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(CASE REPORT)

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Malignant transformation of plexiform neurofibroma to high-grade malignant peripheral nerve sheath tumor in neurofibromatosis Type 1: Case report and brief literature review

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Abstract

Malignant peripheral nerve sheath tumors (MPNSTs) represent a life-threatening complication of neurofibromatosis type 1 (NF1), often arising from the malignant transformation of pre-existing plexiform neurofibromas. We present the case of a 32-year-old male with NF1 who developed a rapidly enlarging, painful thigh mass at the site of a previously debulked plexiform neurofibroma. Imaging and core needle biopsy confirmed a high-grade MPNST. Molecular and immunohistochemical (IHC) profiling revealed biallelic NF1 inactivation, CDKN2A homozygous deletion, TP53 mutation, and the characteristic loss of H3K27 trimethylation (H3K27me3). The patient was treated with neoadjuvant chemoradiation followed by wide local excision with en bloc sciatic nerve sacrifice, achieving R0 margins and greater than 90% tumor necrosis. Three years post-resection, he developed a local recurrence and oligometastatic pulmonary disease. Rather than pursuing palliative care, a curative-intent salvage strategy was adopted, comprising systemic chemotherapy followed by surgical re-excision and video-assisted thoracoscopic surgery (VATS) metastasectomy. The patient remains disease-free for two years following the salvage treatment. This case underscores the aggressive clinical course of NF1-associated MPNSTs and highlights the critical role of sustained multidisciplinary management. Furthermore, it demonstrates that aggressive surgical salvage for oligometastatic recurrence can yield prolonged survival, challenging the historically dismal prognosis associated with metastatic MPNST.

Keywords: Malignant Peripheral Nerve Sheath Tumors; Immunohistochemical; CDKN2A Deletion; Schwannian Lineage; NF1 Mutations

1. Introduction

NF1 is an autosomal dominant neurocutaneous disorder affecting approximately 1 in 3,000 individuals worldwide, caused by mutations in the NF1 tumor suppressor gene on chromosome 17q11.2. [1,2] Loss of neurofibromin function leads to dysregulated cell proliferation and the development of multiple peripheral nerve sheath tumors, including localized and plexiform neurofibromas. [3] Plexiform neurofibromas are a hallmark feature of NF1 and carry clinical significance due to their potential for progressive growth, disfigurement, and malignant transformation. [4]

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Although most neurofibromas remain benign and are managed with surveillance, approximately 8–13% may transform into MPNSTs, an aggressive form of soft tissue sarcoma associated with poor prognosis. [5] The risk is significantly higher in patients with internal plexiform neurofibromas, with studies suggesting up to a 20-fold increased likelihood of malignant transformation. [6] MPNSTs most commonly arise during adolescence and early adulthood and may present rapid tumor growth, new-onset pain, increasing firmness of a previously soft lesion, or associated neurological deficits. [2]

Distinguishing benign plexiform neurofibromas from early malignant transformation remains a major clinical challenge due to overlapping imaging characteristics and sampling limitations related to tumor heterogeneity. Consequently, diagnosis is often delayed, adversely affecting outcomes. [1] Management of NF1-associated MPNST requires a multidisciplinary approach, with treatment strategies guided by tumor location, disease extent, and functional considerations. Despite advances in imaging and therapeutic modalities, these tumors frequently exhibit resistance to systemic therapies, particularly in recurrent or metastatic settings. [1,4]

We report a case of malignant transformation of a previously stable plexiform neurofibroma into a high-grade MPNST, highlighting the diagnostic complexity and the importance of vigilant surveillance and early multidisciplinary intervention in patients with NF1.

2. Case Presentation

2.1. Clinical Presentation & Initial Assessment

A 32-year-old male with a childhood diagnosis of Neurofibromatosis type 1 presented with a several-month history of a rapidly enlarging, painful mass in the right thigh and new paresthesia radiating down the medial leg. Two years earlier, he had undergone debulking of a plexiform neurofibroma at the same site; complete resection had not been achievable given sciatic nerve involvement. He had been stable on surveillance until this presentation.

His NF1 diagnosis rested on the classic criteria of multiple café-au-lait macules, axillary freckling, and tibial bowing. Family history was significant for NF1 in his mother and the death of a maternal uncle from a retroperitoneal nerve tumor, raising concern for familial MPNST predisposition. Examination revealed a firm, poorly circumscribed, tender 7 × 5 cm posterior right thigh mass with a positive Tinel sign, mild knee flexor weakness, and diminished medial thigh sensation. No lymphadenopathy was found.

Initial laboratory work showed mild normocytic anemia and a modestly elevated LDH of 310 U/L. The clinical impression was strongly suspicious for malignant transformation of the prior plexiform neurofibroma, and urgent multidisciplinary evaluation was initiated.

2.2. Imaging, Additional Testing & Differential Diagnosis

Gadolinium-enhanced MRI of the right thigh demonstrated a heterogeneous 8.2 × 5.6 × 4.9 cm mass with irregular peripheral enhancement, central necrosis, ill-defined margins, and sciatic nerve encasement, a marked departure from the prior lesion's benign plexiform morphology. FDG-PET/CT revealed a SUVmax of 11.4 at the thigh mass with no regional nodal or distant metastatic disease. Chest CT was clear. Electrodiagnostic studies confirmed partial sciatic neuropathy with axonal features at mid-thigh.

The differential diagnosis was led by a high-grade malignant peripheral nerve sheath tumor (MPNST) arising within the prior plexiform neurofibroma. Alternative considerations included benign recurrence or growth of residual plexiform neurofibroma, atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP), synovial sarcoma, undifferentiated pleomorphic sarcoma, and cellular schwannoma. The imaging profile and clinical context strongly suggested MPNST, and tissue confirmation was pursued.

2.3. Multidisciplinary Tumor Board: Biopsy, Excision & Recommendations

At the multidisciplinary sarcoma tumor board, the primary discussion centered on the approach to biopsy, the extent of resection, and the role of neoadjuvant therapy. CT-guided core needle biopsy was recommended to use a single-compartment trajectory to preserve future surgical planes, with attention to sampling viable, non-necrotic tissue. An open incisional biopsy, if needed, was to be performed only by a surgeon.

Wide local excision with negative margins (R0) was identified as the oncologic goal. Given the sciatic nerve encasement, the board debated the feasibility of nerve-sparing versus en bloc nerve sacrifice; the final determination was deferred

pending biopsy and histologic assessment of perineural invasion. Neoadjuvant ifosfamide-based chemotherapy and pre-operative external beam radiation were discussed as strategies to improve resectability and reduce local recurrence risk. Genetic counseling, germline NF1 sequencing, and enrollment in a sarcoma clinical trial were also recommended.

2.4. Pathology, IHC, Molecular Studies, Management & Follow-Up

Core biopsy revealed a highly cellular spindle cell neoplasm with fascicular architecture, marked pleomorphism, more than 10 mitoses per 10 HPF, and geographic necrosis. (Figure 1 A, B, C) IHC studies demonstrated loss of H3K27 trimethylation, a hallmark of high-grade MPNST, focal S-100 and SOX10 positivity, and negativity for SMA, desmin, STAT6, TLE1, and CD34, excluding the principal sarcoma mimics. Ki-67 approached 45%. Next-generation sequencing (NGS) identified a pathogenic NF1 frameshift mutation, CDKN2A homozygous deletion, and TP53 mutation, consistent with biallelic NF1 inactivation. No targetable fusions were detected. The integrated final diagnosis was high-grade MPNST, Grade 3, arising in NF1.

Three cycles of neoadjuvant ifosfamide and doxorubicin with concurrent pre-operative radiotherapy (50 Gy / 25 fractions) produced moderate tumor reduction to 5.1 × 3.8 cm. Wide local excision with en bloc sacrifice of the sciatic nerve achieved R0 margins; postoperative pathology showed greater than 75% tumor necrosis, indicating a favorable response. Three adjuvant chemotherapy cycles followed. The patient underwent prosthetic fitting and neurorehabilitation and, at 24-month surveillance, remained disease-free.

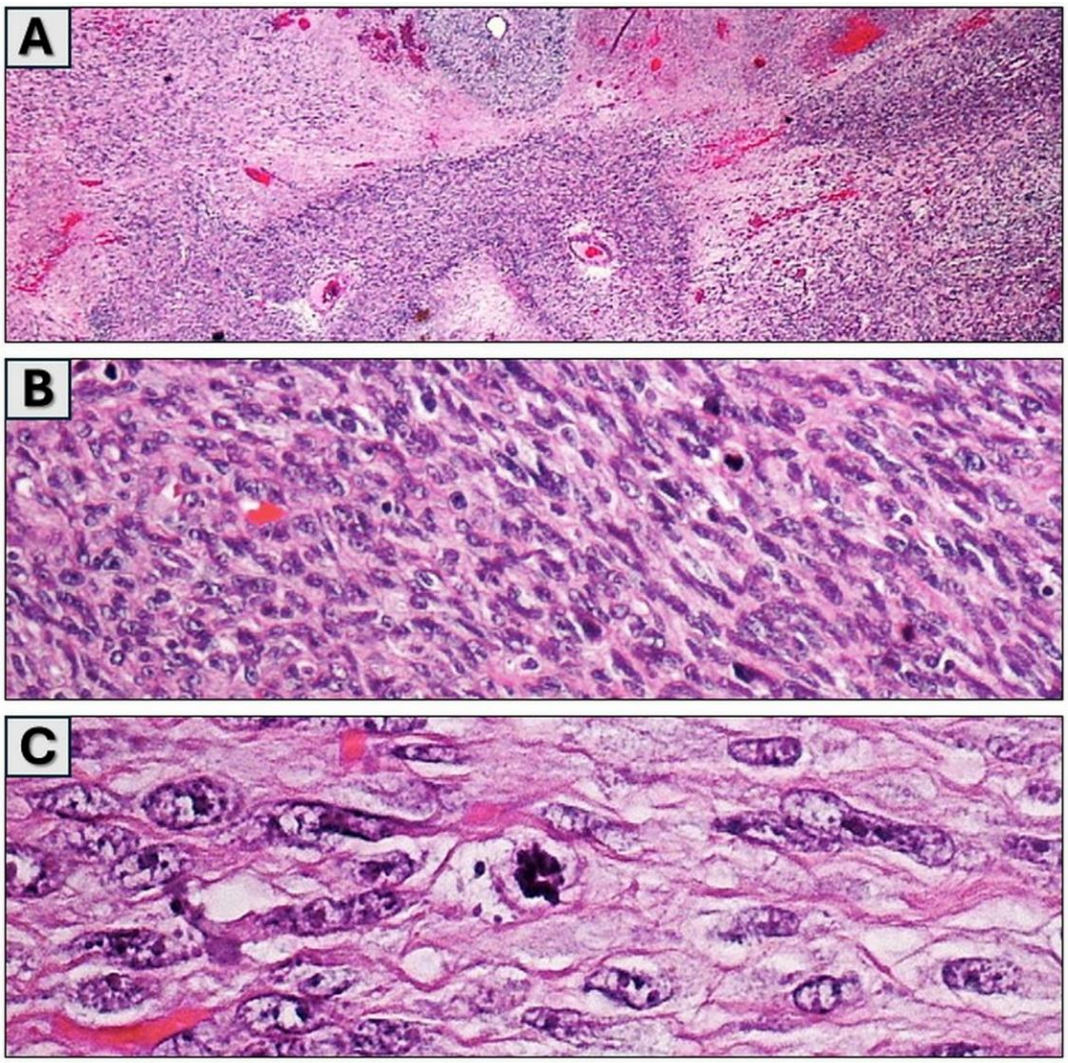
2.5. Three-Year Recurrence, Metastasis, Salvage Treatment & Outcome

Three years after definitive resection, surveillance imaging identified a 3.4 cm local recurrence adjacent to the prior surgical bed and two FDG-avid right lower lobe pulmonary nodules (1.8 cm and 1.2 cm; SUVmax 7.8 and 6.5). CT-guided biopsy of the dominant nodule confirmed metastatic MPNST with the same molecular profile as the primary tumor. No additional metastatic sites were identified.

At the second tumor board, the oligometastatic burden was deemed amenable to curative-intent combined treatment. Re-excision of the local recurrence was considered feasible despite prior radiation and scarring, with plastic surgery involvement planned for reconstruction. VATS (Video-Assisted Thoracoscopic Surgery) metastasectomy of both pulmonary nodules was preferred over SBRT (Stereotactic Body Radiation Therapy) to provide histologic confirmation and optimize local control. A staged strategy was adopted: systemic chemotherapy first to assess disease biology, followed by surgical management of both sites if stable.

The patient completed four cycles of gemcitabine and docetaxel with stable disease on restaging. He then underwent re-excision of the local recurrence with R0 margins, followed three weeks later by right lower lobe VATS wedge resection removing both pulmonary nodules with negative margins. Final pathology confirmed viable metastatic MPNST at both sites without treatment response, highlighting the chemoresistance typical of recurrent disease. Two additional cycles of adjuvant gemcitabine and docetaxel were administered.

Two years following treatment of recurrence and metastases, the patient remained alive with no evidence of disease on surveillance imaging. He was ambulatory and engaged in ongoing rehabilitation and psychosocial support. His molecular profile, particularly the CDKN2A deletion, made him a candidate for emerging CDK4/6 inhibitor and MEK inhibitor trials. His case continued to be reviewed annually at the sarcoma tumor board as part of a long-term survivorship program, underscoring the necessity of sustained multidisciplinary follow-up in NF1-associated MPNST.



1A: Low power view showing residual viable tumor and post-treatment effect with geographic necrosis (H&E X20).; **1B:** Intermediate power view showing a highly cellular spindle cell neoplasm with fascicular architecture and abundant mitosis (H&E X40).; **1C:** High power view showing marked pleomorphism and abnormal mitosis (H&E X60).

Figure 1 Microscopic features of malignant peripheral nerve sheath tumor (MPNST)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

While patients with NF1 are prone to developing various benign nerve sheath tumors, their most severe oncologic complication is the development of MPNSTs. Individuals with NF1 harbor an estimated 8% to 13% lifetime risk of developing an MPNST, a rate exponentially higher than that of the general population. [4]

The earliest reported case of MPNST dates to 1952. [19] It was described as an unclassified tumor resembling a neurofibroma in a Caucasian male. In 1984 Ducatman et al. documented 16 cases of MPNSTs in children under 16 years old, noting a mean survival time of only 1.8 years. [20]

These highly aggressive sarcomas typically arise from the malignant transformation of pre-existing benign plexiform neurofibromas or atypical neurofibromatous neoplasms of uncertain biological potential (ANNUBP). [7] The peak incidence of MPNST in the NF1 population occurs during the third to fourth decades of life, which is significantly earlier than the presentation of sporadic MPNSTs. [4]

Under the 2020 World Health Organization (WHO) classification of soft tissue tumors, MPNSTs are recognized as aggressive sarcomas of Schwannian lineage. [8] A complex sequence of genomic alterations drives the pathogenesis of NF1-associated MPNST. [7,9]

3.2. Pathogenesis, Pathophysiology

The spinal nerve roots play a vital role in the development of plexiform neurofibroma, as the disease arises from the embryonic PLP+; Nf1−/− Schwann cells or their precursors. The development of plexiform neurofibroma begins with a deletion of the NF1 gene on chromosome 17. [10] NF1 encodes the neurofibromin protein. This tumor suppressor gene works by inhibiting the Ras signaling pathway, in which it hydrolyzes Ras from its active guanosine triphosphate (GTP) to its inactive guanosine diphosphate (GDP)- bound conformation. Thus, when the neurofibromin gene is mutated, the RAS signaling protein remains activated, which, in turn, activates mitogenic pathways such as mitogen-activated protein kinase (MAPK) and Akt, leading to enhanced proliferation and survival in multiple cell types. Furthermore, most NF1 mutations occur spontaneously, leading to premature truncation of the neurofibromin protein. [7,9] [11]

Plexiform Neurofibroma grows along the length of the nerve fascicles and extends into the skin, bone, muscles, and internal organs. [12] Different phenotypic effects depend on the type of mutation and when it occurs. Pigmentation defects tend to develop when NF1 mutations occur post-meiotically. Hence, dermatological changes are often the first signs of the disease, such as hyperpigmentation, cafe au lait, and dermal thickening. [13,14] With an earlier onset, the disease can be further evaluated with histopathology, which can identify the presence of malignant transformation. In plexiform neurofibroma, histopathological analysis demonstrates overgrowth of peripheral nerve components and connective tissue. [15]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

The clinical presentation of our patient, characterized by a rapidly enlarging, painful mass and new neurologic deficits within a pre-existing plexiform neurofibroma, is a classic hallmark of malignant transformation, aligning closely with established literature. [7] The diagnostic workup successfully utilized FDG-PET/CT, where a high SUVmax (11.4) strongly correlated with high-grade malignancy, consistent with studies identifying elevated metabolic activity as a reliable indicator of MPNST. Furthermore, the molecular profile of this case, featuring an NF1 frameshift mutation, a CDKN2A homozygous deletion, and a TP53 mutation perfectly mirrors the known genomic landscape that drives the aggressive biology of NF1-associated MPNSTs. [9] The observed loss of H3K27me3 expression further corroborates the recent literature, which establishes it as a highly sensitive and specific diagnostic marker for MPNST. [8]

However, the clinical trajectory and management outcomes of this case present notable deviations from typical literature reports. The 5-year survival rate for NF1-associated MPNST remains notoriously poor, often cited between 16% and 32%, largely due to primary chemoresistance and a high propensity for metastasis. [17] In contrast, our patient initially demonstrated a remarkable response to neoadjuvant ifosfamide and doxorubicin with concurrent radiotherapy, achieving greater than 75% tumor necrosis. This robust histologic response is relatively uncommon in this chemoresistant sarcoma.

Moreover, the management of his recurrence diverges from standard palliative paradigms. When the patient presented with local recurrence and pulmonary oligometastases three years post-resection, a staged, curative-intent surgical strategy (re-excision and VATS metastasectomy) was successfully employed. Long-term survival following the resection of pulmonary metastases in NF1-MPNST is exceedingly rare in literature. [18] This aggressive salvage approach resulted in a sustained disease-free status two years post-recurrence, highlighting a potential paradigm shift and demonstrating that highly selected patients with oligometastatic disease can achieve durable remission through aggressive, multidisciplinary surgical intervention.

4. What Have We Learned from This Case?

This case illustrates several key clinical considerations in the management of NF1 associated plexiform neurofibromas and the associated risk of malignant transformation. Clinicians should maintain a heightened index of suspicion for MPNST in patients who were previously stable but develop rapid tumor enlargement, new onset of pain, and neurological deficits.

Early evaluation with contrast-enhanced MRI and FDG-PET/CT is essential for distinguishing malignant transformation from benign disease, particularly by identifying heterogeneous morphology and increased metabolic activity. This case highlights the value of multidisciplinary management, involving coordinated input from oncology, radiology, pathology,

and surgical teams to guide treatment planning. Recurrence and metastasis frequently occur in NF1-associated MPNST, even with aggressive multimodal therapy such as neoadjuvant chemotherapy, radiation, and surgical excision. Therefore, long-term surveillance is critical. Finally, molecular profiling may also provide prognostic insights and identify candidates for targeted therapies or for enrollment in clinical trials in recurrent or advanced diseases.

Abbreviations

- Malignant peripheral nerve sheath tumors (MPNSTs);
- Immunohistochemical (IHC);
- Video-assisted thoracoscopic surgery (VATS);
- Atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP).

5. Conclusion

We presented a challenging case of a 32-year-old male with NF1 who developed a high-grade MPNST from a pre-existing plexiform neurofibroma, successfully managed through aggressive multidisciplinary interventions for both primary and oligometastatic recurrent disease. We report this case to illustrate the critical importance of vigilant clinical surveillance for malignant transformation in NF1 patients and to demonstrate the clinical utility of integrating molecular profiling, such as CDKN2A and TP53 status, into diagnostic and therapeutic algorithms. Most importantly, this case adds significant value to the medical community by providing rare, compelling evidence that an aggressive, curative-intent surgical salvage strategy for oligometastatic recurrence can yield prolonged disease-free survival. By highlighting the feasibility of metastasectomy and the potential of targeted therapies in the survivorship phase, this report encourages a proactive, multidisciplinary approach. It challenges the traditional paradigm of therapeutic nihilism in recurrent NF1-associated MPNSTs.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis. No patient contact or intervention was involved, and informed consent was not required in accordance with institutional policies.

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