

Recurrent MPNST in Mosaic Localized Neurofibromatosis: A Rare Scenario – Review

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Abstract

Introduction: Mosaic localized neurofibromatosis is a rare subtype of Neurofibromatosis type 1 (NF1) which is largely underdiagnosed till recently. The occurrence of Malignant Peripheral Nerve Sheath Tumor (MPNST) in such a setting is extremely rare with only 5 cases reported in literature till date. **Method:** Narrative review based on published case reports, obtained by searching on PubMed and Google scholar. **Results/ Discussion:** The pattern of recurrence and prognosis are different from conventional MPNST. The cases are of variable histologic grade, but showed improved survival outcome with surgical treatment alone. Even though local recurrence is common, none of these cases showed distant metastasis. This is in contrast with conventional MPNST which shows poor survival and frequent metastasis even with multimodality treatment. Specific treatment guidelines are yet to be established because of its rarity. **Conclusions:** Even though histomorphology remains the mainstay of diagnosis of MPNST, further cytogenetic and molecular analysis of these cases are crucial in the invention of new targeted drugs. In this review, we discuss the clinical outcome of this rare entity and highlight the importance of understanding the molecular events for future targeted therapies.

Keywords: Malignant peripheral nerve sheath tumor (MPNST), Neurofibromatosis type 1 (NF1), Mosaic localized NF1 (MNF1), Immunohistochemistry (IHC).

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a rare spindle cell neoplasm accounting for approximately 3-5% of soft tissue sarcomas. It often arises from a peripheral nerve, from a pre-existing benign nerve sheath tumor, or in a patient with neurofibromatosis type 1 (NF1). In the absence of these settings, particularly in sporadic or radiation associated tumors, the diagnosis can be more challenging and is based on the histological and immunohistochemical features suggesting Schwannian differentiation [1].

About half of the cases of MPNST are diagnosed in patients with Von Recklinghausen syndrome, NF1 [2]. However the occurrence of MPNST associated with mosaic localized NF1 is extremely rare. Only 5 cases have been reported in literature till date [3,4,5,6]. Among these, Mosaic localized NF1 with MPNST showing multiple recurrences has been reported only in a

single case. Mosaicism results from somatic mutations. Both Neurofibromatosis type 1 and type 2 occur in mosaic forms. It is observed that early somatic mutations result in generalized disease which is clinically indistinguishable from hereditary form. Later somatic mutations cause localized manifestations, often described as segmental.

Segmental neurofibromatosis is a rare variant of NF1. In 2000, Tinschert et al. showed that MNF1 was caused by the somatic mutation of NF1 gene [7]. Genetic testing has proven it to be the result of post-zygotic NF1 mutation leading to somatic mosaicism. Such phenotype is appropriately called as mosaic neurofibromatosis type 1 (MNF1) [8,9]. It is characterized by neurofibromas and/ or cafe-au-lait macules localized to one body segment with no crossing of the midline and no family history. The distribution of lesions is usually unilateral, but can be bilateral in 6% of cases, either in a symmetric or asymmetrical arrangement [10]. The estimated prevalence rate

of MNF1 is approximately 0.0018%, whereas that of NF1 ranges from 0.02 to 0.03%, indicating the rarity of the scenario [11,12].

The rationale for the study is that studies regarding the survival rate of patients with MPNST arising in the setting of mosaic localized NF1 have not been conducted, due to its extreme low incidence. Proper understanding of the disease biology helps in planning treatment. Herein we are discussing the clinical outcome of this rare association and the diverse histomorphologic and immunohistochemistry features that are encountered in the disease course with review of literature.

Method

This study is a narrative review. Previous case reports were collected by searching in PUBMED and GOOGLE SCHOLAR.

The keywords used were Mosaic localized NF1 and recurrent MPNST. The case reports of MPNST arising in the setting of MNF1 alone were selected for review. Four full-text articles including authors' case report and a recently reported case of an aggressive subtype of MPNST developed in a similar setting are analyzed. The details of two initially reported cases were collected from one of these case reports.

Results

The occurrence of MPNST in MNF1 patients is extremely rare. Only 5 cases are reported in literature till date. Additionally, a case of malignant triton tumor which is a rare subtype of MPNST is also described recently in the setting of MNF1. The clinical features, diagnostic modalities and treatment outcome of these cases are summarized in Tables 1 and 2.

Table 1: Clinical features of MPNST cases associated with MNF1.

Clinical features	Schwartz et al [3]	Schwartz et al [3]	Kapsok et al [4]	Hagizawa et al [5]	Marickar and Abraham [6]	Andrew et al [16] (MTT)
Age of onset	43 years	48 years	66 years	16 years	48 years	25 years
Gender	Female	Female	Female	Male	Female	Female
Symptom	Pain	Radiating pain	Skin lesion	Pain & swelling	Swelling	Pain, sensory deficit, swelling
Location	Anterior thigh	Intrapelvic	Left thigh-skin plaque	Right knee-medial aspect	Left elbow-lateral aspect	Left thigh- anteromedial
Nerve of origin	Lateral femoral cutaneous nerve	Posterior femoral cutaneous nerve	Not identified	Suggested as iliohypogastric nerve	Radial nerve	Femoral nerve branch
MNF1 features	Not identified in available literature	Not identified in available literature	Neurofibroma-Mons pubis	Café- au-lait spots- leg	Neurofibroma - elbow	Inguinal freckling and multiple café-au-lait spots extremity

Table 2: Diagnostic profile and treatment outcome with follow up of MNF1 cases with MPNST.

Parameters	Schwartz et al [3]	Schwartz et al [3]	Kapsok et al [4]	Hagizawa et al [5]	Marickar and Abraham [6]	Andrew et al [16] (MTT)
Histologic type	Superficial High grade	Deep	Superficial Low grade	Subcutaneous High grade	Superficial and deep Low intermediate grade	High grade
IHC profile	–	–	S100+ HMG45- CD34-	S100 scattered positive; Vimentin diffuse positive; CK-, BCL2-, TLE1-, STAT6-, H3K27me3 partially lost	S100 patchy positivity; SOX10-, CK diffuse strong +; BCL2+, TLE1-, STAT6-	S100+ SOX10+ Desmin & Myogenin- focal positivity
Genetic study	-	-	-	RT- PCR: SYT-SSX1 & SYT-SSX2 chimeric transcripts not detected; NF1 microdeletion in affected skin identified.	FISH test for SYT break apart analysis- Negative	Gene mutation in NF, TP53, CDKN2A/B, EED. Large structural chromosomal abnormalities.

Treatment	Operation+ Radiation+ chemotherapy	Operation+ chemotherapy	en bloc excision	Wide resection	Multiple excisions, Chemoradiation, Above elbow amputation	En bloc resection, intra operative & post operative radiotherapy.
Recurrence	at 26 months	at 2 months	No recurrence till 16 months	No recurrence till 1.5years after surgery	13 times in 13 years	at 3 months post-surgery.
Distant metastasis	Nil	Nil	Nil	Nil	Nil	Nil

Clinical features

The age of onset of MPNST ranges from 16-66 years in patients with MNF1. There is a female preponderance in the ratio 5:1. The presenting symptom was pain in majority of patients. The most common location is lower extremity along femoral nerve branches. Either neurofibromas or skin lesions characterized MNF1 manifestations.

Diagnostic profile

Histomorphology remains the mainstay of diagnosis. The lesions can be superficial or deep seated with varying histologic grades. IHC study showed S100 positivity at least focally in all cases. Aberrant patterns of CK and BCL2 observed during multiple recurrences warrants cytogenetic studies.

Molecular testing and prognosis

Gene mutation in NF, TP53, CDKN2A/B, EED and large structural chromosomal abnormalities noted in the aggressive subtype. Recurrences tend to be local rather than distant metastasis with a better prognosis.

Schwartz et al. [3] detailed the first observations of 2 cases of MPNST in the setting of segmental neurofibromatosis. Both were females in their 4th decade of life. Histologically one case was superficial high grade while other was deep in location. Both cases had recurrence at 26 months and 2 months respectively.

Kapsok et al. [4] reported a superficial form of low grade MPNST associated with segmental neurofibromatosis. Though rare, superficial forms of MPNST are well recognized earlier. The patient was a 66-year-old female who presented with a skin lesion on the thigh. Biopsy showed a spindle cell neoplasm in the dermis. No epidermal melanocytic dysplasia or dermo-epidermal junctional disturbance was noted. Hypercellularity, diffuse nuclear atypia and few mitosis were identified. IHC study revealed S100+, HMB45- and CD34-. Thus, other differentials in this case such as amelanotic melanoma and dermatofibrosarcoma protuberans were excluded. They couldn't identify associated nerve trunk during surgery. An unusual spatial and chronological relationship was observed

here as the segmental manifestations appeared after the resection of MPNST and were located at two different dermatomes.

Hagizawa et al. [5] described the first case of MPNST in an adolescent patient with MNF1. The diagnosis is based on regional café-au-lait spots and freckles in the affected leg and confirmed by genomic NF1 microdeletion. Microscopy showed a well circumscribed spindle cell tumor in the subcutis, composed of cellular and less cellular areas with hemangiopericytoma-like vessels and myxoid matrix. The tumor cells had moderate to severe nuclear atypia. They also observed consistent limited expression of NF1 in the tumor sample. A report by Perry et al. revealed that NF1 deletion is a characteristic feature of all MPNSTs and its expression varies in plexiform neurofibroma, demonstrating the deletion of NF1 as a useful indicator of appropriate diagnosis [13]. Additionally, this NF1 microdeletion was observed in both generalized and localized NF1 [14].

Marickar and Abraham [6] reported a unique case of multiple recurrent MPNST about 13 times during a period of 13 years and finally ended up in above-elbow amputation. All the recurrences occurred in a particular dermatomal segment along the course of radial nerve in the arm and forearm as multiple swellings. The histopathology of the tumor during recurrences ranged from plexiform neurofibroma to MPNST, fibrosarcoma, Myxofibrosarcoma and cellular neurofibroma (Table 3).

The histomorphologic diversity of the tumor is depicted as detailed below. Microscopy of the recurrent MPNST showed monomorphic spindle cells in fascicles infiltrating fascia at the periphery (Figure 1). There was presence of metaplastic bone within tumor tissue (Figure 2). It also showed plexiform pattern of tumor and its origin from radial nerve (Figure 3). There was appearance of low-grade tumor with uniform spindle cell population, absent mitosis and necrosis (Figure 4). Some areas resembled myxofibrosarcoma (Figure 5).

Initially the swellings were superficial in location. Later they became muscle deep and encircled the radial nerve, which was salvaged multiple times during surgery. On the last three

Table 3: IHC profile of MPNST during recurrences in a single case of MNF1 [6].

Recurrences	Morphologic diagnosis	IHC profile
2007 (initial swelling)	Neurofibroma	-
2007 (recurrent)	MPNST	S100+
2011	PNF	-
2012	MPNST	S100+, CK-, BCL2-
2014	Fibrosarcoma/ MPNST	Vimentin+, BCL2-, SMA-, EMA-
2015 (2 swellings lateral aspect arm)	MPNST	-
2016 (2 swellings arm & elbow)	PNF and cellular spindle cell neoplasm with muscle invasion	-
2017	Cellular spindle cell neoplasm of neural origin	-
2017 (Left arm & elbow)	MPNST	-
2018	Cellular neurofibroma	-
2019 (multiple nodules arm)	Myxofibrosarcoma	S100 patchy positivity
2019 (Left arm & elbow)	Grade 1 sarcoma -	-
2020 (multiple swellings same site)	MPNST	-
2020 (AE amputation)	MPNST	S100 patchy positivity, CK diffuse strong +, BCL2+, SOX10-, TLE-1-, STAT-6-, IHC ERGSMASMINCD34-, CD99-, EMA-

Figure 1

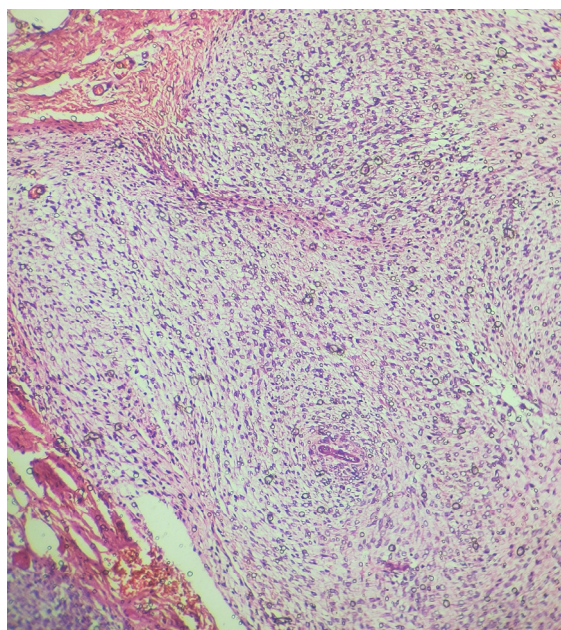


Figure 1: Microscopy of recurrent MPNST showing monomorphic spindle cells in fascicles infiltrating fascia at the periphery (H&E x400).

Figure 2

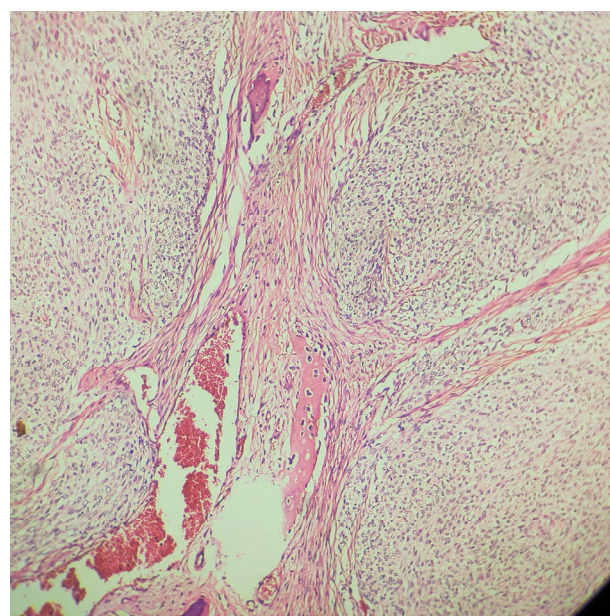


Figure 2: Presence of metaplastic bone within tumour tissue (H&E x400).

Figure 3

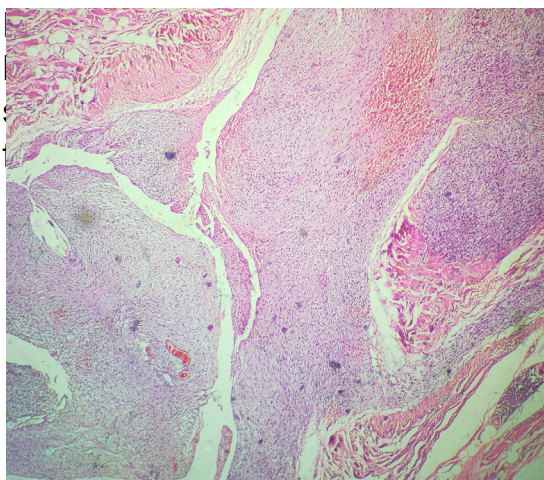


Figure 3: Plexiform pattern of tumour and its origin from radial nerve (H&E x400).

Figure 4

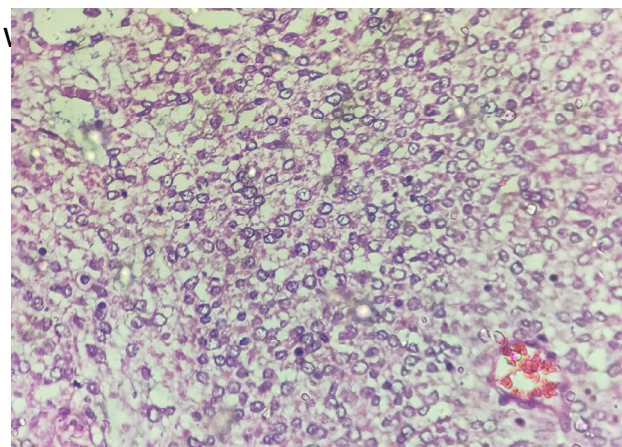


Figure 4: Low grade appearance of tumour with uniform spindle cell population, absent mitosis and necrosis (H&E x400).

Figure 5

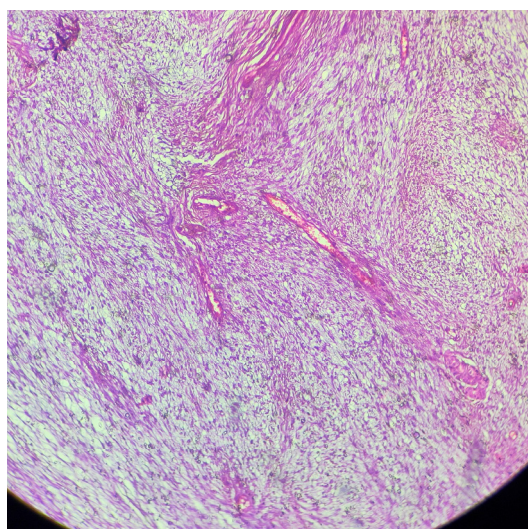


Figure 5: Morphology resembling Myxofibrosarcoma (H&E x400).

Figure 6

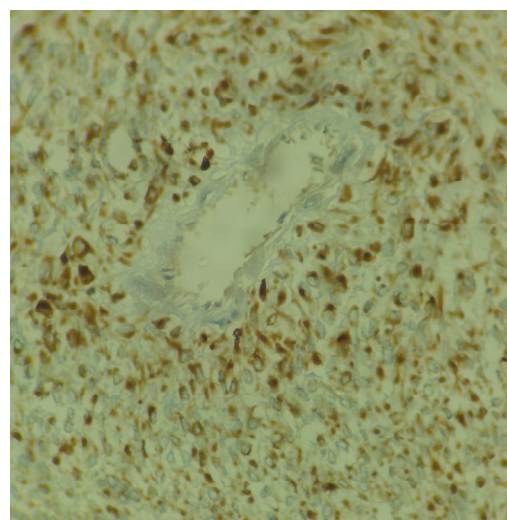


Figure 6: Cytokeratin (CK) immunostaining: diffuse strong positivity with intense perinuclear zone reactivity (CK IHC x400).

occasions the tumor had to be shaved off from the humerus. Final amputation specimen showed a single fleshy tumor infiltrating the humerus. Microscopic findings were typical of MPNST, with hypercellular and hypocellular areas of fascicles of spindle cells in a myxoid stroma. An extensive IHC panel was done in the amputation specimen in view of diverse morphologic diagnosis in recurrences. Cytokeratin (CK) immunostaining showed diffuse strong positivity with intense perinuclear zone reactivity (CK IHC x400) as seen in Figure 6. BCL2 immunostaining showed positivity (Figure 7). S100 (IHC staining x400) showed patchy positivity (Figure 8). SOX10 (IHC staining x400) showed negative pattern (Figure 9) and CD99

(IHC staining x400) showed negative pattern (Figure 10). Its comparison with limited IHC study done earlier in recurrences is given in Table 3. Synovial sarcoma was a close differential clinically, morphologically as well as by IHC as such tumors are also described to arise in association with nerves [15].

IHC sarcoma panel showed patchy positivity for S100. However diffuse strong positivity for Cytokeratin (CK) with intense perinuclear zone reactivity, BCL2 positivity and SOX10 negativity poses diagnostic challenge again. So, we proceeded with cytogenetic study-FISH test for SYT break apart analysis in tissue block. This was negative; hence we

Figure 7

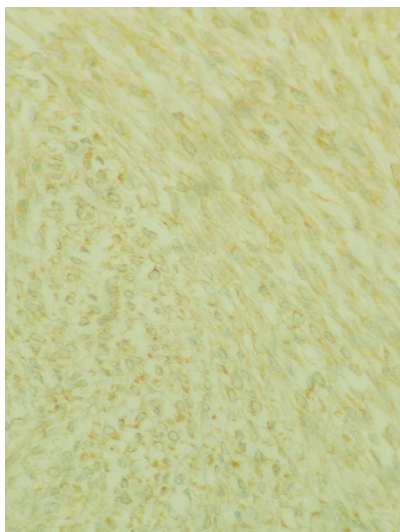


Figure 7: BCL2 (IHC staining x400) immunostaining showing positivity.

Figure 8

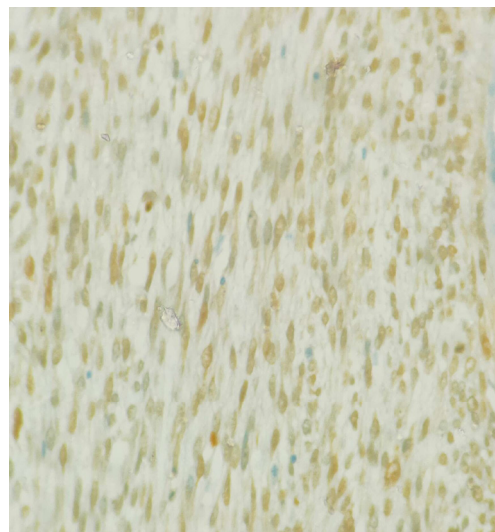


Figure 8: S100 (IHC staining x400) showing patchy positivity.

Figure 9

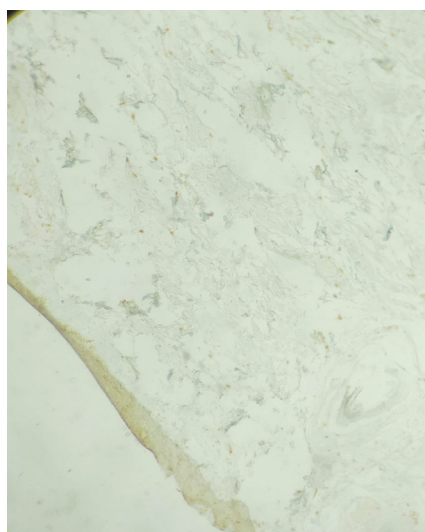


Figure 9: SOX10 (IHC staining x400) shows negative pattern.

Figure 10



Figure 10: CD99 (IHC staining x400) shows negative pattern.

excluded the possibility of synovial sarcoma. We observed an unusual pattern in IHC expression during the course of recurrence. These variations in expression pattern of CK and BCL2 (negative in initial biopsy and later positive in amputation specimen) in MPNST recurrence are not described in literature. However, the final diagnosis of MPNST is strongly supported by involvement of radial nerve, features of MNF1 and exclusion of synovial sarcoma by cytogenetic study. The corresponding author is very meticulous in keeping patient records which is the sole factor that allowed retrospective comparison of histopathology and IHC pattern during disease course. The strong bondage and trust of the patient to her

surgeon is well appreciated as all the 14 surgeries were done by the corresponding author.

Recently a single case of malignant triton tumor (MTT), a highly aggressive subtype of MPNST displaying rhabdomyoblastic differentiation has been reported in a setting of MNF1 [16]. MTTs make up to less than 10% of all MPNSTs with a 5-year overall survival rate of 10-15% [17-20]. 40-70% of MTT have been found in NF1 patients [21-23]. Here it presented as anteromedial thigh pain and swelling in a 25-year-old female. All the 3 diagnostic criteria for MTT as proposed by Woodruff et al. [24] were met in this case

as the tumor was located along the femoral nerve in the setting of segmental neurofibromatosis, and contained both Schwann cell and rhabdomyoblastic characteristics by IHC. Histopathology showed a highly cellular spindle cell proliferation in fascicular pattern, focal pleomorphism, bizarre multinucleated giant cells and abundant mitotic figures. IHC showed S100 and SOX10 positively, focal positivity for desmin and myogenin supporting rhabdomyoblastic differentiation. Cytogenetic profiling revealed gene mutation to NF, TP53, CDKN2A/B, EED and large scale structural chromosomal abnormalities [18,23,25]. Despite the en-bloc dissection with negative margins and adjuvant intraoperative radiotherapy, she had recurrence at 3 months postoperative period.

There are no current treatment guidelines for these rare aggressive tumors because of the rarity. Available data suggests that en-bloc tumor removal with negative margins is the mainstay determining survival chance [17,18,23,26]. Kostler et al. documented a long term MTT survivor with retinoic receptor mutations by genetic analysis and treated with isotretinoin and interferon [27]. Thus, further cytogenetic and molecular analyses of these cases are crucial in the invention of new targeted drugs.

Discussion

Mosaic localized Nf1 - an overview

As already known, NF1 is a genetic disorder mainly affecting cells of the neural tissues, with an autosomal dominant inheritance pattern. The etiology is mutation in the NF1 gene located in chromosome 17q11.2. It affects approximately 1 in 3500 individuals worldwide and shows nearly 100% penetrance of the disease [28].

Segmental neurofibromatosis is a rare subtype, first described by Crowe et al. in 1956 [29]. They termed it as sectorial neurofibromatosis. In 1977, Miller and Sparkes established the term segmental neurofibromatosis by reporting a case of multiple pigmented macules, café-au-lait spots and a neurofibroma in a specific region of the body [30]. In 1982, Riccardi proposed sub classification of NF into 8 types. Segmental NF is NF5, which is defined by the limitation of café-au-lait spots, freckles and/ or cutaneous neurofibromas in a single unilateral segment of the body without crossing midline, no family history, and no systemic involvement [31]. Roth et al. have further subdivided segmental NF into 4 categories: True segmental (NF5), localized with deep involvement, hereditary and bilateral segmental [32]. Weiss et al. [33] modified the classification of NF1, after considering the variant forms in which the features are incomplete or atypical. The categories are Classic NF1, Whole gene deletion phenotype NF1 and alternate forms of NF1 (with incomplete or atypical features). Segmental NF1 is included in the third category as it is a localized form of the disease.

Gutmann et al. proposed the term mosaic NF1 in 1997 [34].

Mosaic NF1 is further classified into mosaic generalized, mosaic localized and gonadal NF1 by Ruggieri and Huson, in 2001 [8]. Gonadal is the rarest type and is suspected when two or more of otherwise unaffected parents develop the disease.

In a systematic review of MNF1 cases by Garcia-Romero et al. [35], majority of individual patients had neurofibromas only. This most common presentation occurs in a dermatomal distribution. Ruggieri et al. classified 124 patients with MNF1 into four categories: pigmentary changes only, neurofibromas only, pigmentary changes and neurofibromas, and isolated plexiform neurofibromas only. In this study, majority of cases (86 patients) were included in the pigmentary change only category, 20 patients in neurofibroma only, 10 in the pigmentary change and neurofibroma category and 8 in the isolated plexiform neurofibroma only category [8].

Even though 50% of MPNST occurs in the setting of NF1, its association with MNF1 is extremely rare. Various hypothesis for this rare incidence include: i) cells with genetic mutation in MNF1 are limited to the affected region and the number of cells that can mutate to MPNST is higher in NF1 compared to MNF1, ii) MNF1 is often underdiagnosed [11]. iii) Hiroki et al. hypothesized that proportion of MNF1 patients who present with neurofibroma is low, as majority of MPNST occurs by malignant transformation of neurofibroma in NF1 [5].

Neurofibromatosis and associated malignancies

Increased risk of certain malignancies in association with NF1 is well documented. As compared to general population, NF1 patients are at 2-3 times increased risk of developing carcinoma esophagus, stomach, colon and lung; 3-7 times increased risk for cancer of liver, thyroid, ovary, breast, malignant melanoma, non-Hodgkin's lymphoma and chronic myeloid leukemia; 15 times more risk for small intestine tumors and 20 times more risk for bone malignancies [36]. Genetic aberrations in NF1 are far wider in extent and severity, that attribute a higher malignant potential for NF1 patients.

Dang et al. [37] reviewed published reports of patients with segmental neurofibromatosis who developed malignancy in the disease course. The incidence of malignancy in these patients is approximated to be 5.3%. Ten such cases were identified. The most common malignancies in such patients are MPNST comprising 3 cases and malignant melanoma comprising 2 cases. Both these malignancies are derived from neural crest cells. The other reported tumors include breast cancer, colon cancer, gastric cancer, lung cancer and Hodgkin lymphoma, single case each. They concluded that the incidence of malignancy in patients with segmental neurofibromatosis may approach that of patients with NF1.

The prognosis of patients with mosaic localized NF1 is better than that of NF1 patients. Individuals with mosaic form are less likely to have severe disease. The risk of having a child with NF1 is roughly 5% for a parent with MNF1 due to gonadal

mosaicism [8]. Thus, recognition of mosaic phenotypes is clinically important. Genetic counselling should be offered to such patients.

MPNST – Diagnostic challenges and prognosis

MPNSTs are well known for its diagnostic challenges both morphologically as well as by advanced techniques. They usually present as high-grade malignant spindle cell neoplasms and typically develop in association with larger nerves and plexiform neurofibromas (PNF). About 5% of plexiform neurofibromas undergo malignant degeneration. A small subset of MPNST considered as low grade may represent areas of malignant change in PNF in NF1 [38]. A recently published consensus [39] proposed the designation of atypical neurofibromatous neoplasms of uncertain biological potential (ANNUBP). This group includes tumors with some worrisome histologic features, but does not clearly confirm a diagnosis of malignancy. Criteria for the designation of ANNUBP include neurofibromas with at least 2 of the following 4 features: histologic atypia, loss of the typical neurofibroma architecture, hypercellularity, and increased mitotic activity ($>1/50$ but less than 3 mitotic figures per 10 high power field or <1.5 mitosis/mm²). Such cases need additional evaluation and close clinical follow up.

The diagnosis of low grade MPNST is usually made in the context of NF1-associated neurofibromas with areas of ANNUBP transitioning to low grade MPNST. The proposed criteria include the presence of changes typical of ANNUBP but, in addition, greater increase in mitotic activity (1.5-4.5 mitosis/mm²) or 3 to 9 mitotic figures per 10 HPFs and no necrosis [40]. High-grade MPNST are characterized by increased mitotic activity and frequent necrosis.

Histopathology of MPNST displays an array of patterns including “fibrosarcoma like” herringbone pattern of tumor cells, “hemangiopericytoma-like” vascular pattern, focal palisading pattern [41], whirling and fascicular growth pattern of tumor cells. The morphologic differentials range from benign neurogenic tumors, nodular fascitis, intermediate tumors like hemangiopericytoma, low grade sarcoma like fibromyxoid sarcoma to high grade sarcomas like fibrosarcoma, leiomyosarcoma, angiosarcoma, synovial sarcoma, melanoma and epithelioid sarcoma especially in epithelioid variants [42]. Epithelioid or other heterogeneous components can be observed in 15% of MPNST [43-45]. They include rhabdomyoblasts [23,45,46], cartilaginous [45,47], osseous [45,47] and very occasionally glandular [45,48-51], smooth muscle [52] and liposarcomatous components [53].

Immunohistochemical features

Traditionally S100 is regarded as the best marker for MPNST, but has limited diagnostic utility and shows positivity only in 50-90% of tumors [46]. Only scattered or focal positivity is seen in high grade tumors. Recent studies suggest Nestin, an intermediate filament protein more sensitive for MPNST

[54]. Overlapping staining patterns of S100 and cytokeratin in synovial sarcoma and MPNST pose diagnostic difficulties. So, combination markers like EMA/CK7 for synovial sarcoma and nestin/S100 for MPNST yielded high specificity and positive predictive values [55]. Recently expression of HMGA2 marker is considered a feature of MPNST [56]. In addition, molecular tests to demonstrate SYT-SSX fusion transcript can be useful in diagnosis of synovial sarcoma [57].

Lucas et al. identified a subset of MPNSTs with a distinct immunophenotypic profile, that have improved local control with adjuvant radiotherapy in their single institution cohort study [58]. They identified 2 subgroups of tumors on hierarchical clustering based on large IHC panel. Cluster 1 was characterized by retention of H3K27me3 and Neurofibromin staining, relative increased S100, SOX10, and p16 immunoreactivity, and relatively limited EGFR staining. In contrast, Cluster 2 was characterized by decreased Neurofibromin (7% vs 80%), H3K27me3 (17% vs 92%), SOX10 (3% vs 28%), S100 (13% vs 55%), and p16 staining (3% vs 34%), as well as increased EGFR staining (56% vs 21%) and higher Ki-67 labelling (64% vs 42%). Consistent with IHC results, clinical NF1 status was the only clinical characteristic that differed between subgroups, with Cluster 2 enriched for NF1 patients. In the study, the 5-year overall survival (OS) was 58%, 5-year metastasis-free survival (MFS) was 68%, and 5-year loco regional failure free rate (LFFR) was 66%. Patients who received adjuvant radiotherapy demonstrated no significant benefit with regard to OS or MFS, but adjuvant radiotherapy improved LFFR. Patients who received adjuvant chemotherapy demonstrated no significant benefit to OS, MFS or LFFR. There were no significant differences between NF1-associated and sporadic MPNSTs for OS, MFS or LFFR. They demonstrated a trend towards improved LFFR with adjuvant radiotherapy among cluster 2 patients alone. Their data suggests that IHC profiles have prognostic and predictive role in treatment outcome.

The treatment options for MPNSTs are limited and remain controversial due to their rarity. Surgical resection with negative margin remains the mainstay [59,60]. Ill-defined margins in MPNST are a barrier to successful surgical resection [61,62]. Ionizing radiation and chemotherapy are primarily reserved for high risk features—such as large tumor size, deep location, or subtotal resection—unresectable disease, or salvage treatment [63-65]. There are currently no effective treatment options for patients with recurrent or metastatic disease or inoperable tumors.

In general, the clinical course of MPNSTs is marked by high metastatic risk and poor overall prognosis [41,59,60]. The 5-year overall survival rate for patients with MPNST was approximately 34-64% in many studies [41,66]. The median survival period is 32 months [67], with deaths occurring in 63%, usually within 2-year of diagnosis. The established range for recurrences is 40-65% and for distant metastasis is 40-68% [68,69].

Molecular events

The defining genetic event for all neurofibroma subtypes is inactivation of the NF1 gene (chromosome locus 17q11.2), encoding neurofibromin, a GTPase-activating protein that is expressed in many cell types in the central and peripheral nervous system. It regulates RAS signaling by mediating the conversion of Guanosine triphosphate (GTP)-bound RAS (active) to its Guanosine diphosphate (GDP)-bound state (inactive). NF1 gene inactivation is the sole recurring abnormality in neurofibromas. Additional alterations are acquired as part of atypical and malignant progression. Deletion of p16INK4A is the most common cooperating mutation with NF1 loss, occurring in about 75% of cases [70-72]. In 40% of MPNSTs, TP53 mutations are also common occurrence [72].

Even though the loss-of-function mutations in TP53 and CDKN2A contribute to MPNST tumorigenesis, their presence in atypical neurofibroma and low-grade MPNST means that defects in these genes cannot differentiate between non-malignant and malignant tumors.

Recent studies have identified recurrent mutations in polycomb repressive complex 2 (PRC2) core components, embryonic ectoderm development protein (EED) and suppressor of zeste 12 homolog (SUZ12), in MPNST. These mutations result in global loss of the histone H3 lysine 27 trimethylation epigenetic mark, normally deposited by PRC2, and subsequent gain in acetylation at this residue. This altered chromatin state is associated with progression from PNF to MPNST. The SUZ12 and EED mutations are mutually exclusive and occur in 55% and 40% of MPNSTs respectively. The frequencies of these mutations were established in a meta-analysis of next-generation sequencing studies of MPNST [72-76]. The frequency of PRC2 mutations in MPNST has shown H3K27me3 as a potentially useful biomarker in the diagnosis of MPNST and to distinguish it from Atypical and PNF [73]. The loss of H3K27me3 is considered a predictor of poor outcome as PRC2 is frequently inactivated in MPNST.

Future Prospects

Currently available data indicate that premalignant NF-1 associated neoplasms likely respond better to pharmacologic intervention than MPNSTs, and they are more amenable to surgical cure. Drugs to treat PNF and delay or even prevent progression to MPNST, may prove to be beneficial for individuals with NF-1. The activity of MEK inhibitor selumetinib has showed promise in this context [77].

Despite advances in the understanding of MPNSTs, progress in treatment is still hindered by lack of comprehensive genetic data on MPNST cell lines. The identification of germline and somatic mosaicism has a profound impact on diagnosis and treatment of disease. It provides insights into the biological

basis of disease. New technologies for genomic identification of mosaicism includes high depth and long read sequencing; computational and cell-free DNA methods for identifying variants. Even in our unique case of multiple recurrent low grade MPNST in the setting of MNF1, advanced genetic testing would have unraveled hidden molecular pathogenesis in sequential pattern, but is still unresolved due to financial constraints. It is high time that a promising pharmacological treatment regimen is initiated for the treatment of this malady in future. It is hoped that the researchers in Pharmacology would be instigated to find a new solution.

Limitations

This study was based on a narrative review. Since this is an unsystematic and opportunistic search for information, it has two basic weaknesses. First, there is no rule on how to obtain primary data and how to integrate the results; that is the subjective criterion of the reviewer. Second, the narrative reviewer does not quantitatively synthesize the data found in the different publications; therefore, these reviews are highly susceptible to inaccuracies and biases.

Conclusion

MPNST usually poses a diagnostic challenge by its multifaceted morphology and absence of defining IHC pattern/ specific genetic abnormalities. In the context of mosaic localized NF1 also, MPNST shows these variations during multiple recurrences. They tend to be of variable histologic grades. The prognosis is better in these patients compared to NF1 with long survival period and absence of distant metastasis. Genetic tests like Next generation sequencing are required for better understanding of sequential molecular abnormalities incurred in the disease course of this rare entity. This will pave the way for future targeted therapy and improves disease free interval.

Highlights

- Malignant transformations of plexiform neurofibroma in the setting of mosaic localized NF1 warrants regular follow up.
- The prognosis of patients with MPNST associated with mosaic localized NF1 is better compared to conventional type with long survival rate and absence of metastasis.
- Identification of sequential genetic events that contribute to cell transformation to MPNST, its further progression and metastasis are crucial for the development of predictive biomarkers and effective preventive and treatment strategies.

Conflict of Interest

The authors have no conflict of interest to declare.

Role of Authors

Author 1 collected references and reviewed all the papers and discussed the paper in relation to the paper published earlier as a case report - Malignant peripheral nerve sheath tumour – A long story: Case report by Marickar and Abraham [6].

Author 2 gave the ideas and supervision for preparing the paper and finalized the paper with editing.

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