www.wcprj.com 2025 Page: 01-05

Review Article

World Current Pharmaceutical Research Journal

ISSN (O): Applied

Volume: 01
Issue: 01

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR: NARRATIVE REVIEW

Dr. Pradakhshana Vijay[1], Dr. Priyanka Singh[2*], Dr. Mohd. Parvez Khan[3], Dr. Nilesh Pardhe[4]

[1]Assistant Professor, Dept. of Oral Pathology, Indira Gandhi Govt. Dental College, Jammu

[2]Additional Professor, Dept. of Oral Pathology, FODS, KGMU, LKO.

[3]Professor, Dept. of Anesthesia and critical care, KGMU, LKO.

[4]Dean, Swargiya Dadasaheb Kalmegh Smruti Dental College & Hospital, Nagpur.

Article Received: 21 Feburary 2025

Article Revised: 11 March 2025

Published on: 01 April 2025

***Corresponding Author: Dr. Priyanka Singh**

Additional Professor, Dept. of Oral Pathology, FODS, KGMU, LKO.

Email ID: priyanka.0100@gmail.com,

ABSTRACT

Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are rare, aggressive soft tissue sarcomas that originate from peripheral nerves or demonstrate nerve sheath differentiation. They account for approximately 5–10% of all soft tissue sarcomas and are associated with poor prognosis due to high recurrence rates and limited therapeutic options. This review provides a comprehensive narrative on the current understanding of MPNSTs, covering aspects such as epidemiology, pathogenesis, molecular biology, diagnostic approaches, treatment strategies, and recent advances in research.

KEYWORDS: sarcoma, peripheral nerves, molecular, recurrence, prognosis, pathogenesis.

INTRODUCTION

MPNSTs represent a biologically aggressive subset of soft tissue sarcomas that arise either de novo or in association with neurofibromatosis type 1 (NF1). Their diagnosis and management are particularly challenging due to their rarity, overlapping features with benign nerve sheath tumors, and limited response to conventional therapies. Advances in genomics and molecular pathology have begun to illuminate the underlying biology of MPNSTs, offering hope for targeted therapeutic strategies.

Copyright@ Dr. Priyanka Singh |

Epidemiology

MPNSTs are rare, with an incidence of approximately 0.001% in the general population. However, they occur more frequently in individuals with **NF1**, a genetic disorder affecting 1 in 3,000 individuals, where lifetime risk of developing MPNST may be as high as 10%. Most cases present between the ages of 20 and 50, with no strong gender predilection. NF1-associated MPNSTs often arise from malignant transformation of pre-existing plexiform neurofibromas.

Pathology and Histogenesis

MPNSTs are spindle cell sarcomas that typically arise from peripheral nerves or exhibit Schwannian differentiation. Histologically, they show dense cellularity, nuclear atypia, high mitotic activity, and areas of necrosis. Immunohistochemically, S100 protein expression is variable and often focal, distinguishing them from benign schwannomas. Other markers like SOX10, CD34, and H3K27me3 loss are also used diagnostically.

The tumors can arise sporadically, post-radiation, or in the context of NF1. Histologic variants include epithelioid MPNSTs and those with rhabdomyoblastic differentiation (malignant Triton tumor), both of which tend to have worse outcomes.

Molecular and Genetic Features

MPNSTs are genetically complex tumors. In NF1-associated cases, biallelic loss of **NF1** is a primary event. Subsequent mutations in **TP53, CDKN2A, SUZ12**, and **EED**—components of the polycomb repressive complex 2 (PRC2)—lead to global epigenetic dysregulation, notably **loss of H3K27me3** expression, which is a useful diagnostic marker.

Recent genomic studies have identified common alterations including:

- Chromosomal instability
- Overexpression of EGFR
- Loss of tumor suppressor genes (e.g., PTEN)
- Aberrations in RAS-MAPK and PI3K-AKT pathways

These discoveries have opened potential avenues for targeted therapy.

Clinical Presentation

MPNSTs typically present as rapidly enlarging, painful soft tissue masses, often deep-seated and located along major nerve trunks (e.g., brachial plexus, sciatic nerve). In NF1 patients,

any rapid growth or pain in a pre-existing neurofibroma warrants suspicion. Symptoms vary based on tumor location and may include motor or sensory deficits.

Diagnostic Approaches

Diagnosis is based on a combination of **clinical assessment, imaging, histopathology, and molecular studies**. MRI is the imaging modality of choice, often revealing a heterogeneous mass with necrotic areas. PET-CT can help in staging and assessing treatment response.

Histopathological diagnosis can be challenging due to overlap with other spindle cell tumors. Immunohistochemistry and molecular profiling, including assessment for H3K27me3 loss and NF1 mutations, aid in accurate diagnosis.

Treatment

Surgery

Complete surgical resection with negative margins is the cornerstone of treatment and offers the best chance for cure. However, due to tumor location, achieving clear margins is often difficult.

Radiation Therapy

Adjuvant radiation improves local control, especially in high-grade or incompletely resected tumors. Preoperative radiation is sometimes used to shrink the tumor before surgery.

Chemotherapy

MPNSTs are relatively resistant to chemotherapy. Regimens including doxorubicin and ifosfamide are used, particularly in metastatic or unresectable cases, but responses are modest.

Targeted and Emerging Therapies

Research into molecular pathways has led to trials investigating MEK inhibitors (e.g., selumetinib), mTOR inhibitors, and PRC2-targeting agents. While early results are promising, no targeted therapies have yet demonstrated significant survival benefit in randomized trials.

Prognosis

MPNSTs carry a poor prognosis with 5-year survival rates ranging from **30% to 50%**, depending on factors such as tumor size, location, resectability, and association with NF1.

NF1-associated MPNSTs tend to have worse outcomes. Local recurrence and distant metastases (most commonly to the lungs) are common, underscoring the need for improved systemic therapies.

Future Directions

Emerging genomic insights are shaping the future of MPNST management. Biomarkers for early detection, especially in NF1 patients, are a key research focus. Precision medicine approaches, including genomic profiling and immunotherapy trials, may eventually transform the treatment landscape. However, large multicenter studies are needed to validate these approaches and develop standardized treatment protocols.

CONCLUSION

MPNSTs are aggressive sarcomas with significant diagnostic and therapeutic challenges. Advances in molecular biology have improved our understanding of their pathogenesis, particularly in the context of NF1. While surgery remains the mainstay of treatment, novel targeted therapies and immunotherapies hold promise for improving outcomes in this difficult disease. Continued research is critical to develop more effective and individualized treatment strategies.

REFERENCES

1. Stucky CCH, Johnson KN, Gray RJ, Pockaj BA, Ocal IT, Rose PS, et al. Malignant peripheral nerve sheath tumors (MPNST): The Mayo Clinic experience. *Ann Surg Oncol.*, 2012; 19(3): 878–885. doi:10.1245/s10434-011-1978-7
2. Farid M, Demicco EG, Garcia R, Ahn L, Merola PR, Cioffi A, et al. Malignant peripheral nerve sheath tumors. *Oncologist.*, 2014; 19(2): 193–201. doi:10.1634/theoncologist.2013-0328
3. Pemov A, Li H, Patidar R, Hansen NF, Sindiri S, Hartley SW, et al. The primacy of NF1 loss as the driver of tumorigenesis in neurofibromatosis type 1–associated plexiform neurofibromas. *Oncotarget.*, 2017; 8(5): 8229–8240. doi:10.18632/oncotarget.14011
4. Pekmezci M, Cuevas-Ocampo AK, Perry A. Neurofibromatosis type 1 (NF1)-related tumors: classification, pathologic features, and molecular genetics. *J Neuropathol Exp Neurol.*, 2021; 80(9): 789–803. doi:10.1093/jnen/nlab062
5. Reuss DE, Habel A, Hagenlocher C, Mucha J, Capper D, von Deimling A. ATRX and H3K27me3 loss and coexistence with TP53 alterations in MPNSTs. *Acta Neuropathol.*, 2015; 129(6): 867–878. doi:10.1007/s00401-015-1439-3

6. Watson KL, Al Sannaa GA, Kivlin CM, Ingram DR, Landers SM, Patel RM, et al. Patterns of recurrence and survival in sporadic, neurofibromatosis type 1–associated, and radiation-induced malignant peripheral nerve sheath tumors. *J Neurosurg.*, 2017; 126(2): 319–329. doi:10.3171/2016.1.
7. Dodd RD, Mito JK, Kirsch DG. Animal models of NF1-associated malignant peripheral nerve sheath tumors. *Biochim Biophys Acta Rev Cancer,* 2012; 1826(1): 207–217. doi:10.1016/j.bbcan.2012.04.004
8. Widemann BC, Babovic-Vuksanovic D, Dombi E, Fisher MJ, Korf B, Martin S, et al. Targeted therapy for MPNSTs: Clinical trial strategies in NF1 patients. *Cancer Treat Rev.*, 2021; 98: 102211. doi:10.1016/j.ctrv.2021.102211