

Research Article

A clinicopathological and immunohistochemical study of malignant peripheral nerve sheath tumors

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ABSTRACT

Background: Malignant Peripheral Nerve Sheath Tumor (MPNST) is a rare aggressive sarcoma that develops within a peripheral nerve and forms a diagnostic challenge in view of its varied histomorphology. This short series highlights the clinicopathological spectrum of 11 cases of MPNST and the incidence of neurofibromatosis 1 (NF1) association.

Methods: This retrospective and descriptive study on MPNST was done in the department of pathology, Kasturba medical college Mangalore (Manipal University), India over a period of three years from January 2008 to December 2010. Cases which were histopathologically diagnosed as MPNST were reviewed & immunostains was done where ever indicated to rule out the differentials.

Results: A total of 11 cases of MPNST were documented with a wide age range of 17-85 years. Male:female ratio was 2.6:1. Extremities (63.64%) were found to be the most common site. Location wise most of the tumors were deep seated (63.64%) and maximum cases were high grade (54.55%). NF1 association was seen in 2 cases. Heterologous elements in the form of chondroid differentiation was seen in one case. Immunostain with S-100 was focally positive in all the cases.

Conclusion: MPNST is a highly aggressive sarcoma with poor prognosis characterized by a challenge in its diagnosis as it has several mimics. Its diagnosis necessitates the incorporation of clinicopathological features and IHC with S-100 protein.

Keywords: Malignant peripheral nerve sheath tumor, Neurofibromatosis (NF-1), Heterologous differentiation

INTRODUCTION

Malignant Peripheral Nerve Sheath Tumor (MPNST) is a rare variety of soft tissue sarcoma of ectomesenchymal origin and accounts for 5% of all soft tissue tumors.¹ WHO coined the term MPNST replacing previous heterogeneous and often confusing terminologies, such as malignant schwannoma, malignant neurilemmoma and neurofibrosarcoma for tumors of neurogenic origin. These tumors often create diagnostic problems because of their cellular origin and histopathological similarities

with other spindle cell sarcomas like fibrosarcoma, leiomyosarcoma and monophasic synovial sarcoma.

MPNST arise from a major or minor peripheral nerve branches or sheath of peripheral nerve fibres. The cellular components of MPNST are malignant schwann cells, perineurial cells and fibroblast.²

These tumors can either arise spontaneously or show NF1 association. Most of the sporadic MPNSTs seen between 40 to 50 years of age, while those cases associated with

NF1 present a decade earlier. MPNST associated with NF1 are more aggressive than the sporadic ones and they are known to metastasizes within 2 years of diagnosis.^{2,3}

This short series on MPNST is a comprehensive clinicopathological study with special emphasis on its varied morphology, NF1 association and immunohistochemical analysis of S-100 protein.

METHODS

The present study on MPNST was conducted in the department of pathology, Kasturba medical college, Mangalore over a period of three years from January 2008 to December 2010. This study is a retrospective and descriptive study.

Cases which were histopathologically diagnosed as MPNST were studied. The specimens were either incisional biopsies or wide excision of the tumors.

The clinical history and radiological findings were received from the hospital records.

Specimens were fixed in 10% formalin, paraffin embedded and stained by the routine hematoxylin and eosin. In addition to conventional light microscopic studies, immunohistochemistry was performed on paraffin sections using a two-step process; first, the binding of primary antibody to the antigen of interest and second the detection of bound antigen by a chromogen. Appropriate positive and negative controls were used.

The various antibody markers utilized to substantiate a diagnosis of MPNST and to sort it out from various differential diagnosis included S-100 (polyclonal, Dako Cytomation), EMA (E29, Dako Cytomation) CD34 (polyclonal, Dako Corporation, Carpinteria CA, USA), CD99 (monoclonal, Biogenex San Ramon CA USA), cytokeratin (AE1 + AE3, monoclonal, Biogenex), SMA (polyclonal, 1A4, Dako) and vimentin (vim 3B4, polyclonal, Dako Cytomation). Immunohistochemical staining was done with envision detection kit from Dako Corporation and DAB as chromogen

All slides were examined under the light microscope and analysis was carried out on the following parameters.

- Age, gender, clinical features and tumor location
- Histological features
- Grade of the tumor

Diagnostic criteria were as defined by Enzinger.⁴ An MPNST was defined by one of the three criteria.

1. A tumor arising from a nerve.
2. A tumor arising from a pre-existing benign nerve sheath tumor, usually a neurofibroma.

3. Tumor displaying a constellation of histologic features like-
 - a) Dense and hypodense fascicles alternating in a marble like pattern consisting of asymmetrically tapered spindle cells with irregular buckled nuclei.
 - b) IHC or electron microscopic evidence of schwann cell differentiation in the context of a fibrosarcomatous appearing tumor.
 - c) Other less specific features but frequently occurring in schwann cell tumors are nuclear palisading, whorled structures, peculiar "hyperplastic" perivascular change and occasional heterologous elements i.e. cartilage, bone, skeletal muscle etc.
4. Abundant mitosis and geographic areas of necrosis with tumor palisading at the edges.
5. Marked contrast between the deeply hyperchromatic nuclei and the pale cytoplasm ("punched out nuclei").
6. Presence of large gaping vascular spaces resulting in a hemangiopericytoma like appearance.
7. Further, these tumors were classified as low and high grade on the basis of their cellular differentiation, mitotic count and tumor necrosis.

Grading of MPNST

Tumors were classified as low and high grade on the basis of their-

- Cellular differentiation
- Mitotic count
- Tumor necrosis

Tumor necrosis was evaluated with scoring as 0, 1 and 2 depending on the percentage as 0%, <50% and > 50% respectively.

Mitosis was also evaluated likewise as 0, 1 and 2 depending on numbers as <5, 5-10 and >10/HPF respectively.

Mitoses >10/HPF were considered as high grade tumor.

RESULTS

In the present study MPNST constituted 13.75% of all peripheral nerve sheath tumors. Among the 11 cases of MPNST studied, a wide age range was noted, with the youngest patient being 17 years and the oldest, 85 years. Maximum number of cases (36.37%) was seen in the age group 21-40 years. Males (72.73%) outnumbered female patients (27.28%) and the M:F ratio was 2.6:1 (Figure 1).

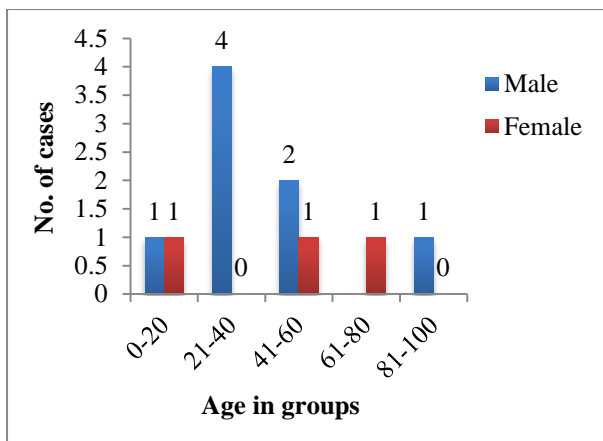


Figure 1: Age and gender distribution of 11 cases of MPNST.

Location wise 7 cases were deep seated (63.64%) whereas 4 cases (36.37%) were superficially located (Figure 2).

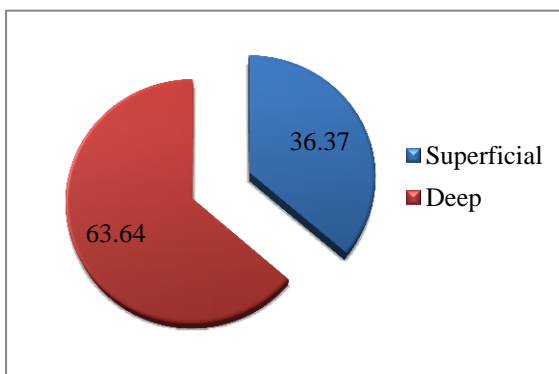


Figure 2: Location distribution of 11 cases of MPNST.

The most common site of involvement was the extremities (63.64%) followed by head and neck (9.09%) and trunk (9.09%). One case each was seen in posterior mediastinum and right inguinal region (Table 1).

Table 1: Site distribution of 11 cases of MPNST.

Site	Total No. of cases	Percentage (%)
Head & neck	1	9.09
Extremities	7	63.64
Trunk	1	9.09
Other Sites	2	18.19
Total	11	100

In 6 cases (54.55%) tumor size was >5 cm and rest of the cases (45.46%) the size was <5 cm (Table 2).

NFI association was seen in 18% of the cases (2/11cases) and remaining cases did not show any association (Figure-3).

Table 2: Distribution of tumor size in 11 cases of MPNST.

Tumor size (cm)	No. of cases	Percentage (%)
1-5	5	45.46
6-10	2	18.19
11-15	1	09.09
>15	3	27.28
Total	11	100

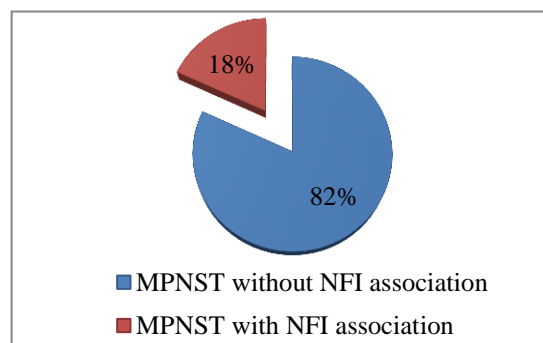


Figure 3: MPNST vs. NF 1.

Tumor necrosis score was one in 54.55% of cases and two in 45.46% of cases. In our study 54.56% of cases were high grade whereas 45.46% of cases were low grade (Table 3, 4).

Table 3: Correlation of tumor necrosis and mitosis in grading of MPNST.

	No. of cases	Percentage (%)
Tumor necrosis		
0% necrosis	0	0
<50% necrosis	6	54.55
>50% necrosis	5	45.46
Total	11	100
Mitosis		
<5 per 10/HPF	5	45.46
5-10 per 10/HPF	3	27.28
>10 per 10/HPF	3	27.28
Total	11	100

Table 4: Distribution of cases of MPNST according to grade.

Grade	No. of cases	Percentage (%)
Low	5	45.46
High	6	54.55
Total	11	100

Almost, all the cases of MPNSTS showed hypocellular and hypercellular areas giving the peculiar “marbleized appearance”. Myxoid change, geographic necrosis,

hemangiopericytomatous vascular pattern and subendothelial herniation by the tumor cells was noted in many cases. Heterologous differentiation was identified in one case showing chondroid differentiation.

Two cases which were initially diagnosed as ancient schwannoma and cellular neurofibroma were reviewed, which on IHC was diagnosed as high grade MPNST and low grade MPNST respectively.

The case which was diagnosed as ancient schwannoma, showed hyper and hypocellular areas with nuclear pleomorphism, multinucleate giant cells, brisk mitotic activity and necrosis. IHC with S-100 protein showed focal positivity. Hence the diagnosis of high grade MPNST was made. Whereas in other case the patient had history of NF1 with multiple swellings all over the body. Swelling on the face was excised which on microscopic examination revealed increased cellularity and mitoses. In view of these findings, IHC was done which showed focal positivity with S-100 protein.

S-100 staining was performed in all the cases of MPNST. It was found to be positive in all of them. S-100 positivity was invariably focal within the tumor cells. EMA was positive in 3 cases of MPNST suggesting perineurial cell participation in MPNST.

DISCUSSION

MPNST is a rare and aggressive soft tissue sarcoma. It is synonymous with the earlier used terms like neurogenic

sarcoma, neurofibrosarcoma and malignant schwannoma.⁵

In the present study, a total of 11 cases of MPNSTs were studied. A wide age range was seen from 17 to 85 years. Majority of cases were seen in the 2nd to 4th decade. This corresponds to the age range from the study of Rekhi et al.⁵ where the patients age ranged from 8 to 75 years. In their study mean age at presentation was 38.1 years.

In the present study males (8/11) outnumbered female patients (3/11) which is in congruence with studies by Kar et al.⁶ and Rekhi et al.⁵

Rekhi et al.⁵ found that majority of the patients presented with swelling and pain. In their study, most of the tumors were deep seated (60.3%) and remaining (39.6%) were superficially located and most common site of involvement was extremities, followed by head and neck region, shoulders, back, retroperitoneum and groin, which was at par with our study. In our study 63.64% were deep seated and 36.37% cases were superficial

Kar et al.⁶ also found that extremities were the common site involved followed by chest wall, trunk, pelvis, head and neck, and they too opined that MPNSTs occurred frequently in males with median age of 40 years and most common site being extremities (Table 5).

But Ducatman et al.³ found that trunk was the most common site (46%) involved by MPNSTs in their study (Table 5).

Table 5: Comparison of clinical data of MPNSTs.

Authors	Common site	Superficial location	Deep location	NF1 association
Ducatman et al. ³	Trunk (46%)	-	-	52% (62/120)
Wanebo et al. ⁸	Extremities (25%)	-	-	53.58% (15/28)
Kar et al. ⁶	Extremities (62.50%)	8% (2/24)	92% (22/24)	21% (5/24)
Gabhane et al. ⁹	Extremities (75%)	-	-	25% (2/8)
Rekhi et al. ⁵	Extremities (39.6%)	39.6% (25/63)	60.3% (38/63)	15.9% (10/63)
Present study	Extremities (63.64%)	36.37%	63.64%	18.19%

The association of MPNSTs with NF1 is well known and the series reported that 5%-42% NF1 patients developed MPNST.²

Ducatman et al.³ in their study opined that MPNST in NF1 patients is more common than in the general population.

In the present study, only 2 cases (18.19%) showed NF1 association, whereas NF1 association was seen in 21% of cases in the studies conducted by Kar et al.⁶ and 15.9% (10/63) cases of Rekhi et al.⁵

Patients with NF1 were younger (mean age - 28.7 years) than patients without NF1 (mean age - 39.7 years) in the studies by Ducatman et al.³ and Wanebo et al.⁸ respectively but in the present study one patient with NF1 presented at 50 years and other patient at 18 years. The presence of multiple neurofibromas and café-au-lait spots were the two most common criteria fulfilled by these two patients.

The size of tumor ranged from 1 cm to 17 cm and 54.54% cases had size >5 cm and maximum cases (55%)

were high grade tumor in the current study, similar to the studies conducted by Kar et al.⁶ and Rekhi et al.⁵

In our study we observed that one patient had a second primary which was non neurogenic (multiple myeloma). Similar finding was seen in the study by Ducatman et al.³ where they found that 17.5% of patients had a history of concurrent or second non neurogenic tumor of which glioma was the most frequent neoplasm. Wanebo et al.⁸ also found that three patients had second primary malignancy including an ovarian cystadenocarcinoma, an occipital lobe ganglioglioma and a pheochromocytoma.

Histopathological features

Histopathological patterns included short fascicles, sweeping fascicles, whorls, hemangiopericytoma-like vascular pattern and herringbone pattern. Almost all the cases of MPNST showed hypocellular and hypercellular areas. Myxoid change, geographic necrosis and subendothelial herniation by the tumor cells was noted in many cases. Heterologous element was identified in one case, showing chondroid differentiation. The presence of heterologous elements was not found to have a significant impact on survival, in the studies by Ducatman et al.³ and Kar et al.⁶

Histopathologically, these tumors were diagnosed either as MPNSTs or other neural tumors. IHC with S-100 protein was done in all the cases; a positive expression of S-100 protein in all the cases and negative expression of several other markers helped us to out the differentials. The expression of S-100 protein was mostly focal in tumor cells showing both nuclear and cytoplasmic positivity.

Hirose et al.⁹ studied of 12 cases of MPNST immunohistochemically and ultrastructurally, and they found that MPNST is composed of schwann cells, perineurial cells, fibroblastic cells. They observed that EMA was positive in 5 cases of MPNSTs. Several other studies have demonstrated EMA immunoreactivity in MPNST and these studies indicate that EMA is a marker of perineurial cells.^{2,10}

In the present study EMA positivity was noted in three cases, suggesting a perineurial cell participation in MPNST. Hirose et al.² opined that MPNST with perineurial differentiation have more favorable prognosis than conventional MPNST.

We encountered a case, which on microscopic examination had features similar to synovial sarcoma along with entrapped nerve fibres at the periphery and within the tumor. The patient had history of surgery for neurofibroma 10 years back in the same region with a clinical diagnosis of recurrent neurofibroma. IHC showed focal positivity of tumor cells for S-100, EMA-positive, CD99- negative, cytokeratin-negative. In view of clinical

history, microscopy and IHC findings, a diagnosis of low grade MPNST was made.

Smith et al.¹¹ found that ten cases of Monophasic Synovial Sarcoma (MSS) demonstrated focal S-100 immunoreactivity and 90% of the cases were positive for CK7 and CK 19 negative. The authors concluded that MSS and MPNST are sarcomas with overlapping histologic and immunophenotypic features.

In addition, Ducatman et al.³ observed that tumors in the extremities had a better outcome than cases in the head and neck. Rekhi et al.⁵ opined that this might have been due to the possibility of better clearance in extremity lesions, but Kar et al.⁶ opined that site of the tumor had no impact on the survival of the patients. However we did not analyze this aspect.

Enzinger⁴ noticed that grade of the tumor, necrosis, vascular invasion and presence of mitoses have a significant influence on survival of the patients.

MPNST has several mimics because of its histopathological similarities with other spindle cell tumors. Except cases arising in the context of NF1, MPNSTs often present with challenging diagnostic problems. These tumors may histopathologically resemble fibrosarcoma, synovial sarcoma, hemangiopericytoma and epithelioid angiosarcoma. Because of the confusion engendered by this microscopic overlap, strict histopathological criteria were observed along with IHC.

CONCLUSION

This series highlights clinicopathological features of 11 cases of MPNSTs and its association with NF1. S-100 staining was performed in all of them. It was found to be positive in all the cases. Positive expression of S-100 protein in all the cases and negative expression of other markers helped us to rule out the differentials. S-100 protein was found to be the most reproducible marker in this tumor. Thus a combination of clinical history, gross, microscopic examination and immunohistochemistry help in diagnosing these tumors.

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Conflict of interest: None declared

Ethical approval: Not required

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