered in children without NF1 with a rapidly evolving and painful mass in the peripheral nerve distribution. In this case, the diagnosis was delayed and made after surgery. Due to its morphologic heterogeneity and lack of specific immunohistochemical markers, MPNST remains a diagnostic challenge.

Keywords: malignant peripheral nerve sheath tumour, children, diagnostic challenges.

INTRODUCTION

Malignant peripheral nerve sheath tumour (MPNST) is particularly rare, with an incidence of 0.001% in the general population.[1] It is a very rare spindle cell sarcoma in children accounting for approximately 5–10% of non-rhabdomyosarcoma soft tissue sarcomas.[2] Only 1.7% of the cases have been reported in children less than five years of age, with approximately one-half arise from a benign peripheral nerve sheath tumour (BPNST), especially in the background of neurofibromatosis type 1 (NF1).[3] Depending on its location and amount of nerve involvement, MPNST can present as a painful or painless mass. The tumour is usually found in the lower extremities, and MPNSTs located in the trunk and extremities are typically high-grade and clinically aggressive with a poor prognosis. Most MPNSTs are thought to arise by malignant transformation of neurofibromas, which occurs in about 2% of NF1 patients which is frequently reported.[4] Malignant transformation of schwannomas is an exceedingly rare occurrence, with no hereditary

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predisposition.[5] We highlighted such cases in this report—a case of a rare paediatric MPNST in a 3-year-old female patient with no history of neurofibromatosis type-1.

CASE REPORT

We present a case of a 3-year-old girl with no history of NF-1 referred to Hospital USM for painful right axillary swelling for six months duration in May 2013. The swelling gradually increased in size. She was initially treated as axillary lymphadenitis. Full Tuberculosis workout was normal, and Epstein Bar Virus (EBV) serology was not detected. She defaulted follow up to seek alternative medicine; however, the swelling was worsening after four months. MR images showed features of BPNST at the upper arm with areas of necrotic and haemorrhage within and encasing the vessel (Fig. 1). Initial biopsy was done, and HPE result revealed Schwannoma consistent with the MRI findings of BPNST. Computerised tomography (CT) scan showed lung metastasis. She underwent cervical laminectomy in June 2014, complicated with right upper limb paralysis, and proceeded with tumour debulking surgery in September 2014 (Fig. 2). The final diagnosis after debulking surgery was consistent with MPNST.

Ifosfamide, Carboplatin, and Etoposide (ICE) chemotherapy was commenced post-operation. During follow-up, 12 months later, imaging studies showed persistent lung metastases. She received a total of 8 cycles of ICE chemotherapy following the operation; her disease slowly progressed despite chemotherapy. She later succumbed to respiratory collapse after 20 months of initial diagnosis and died due to severe septicaemic shock with multiorgan failure with underlying advanced MPNST.

Pathological findings

Grossly, a huge partly circumscribed soft tissue mass was noted arising from the site of a nerve with solid greyish yellowish myxoid cut surfaces. Microscopically displayed spindle-shaped cells arranged in hypercellular and hypocellular areas. The hypercellular areas predominantly exhibited fascicular and herringbone patterns with moderate to severe pleomorphism, brisk mitosis, and extensive necrosis. The perivascular tumour accentuation was present. There was no heterologous component. Immunohistochemistry showed patchy S-100 protein staining with loss of expression of H3K27 trimethylation (H3K27me3) (Fig. 3).

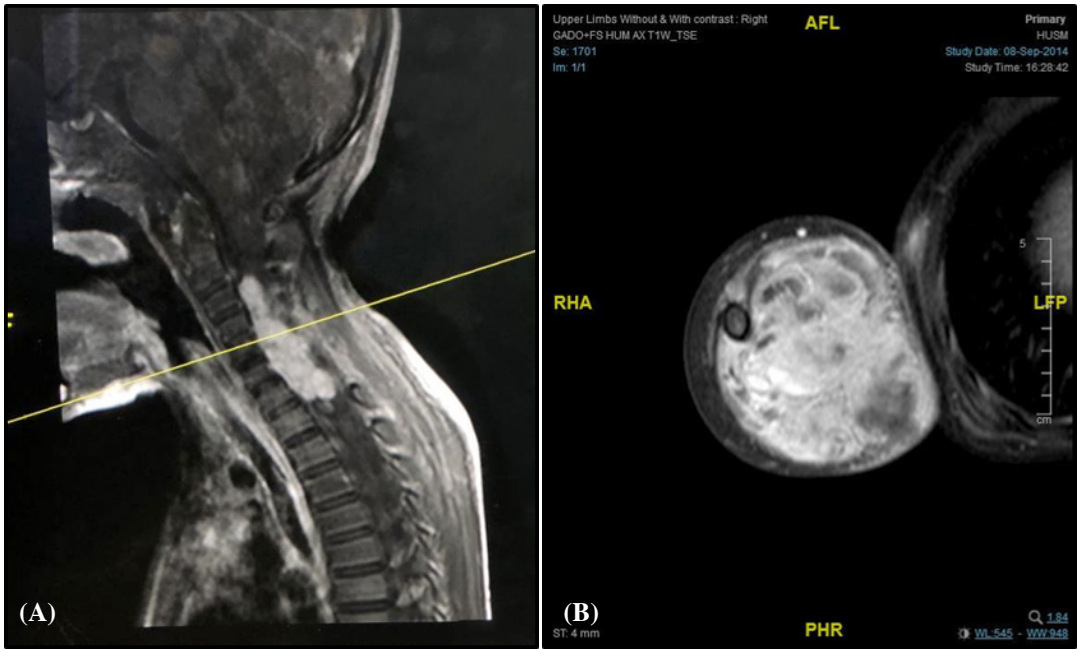

FIG. 1: (A) MRI show intradural extramedullary mass at the right cervical region from the level of C4 to the C8, which appear cystic, heterogeneously hypointense on T1 and hyperintense on T2 and features suggestive of benign peripheral nerve sheath tumour. (B) MRI shows a large intermuscular capsulated mass at the right medial side of the proximal arm, causing splaying and compression of the surrounding muscle, and this lesion appears solid with cystic component and reported as malignant Schwannoma.

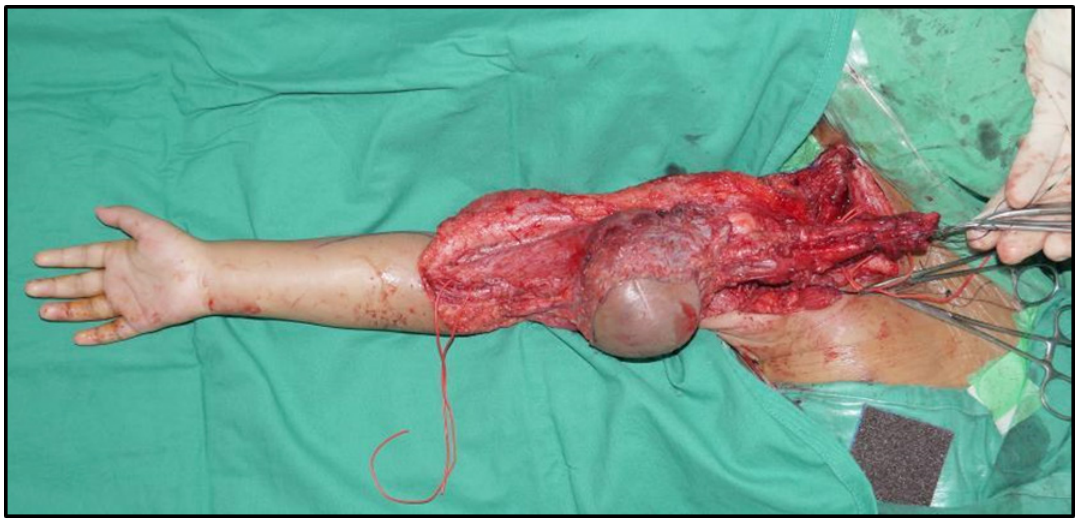

FIG. 2: Intraoperative findings of tumour exhibit a right arm mass with surrounding tissue and overlying skin. The mass is seen eccentrically located from the site of the nerve.

DISCUSSION

In the paediatric age group, the incidence of MPNST increases with age, with more than 80% of cases diagnosed at ten years or older.[6] Most sporadic cases affect adults between 30 and 60 years of age, although the age distribution is wide. With its diversity of histologic appearances, overlapping pattern, the rarity of these tumours, and lacking highly sensitive and specific immunohistochemical antibodies for MPNST, all these may justify the delay in diagnosis. Diagnosis may be delayed since this type of tumours is either asymptomatic or shows minimal discomfort. Many patients reported pain and neurological deficits at the time of presentation. Diagnosis of MPNST in this age group is challenging. This slowly enlarging mass initially exhibits rapid growth at presentation, and two-thirds of the lesions are more than 5cm at the time of diagnosis. Our patient illustrated the potential for these malignancies to present late due to their minimal propensity to produce symptoms and no background history of NF1.

Radiological diagnosis of this tumour is rather challenging. Concerning imaging investigations, our patient was evaluated with an MRI scan. Radiographically, the MRI findings compared with the previous study performed four months before the initial biopsy. This lesion at the upper arm significantly increased in size with more necrotic and haemorrhage within and encasing the vessel. Imaging investigations are essential but are not reliable to detect a malignant transformation. Significant differences between MPNST and BPNST were noted for the largest dimension of the mass, peripheral enhancement pattern, perilesional oedema like zone, and intra-tumoral cystic lesion (e.g., haemorrhage or necrosis).[7] Haemorrhagic or necrotic heterogeneity in MRI or CT may suggest malignancy, but this finding may also be observed in BPNST. If a tumour has two or more of the four statistically significant features, it can be considered highly suspicious of malignancy which showed a sensitivity of 61% and a specificity of 90%, respectively.[8] It should be subjected to a biopsy for early diagnosis.

The definitive diagnosis of MPNST is histopathology. However, the morphologic heterogeneity in MPNST, especially in the biopsy sample, is very challenging. The differentiation between the low-grade MPNST with cellular Schwannoma or MPNST with other histologic mimickers include monophasic synovial sarcoma (SS), solitary fibrous tumours (SFT), or fibrosarcoma, would be difficult. There are no specific markers to diagnose MPNST. S-100 protein and SOX10 patchy positivity or even negative staining typically found in MPNST except for epithelioid MPNST, which will show diffuse intense positivity like in BPNST. CD 34 usually positive and sometimes found extensively. TLE-1, which is supposed to be specific to SS, is also noted to be positive in both MPNST and SFT to up to 30% of cases which makes it more difficult to reach the diagnosis. Recently with a better understanding of MPNST biology, they found an H3K27me3 immunohistochemistry marker which has played

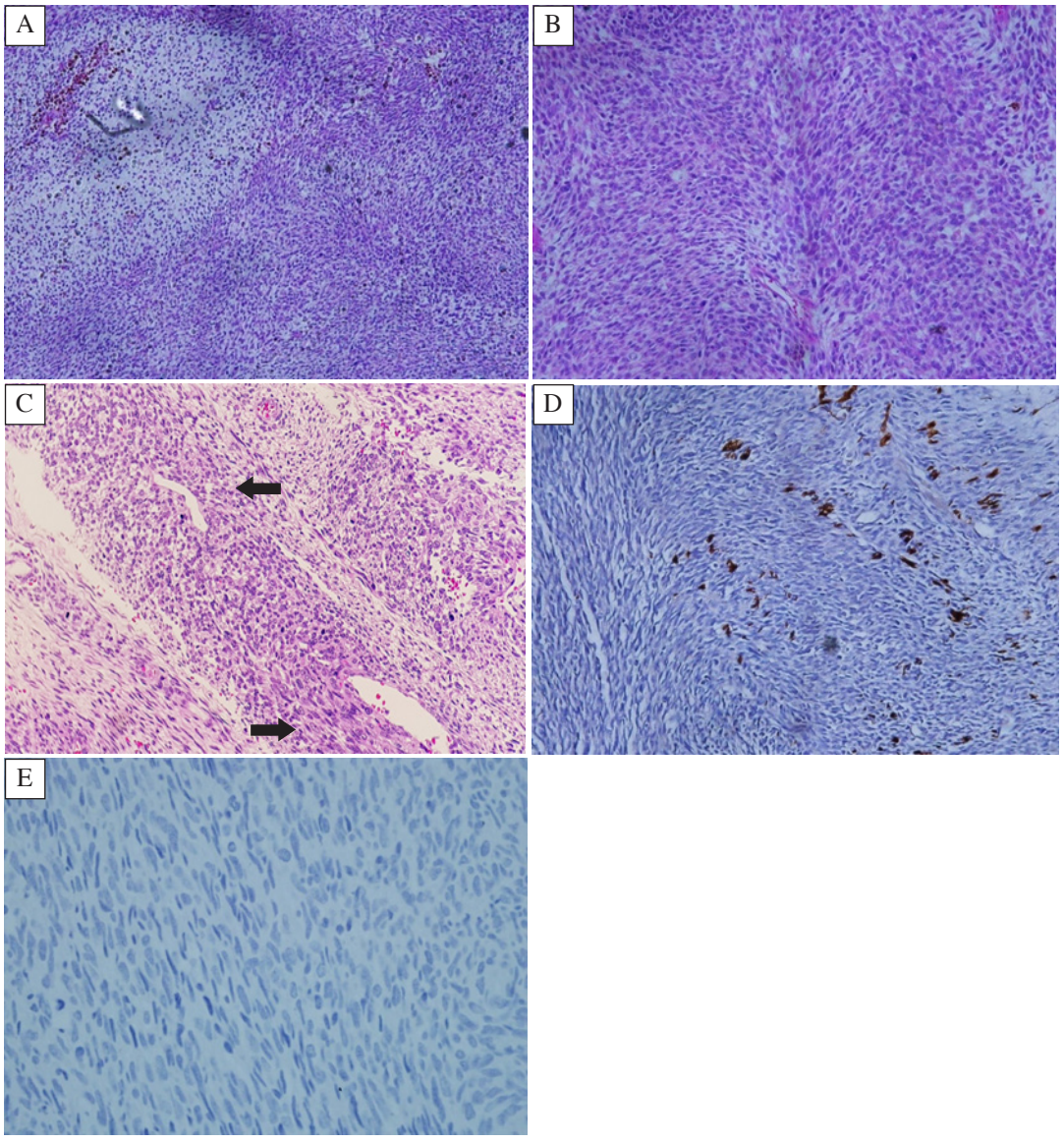

FIG. 3: (A) Malignant spindle-shaped cells arranged in hypercellular areas and loose myxoid hypocellular areas (H&E, x100). (B) Herring-bone pattern architecture (H&E, x200). (C) Perivascular accentuation (arrows) (H&E, x200). Mitoses are brisk. (D) The tumour cells show only focal immunoreactivity towards S-100 protein (x200) and (E) loss of expression of H3K27me3 seen in MPNST (x200).

an important role in the diagnosis of high-grade MPNST. In one study, loss of H3K27me3 was found in 34% of MPNST and up to 90% of high-grade MPNST compared with intact H3K27me3 in all BPNST.[9,10] Distinguishing cellular schwannoma from MPNST is important because Schwannoma has a benign course with rare malignant transformation. Intact H3K27me3 was also noted in MPNST's mimickers like SS (Table 1).

Most MPNSTs are aggressive, high-grade sarcomas with a high likelihood of local recurrence (40% to 65%) and distant metastases (40% to 68%).[11] They frequently metastasise to the lungs followed by bone, whereas lymph node metastases are uncommon. Other sites of metastasis include liver, brain, soft tissue, skin, and retroperitoneum.[11] MPNSTs have a poor outcome if untreated. These tumours are relatively resistant to chemotherapy and radiation therapy and, therefore, complete surgical excision continues to be the gold standard for

TABLE 1: MPNST and its differential diagnosis

Tumour	Morphology	Ancillary test
MPNST	- Spindle cells tumour - Hypercellular and hypocellular pattern. - The tumour cells arranged in fascicles, whorled, fibrosarcomatous like. - Nuclear palisading is uncommon. - Perivascular tumour accentuation is common - HPC-like vessels - Nuclear atypia. - Mitosis - Necrosis	- S-100 / SOX10 patchy or negative - CD34 positive - H3K27me3 loss - EMA may show focal positivity - Desmin positive (in rhabdomyo blastic differentiation/ heterologous component)
Cellular Schwannoma	- Spindle cells tumour - Hypercellular and hypocellular areas. - Lack of verocay bodies/nuclear palisading - No perivascular tumour accentuation. - Mitosis usually absent - Nuclear atypia in ancient type - No necrosis - Hyalinised vessels	- S-100 diffuse positivity - H3K27me3 intact (expressed)
SS	- Spindle cells tumour - The tumour cells arranged in fascicles, whorled, fibrosarcomatous- like. - Perivascular tumour accentuation is not a feature - HPC-like pattern - Wiry stromal collagen - No nuclear atypia - Mitosis rare - Necrosis rare	- EMA positive (even occasional or focal) - CD34 negative - TLE-1 strong diffuse nuclear positivity - H3K27me3 intact (expressed) - S-100/SMA are non- specific - t(X;18) translocation or SSX-SS18 fusion genes by FISH or PCR is specific
fibrosarcoma	- Spindle cell tumour - Herringbone pattern - Diagnosis of exclusion	- SMA positive (tram-track pattern) - Desmin and other muscle markers are negative - CD34 non specific
SFT	- Spindle cell tumour - HPC-like pattern - Pattern less growth pattern - Stromal hyalinisation	- CD34 positive - STAT 6 positive - H3K27me3 intact (expressed)

HPC-like vessels = Hemangiopericytoma-like vessels

treatment.

Complete surgical removal is the only chance for cure. Early radical surgical resection, when feasible, is the treatment of choice. Unfortunately, a number of MPNSTs involve the nerve root, preventing complete removal. Radiation therapy is recommended in cases with residual tumour after surgery; however, no evidence indicates that this improves survival.[12] Studies have reported that adjuvant chemotherapy exhibits only minimal benefit. Our case was treated by wide surgical excision or tumour debulking surgery and adjuvant chemotherapy. Unfortunately, our patient developed lung metastases.

CONCLUSION

Although MPNST is rare in the paediatric age group, the diagnosis should be considered in children without NF1 with a rapidly evolving

and painful mass in the distribution of a peripheral nerve. In this case, the diagnosis was delayed and made after surgery. Due to its morphologic heterogeneity, lack of specific immunohistochemical markers, and sampling errors, MPNST remains a diagnostic challenge. The role of chemotherapy is unclear. Early multidisciplinary diagnosis is important for the best optimal therapy at this young age. We report this case to draw more awareness to this lesion, to avoid incorrect diagnosis and unnecessary intervention.

Authors' contributions: Z.M.S.F. - manuscript writing and co-supervisor. W.I.W.F.N. - Orthopaedic surgeon. M.N. - MPath student. M.N. - Paediatrician. N.A. - Paediatric Oncologist. T.S.S.E. - Concept of the study, writing, editing and main supervisor.

Conflict of interest: The authors declare no conflict of interest.

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