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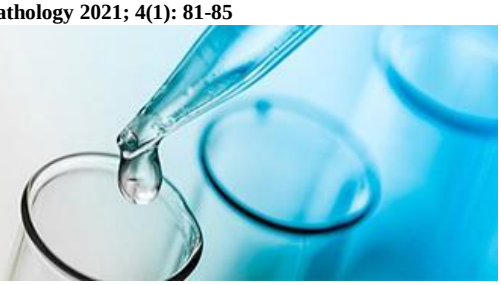

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A histopathological study of neurofibroma and malignant peripheral nerve sheath tumors in a medical institute of Central Karnataka

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Abstract
Neurofibromas comprise a unique subset of peripheral nerve sheath tumors defined by their distinct anatomic location and distinguished by their histologic diversity. Neurofibromas can be a part of Neurofibromatosis 1 (NF1). Most Neurofibromas are histologically benign however, they may experience malignant degeneration especially in the setting of neurofibromatosis. A total of 27 cases of neurofibroma and 5 cases of malignant peripheral nerve sheath tumor and their variants are included in this study. Neurofibromas spans a wide range of histopathological features and associated clinical characteristics. Our study focuses on histopathology of Neurofibroma and Malignant peripheral nerve sheath tumor and emphasizes the histologic attributes to be familiar with these entities and establish their accurate pathological diagnosis in view of their varying biologic behavior.

Keywords: Diffuse Neurofibroma, plexiform neurofibroma, MPNST, malignant triton tumor, histopathology

Introduction
Neurofibromas comprise a unique subset of peripheral nerve sheath tumors defined by their distinct anatomic location and distinguished by their histologic diversity [1]. Historically, Galen and Hippocrates wrote about nerve tumors [2]. In 1800s, peripheral nervous system tumors were not subclassified but termed together as "neuromata" [3]. In 1968, Harkin and Reed provided a modern pathologic classification of peripheral nerve tumors with clear implications for the surgical management of each type [4]. Peripheral nerve tumors often present subtly, with few symptoms and even fewer signs, and most lesions thus become apparent when a mass becomes palpable [5]. The stigmata of neurocutaneous disorders in a patient presenting with vague paresthetic symptoms in a nerve distribution should make the clinicians suspect and investigate for an underlying nerve tumor [6]. Neurofibromas can be a part of genetic tumor predisposition syndrome, most commonly Neurofibromatosis 1 (NF1) [7]. Most Neurofibromas are histologically benign however, they may experience malignant degeneration especially in the setting of neurofibromatosis. Treatment in the form of total surgical removal is therefore indicated in most nerve tumors for histologic diagnosis as well as for relief of symptoms [8]. Our study focuses on histopathology of Neurofibroma and Malignant peripheral nerve sheath tumor and emphasizes the histologic attributes to be familiar with these entities and establish their accurate pathological diagnosis in view of their varying biologic behavior.

Methodology: The material for the present cross-sectional study comprised of peripheral nerve sheath tumors diagnosed in the Department of Pathology, J.J.M. Medical College, Davangere, over a duration of 5yrs between 2005-2009. Clinical history and findings were recorded in each case from the available requisition forms / case records. Both the excision and incision biopsy specimen were included in the study. The specimens were fixed in 10% formalin for 24-48 hours. Large specimens were cut serially at a distance of one to two centimeters before fixing. External appearance and cut sections described. After fixation representative areas were sampled for detailed histopathological examination. Slides were stained with hematoxylin and eosin. Microscopic findings were noted in a detailed manner. Special stains (Toluidine blue, Fite faraco, Perls Prussian blue) and immuno-histochemistry was performed wherever needed.

FNAC correlation was not attempted, as it was not performed as a preoperative procedure in all the cases. Data was analyzed using MS-excel software and results presented using percentages.

Results: A total of 27 cases of neurofibroma and 5 cases of malignant peripheral nerve sheath tumor were included for the study. Neurofibromas (n=27): Majority of neurofibromas occurred in females (59.2%). They were distributed over a wide age-range (10-74 years) and nearly, two-thirds of neurofibromas showed predilection for extremities and head and neck region (62.9%). About 59.2% were conventional neurofibromas, 11.1% were plexiform and 29.6% were diffuse neurofibromas. In our study some of the neurofibromas were seen in clinical setting of NF1. Out of 16 conventional neurofibromas 5 were associated with NF1. All the 3 plexiform neurofibroma were seen in NF1 and 4 out of 8 diffuse neurofibromas were seen in NF1.

Conventional neurofibromas showed equal sex incidence and were distributed over a wide age-group ranging from children to elderly age group. They were located in head and neck region, extremities, back and other sites. Nearly one-third (31.2%) of them were cases of NF1. In the remainder, clinical diagnosis did not correlate with the histopathological diagnosis. Two cases in the neck region were clinically suspected to be lymphadenitis. All of them presented as localized solitary lesions. Grossly, thirteen were non- encapsulated, four lesions were covered by skin, twelve were gray-white. About 94% showed homogenous gray-white on cut-section. Glistening cut-section was seen in five cases. Foci of calcification were seen in one case. On Microscopy: Most of them were non-encapsulated and comprised of hypercellular area and hypocellular areas. Two neurofibromas were intraneural and showed well-formed capsule. In fifteen, tumor cells were arranged in fascicles. Intranuclear inclusions was seen in one, and eleven tumors showed wavy-collagenous fibers. In Four, Wagner-Meissner like corpuscles were seen. Ten cases showed myxoid matrix, four showed collagen matrix. Adipose tissue was seen in one case, foci of calcification was seen in one case. All 16 tumors showed perivascular mast cell infiltration. All the cases showed diffusely scattered lymphocytes. Ten showed dilated blood vessels. One of the neurofibroma arising in the nasal cavity was lined by ciliated columnar epithelium. One neurofibroma showed hemosiderin-laden macrophages. One case showed entrapped adnexa. None of them showed infiltration into the adjacent tissue. Fite foraco staining was done in one and Toluidine blue staining was performed to demonstrate mast cells in all the cases of conventional neurofibromas. A middle-aged female patient who presented with nodular lesion on the hand was clinically considered as leprosy. Excised lesion was a neurofibroma. Fite faraco staining demonstrated mast cells, and was negative for lepra bacilli. In most of the cases (25/27) toluidine blue staining was done to demonstrate mast cells in neurofibromas.

All three plexiform neurofibromas were seen in the adults in their 2nd and 3rd decade and all were associated with NF1 and presented with distorted and contorted large segment of nerve, converted to a thick convoluted mass, which has been likened to a 'bag of worms'. On cut-section three of them showed homogenous gray-white surface, two had glistening surface. In none of the cases secondary changes were seen. On Microscopy: All were non- encapsulated with varying cellularity, one case showed multiple nodules in the backdrop of neurofibromatous tissue. Two showed tumor cells arranged in fascicles. Wagner-Meissner like corpuscles were seen in one case. Two showed wavy- collagenous fibers. Myxoid areas were seen in two, and adipose tissue was seen in one case. Mast cells were seen in all the three cases, while two of the cases showed diffuse scattered infiltration of lymphocytes. None of them showed mitosis and adjacent tissue infiltration.

Diffuse neurofibroma (n=8) showed equal sex distribution and most of them were seen in the 2nd decade. Four cases of diffuse neurofibroma showed association with NF1. Most of them (6/8) were located in the extremities. About 75% diffuse neurofibromas were located in the superficial soft tissue, i.e., skin and subcutaneous tissue. All of them presented as an ill-defined swelling. Grossly, 87.5% were non-encapsulated, 50% were covered by skin, 50% of them were gray-white with smooth surface. On cut-section seven showed homogenous gray-white appearance. On Microscopy: All were non-encapsulated. One showed hyperpigmented skin. Tumor cells are suspended in the uniform matrix of fine fibrillary collagen. In most tumors, cells showed round to ovoid vesicular nuclei (7/8). Curnicule arrangement of tumor cells was seen in one case. Two cases showed melanin pigmented cells. Wagner-Meissner like corpuscles were seen in two cases. In 75% cases there were ectatic blood vessels, whereas in 25% there were thick-walled blood vessels. About 50% cases showed wavy-collagenous fibres. Adipose tissue infiltration was seen in seven cases (87.5%), scattered lymphocytes and mast cells were seen in all the cases. Entrapped adnexa were seen in one. 25% cases showed entrapping of nerves and blood vessels and tendon. Toluidine blue staining was performed to demonstrate mast cells. 75% cases showed positive toluidine blue staining.

Table 1: Descriptive clinical data of malignant peripheral nerve sheath tumor (n=5)

Case no.	Sex	Age	Location	Clinical Diagnosis	NF1	Histopathology Diagnosis
1	F	35	Arm	Sarcoma	+	Malignant triton tumor
2	F	40	Face	Neurofibroma	+	MPNST
3	M	48	Thigh	Soft tissue sarcoma	+	Plexiform Neurofibroma with MPNST
4	M	35	Thigh	Liposarcoma	+	MPNST
5	F	60	Arm	Lipoma	Status not available	Low grade MPNST

Table 1 shows descriptive clinical data of MPNSTs in the study. Grossly, two cases were non-encapsulated and three encapsulated. Two cases were globular masses with one tumor surface covered by skin. cut-surface was homogenous gray-white in three of them. Necrosis and cystic change were seen in one case each. On microscopy, all the MPNSTs showed encapsulation, they were cellular, composed of spindle cells in fascicles, and plexiform pattern was seen in MPNST arising from plexiform neurofibroma. All of them showed pleomorphic nuclei. Hyperchromatic nuclei and prominent nucleoli were seen in all except MPNST arising in plexiform neurofibroma. Rhabdomyoblasts were seen in malignant triton tumor. Mitosis was seen in all MPNSTs. Melanin pigment, giant cells, Wegner-Meissner's like corpuscles in one of the classical MPNST. Lymphocytic infiltration was seen in all except malignant triton tumor. Mast cells were seen in all except plexiform neurofibroma

MPNST. Necrosis was seen only in Malignant triton tumor. Immuno-histochemical study was done in low-grade MPNST, it showed strong and diffuse positivity for S100.

Pictures

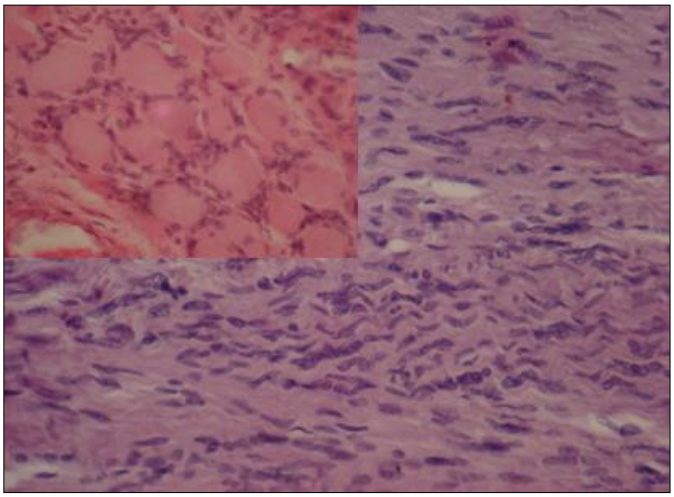

Fig 1: Conventional Neurofibroma; inset shows Wagner-Meissner like corpuscles.

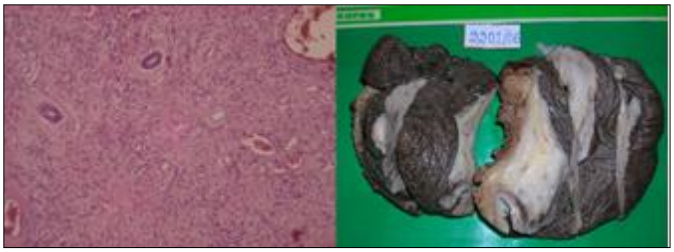

Fig 2: Gross and microscopy of diffuse neurofibroma

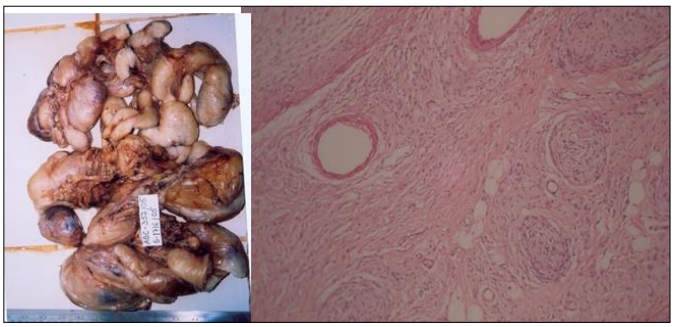

Fig 3: Gross and microscopy of Plexiform neurofibroma

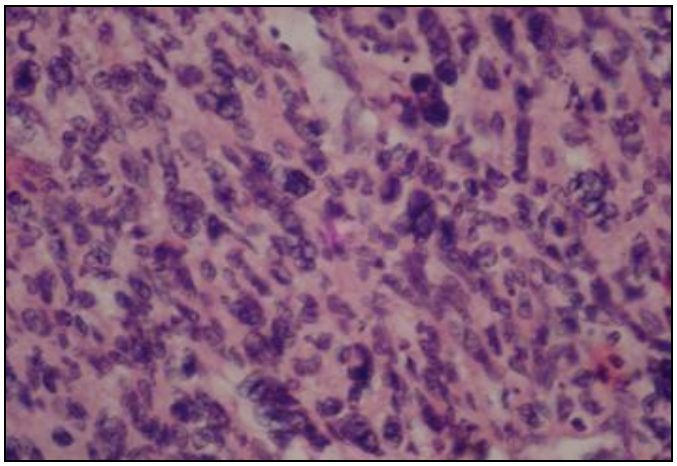

Fig 4: Microphotograph of classical MPNST

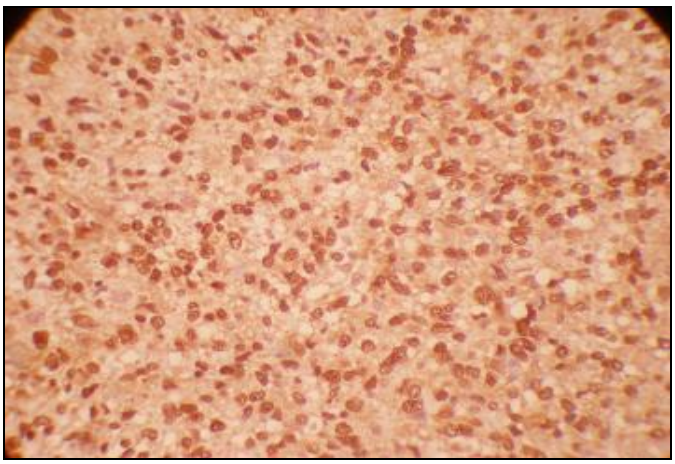

Fig 5: S100 diffuse immunoreactivity in low-grade MPNST

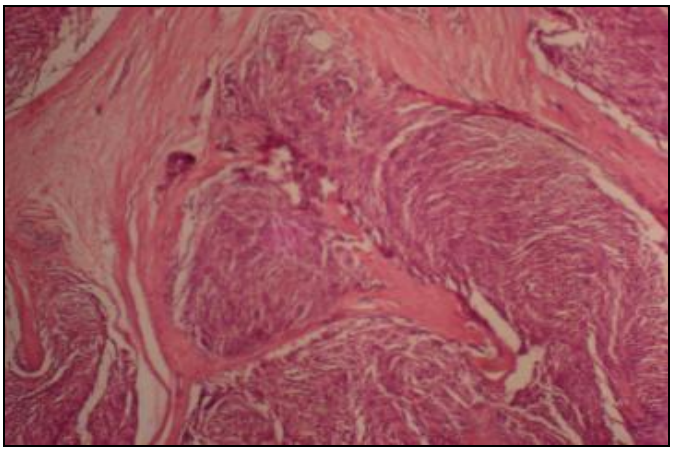

Fig 6: Photomicrograph of MPNST in Plexiform neurofibroma

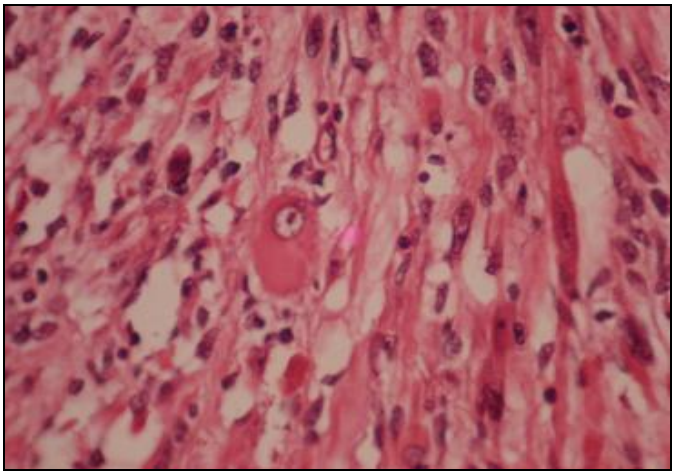

Fig 7: Photomicrograph of Malignant triton tumor

Discussion

Neurofibromas spans a wide range of histopathological features and associated clinical characteristics. The clinical evaluation and histologic recognition of Neurofibromas and MPNSTs have been substantially aided by IHC analysis. Since these immunoprofiles are, in and of themselves, non-specific, this study emphasizes the histologic attributes of neurofibroma and malignant PNSTs. Clinically, MPNST is difficult to detect in NF1 patients and has a poor prognosis because of the highly likelihood of local recurrence and distant metastasis. At present, there is no reliable indicator of early detection of tumor progression or malignant transformation of Neurofibroma to MPNST apart from

classic histopathologic criteria. Accurate designation of peripheral nerve tumors is important because of a dramatic difference in clinical outcome between benign and malignant tumors. Whether arising by malignant transformation of a neurofibroma or schwannoma, or de novo from a peripheral nerve, MPNSTs as a group have a poor prognosis. They have high rate of distant metastasis [9]. Regarding misdiagnosis of a benign peripheral nerve tumor, neurofibroma as a MPNST even low-grade can subject patients to potentially harmful overtreatment [9].

Neurofibroma: Solitary neurofibroma, which is a localized neurofibroma, occurs in non-NF1 cases. Their incidence is obscure due to the trouble in barring the finding of NF1 in certain patients, for example, young age, in whom the initial presentation may only be solitary neurofibroma or patients who have no familial history. In spite of these issues, solitary neurofibromas exceed NF1 in numbers. In the series by Geschickter about 90% of neurofibromas were of the solitary type, while the remainders were found in the setting of NF1. Thus, it is clear that the presence of a solitary neurofibroma does not establish or exclude the diagnosis of NF1 [10]. In our study, we encountered eleven cases of conventional solitary neurofibroma without associated NF1. Three of these cases were in age of <20 years, youngest was a 4 years old child. These cases need to be screened for NF1.

Plexiform neurofibroma are capable of developing anywhere along the length of a peripheral nerve and often locally invasive [11]. Head and neck plexiform neurofibromas may cause disfigurement, compromise the airway, or affect the muscles of mastication. Head and neck lesions also have a 5% to 10% incidence of sarcomatous degeneration [11]. One of our pelxiform neurofibroma was located in neck region. The importance of accurately diagnosing plexiform neurofibromas is that a subset harbors neurofibromatosis [12]. Presence of pelxiform neurofibroma should hint for search of NF1, as it is one of marker for NF1 [11]. In our study all three were in NF1.

As evidenced in the past, MPNSTs, in people who suffer with neurofibromatosis usually arises within the confines of a pre-existing plexiform neurofibroma. In Tucker *et al*. study of association between benign and malignant peripheral nerve sheath tumors in NF1, it was histopathologically apparent that all of the analyzed MPNSTs revealed remnants of benign plexiform neurofibromas [13]. In our study all the 3 cases of plexiform neurofibroma were associated with neurofibromatosis but there was no evidence of malignant change. For the practicing pathologist, it becomes important to submit entire plexiform neurofibromas for microscopic analysis and to alert clinicians about the possibility of malignancies developing in pre-existing plexiform neurofibromas [13]. In Tucker *et al*. study, there was no significant association between superficial plexiform neurofibromas and MPNSTs. Contrary, the association between the presence of internal plexiform neurofibromas and MPNST was very strong, so that the individuals who had internal plexiform neurofibroma were 20 times more likely to have a MPNST than the individuals without them [13]. If the lesion is focal, conservative excision is the choice of treatment with a low risk of recurrence [12]. Subtotal or incomplete resection results in recurrence. Given the invasive nature of plexiform neurofibroma, sacrifice of significant structures may be required during surgical resection. The functional and cosmetic consequences of resection may therefore result in higher level of morbidity than that reported by the patient before surgery [11].

Diffuse and Plexiform Neurofibroma are difficult to differentiate, in most cases of plexiform neurofibroma there is very marked myxoid change and in addition, tumor with similar features to diffuse neurofibroma is often seen in the adjacent soft tissues [14]. Histologically, diffuse neurofibroma, besides sharing histological similarity with cutaneous neurofibroma, shows infiltration of conspicuous diffuse fat. In some cases, the abundance of fat may mask the neurofibromatous component and simulate a fibrolipoma [15]. Diffuse neurofibromas can be difficult to diagnose leading to delay of treatment and potentially the need for a more extensive excision. Once recognized as a neurofibroma, it is important to identify it as a diffuse neurofibroma, given its lack of relationship to neurofibromatosis [12].

An enlarging soft tissue mass is always of concern because of the possibility of malignancy, particularly in patients with NF1 who are at risk of transformation to MPNST. However, malignant transformation in diffuse neurofibroma is virtually unknown [16]. Even after complete excision, clinical recurrences may develop because of the infiltrative growth pattern and the multicentricity of the tumor. Because of possible recurrence and of the potential development of neurofibromatosis, yearly follow-up is recommended. Neurofibromas may undergo histologic transformation to a MPNST. The risk of developing MPNST is greatest in patients with neurofibromatosis and most MPNSTs in these patients are thought to originate in a pre-existing neurofibroma [17]. Neurofibroma with cytologic atypia, should not be mistaken for MPNST unless there is necrosis and significant mitotic activity [17].

MPNSTs rarely arise from superficial neurofibromas or peripheral nerves. Superficial MPNST often have a history of slow growth over a long period followed by a period of rapid growth. MPNST may have an aggressive clinical course. Because of their superficial location, they might come to clinical attention earlier and, historically, have been associated with better overall outcome [18]. In comparison with deep-seated MPNSTs, superficial cases were reported more often in head and neck region in literature review of 23 cases of conventional superficial MPNSTs but they also occur in the trunk and extremities, in 4/5 cases of Allison *et al*. [18] Similarly in our study one case of superficial MPNST was in head and neck region and other 2 in extremities. One might postulate that superficial tumors would be identified at a smaller size than their deep-seated counterparts.

One might also postulate that superficial MPNSTs have a better prognosis than their deep-seated counterparts because they come to clinical attention earlier [18]. Careful clinical and histological evaluation together with immunohistochemical and ultrastructural analysis plays an important role in accurate diagnosis, particularly if the tumor is not associated with NF1 or has no continuity with a nerve [19] (as in our case). No significant correlation has been noted between survival and histological grade [19]. It has been reported that LG-MPNSTs show diffuse and intense staining for S100 protein, as found in Yamaguchi *et al*. study and our case as well. It is thought that most LG-MPNSTs arise in neurofibromas, as in our case. Here the histological criteria that enables a positive diagnosis of LG-MPNST is the presence of hypercellularity, general nuclear enlargement, mitoses and hyperchromasia. The diagnosis of low-grade MPNST is not straightforward. Firstly, it is

usually difficult to distinguish neurofibromas with varying degrees of atypia from MPNST. Secondly, the pathological features of LG-MPNST often overlap with those of other soft tissue tumors [19].

Clinically, MPNST is difficult to detect in NF1 patients and has a poor prognosis because of the high likelihood of local recurrence and distant metastasis. At present, there is no reliable indicator of early detection of tumor progression or malignant transformation of plexiform neurofibroma to MPNST apart from histopathologic criteria though imperfect [20]. In our study, one case of MPNST was arising in PNF with NF1. MPNSTs are histologically diverse and may contain malignant areas of divergent mesenchymal differentiation, the most common is skeletal muscle (rhabdomyosarcoma). MPNST with rhabdomyosarcomatous differentiation is also known as malignant triton tumor [21]. Malignant triton tumor has a worse prognosis than classic MPNST does and the correct diagnosis requires attention to the clinical history and knowledge of the complexities regarding its differential diagnosis [21]. The presence of varying differentiation is prominent indication of NF1. 57% of patients with MTT have NF1 [21]. The rarity of MPNSTs and the lack of any singular diagnostic radiologic or pathologic signature lead to several management challenges. These tumors are best managed as part of a multidisciplinary team so as to optimize patient care and facilitate research. Suspicion of a MPNST based on clinical or radiological alteration of a soft tissue mass in proximity to a peripheral nerve, especially in the context of NF1, should lead to referral to tertiary centre. Early diagnosis followed by oncologic surgery to obtain tumor free margins provides the best chance for long term cure [22].

Conclusion

Neurofibromas and MPNSTs show an interesting histologic variety despite being composed of a limited array of cellular constituents. Key issue for the pathologist is a definitive diagnosis in this histologic diversity for better management. Peripheral nerve sheath neoplasms exhibit histologic features that overlap with those of many other benign and malignant soft tissue tumors. The correct diagnosis relies mainly on histologic findings and IHC profile.

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