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Ankle Malignant Peripheral Nerve Sheath Tumor in A Neurofibromatosis I Patient: A Case Report and Review the Literature

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Malignant Peripheral Nerve Sheath Tumors (MPNST); Neuro Fibromatosis Type 1 (NF1); Peripheral Nerve; Ankle; Plexiform Neurofibroma (NF); Trimethylation at Lysine 27 of Histone-H3 (H3k27me3)

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1. Abstract

1.1. Introduction: Malignant Peripheral Nerve Sheath Tumors (MPNST) are rare and aggressive sarcomata's tumors with an overall incidence of 0.001% [1] derived from Schwann cells or pluripotent cells of the neural crest [2-8]. MPNSTs are typically seen in patients aged 20-50 years, and usually in the setting of Neuro Fibromatosis Type 1(NF1) and following radiation therapy [8]. The most common sites are the trunk and extremities followed by the head and neck area [7, 8].

1.2. Presentation of The Case: This case reports a 50-year-old man with a previous diagnosis five years ago of a Plexiform Neuro Fibroma (NF) in the posterior distal third of the right leg and ankle. In this case, we review the most important pathological findings and review the literature by reason of the rarity of this lesion. Actually, the patient is currently on regular follow-up and ongoing disease extension study in another hospital for surgical or oncologic treatment decision.

1.3. Discussion: The majority of MPNSTs are derived from neuro fibroma or they arise de novo in normal peripheral nerves [9, 2]. It is important to focus on the correct diagnosis and especially in the differential diagnosis with other tumors that can mimic MPNST, which include desmoplastic and metastatic melanomas, as well as synovial sarcoma and fibrosarcomatous dermatofibrosarcoma protuberans [10, 11]. In this article, we discuss a case of a patient with a previous diagnosis of plexiform neuro fibroma that some years later presents as an enlarging painful mass that extends to the ankle, a rare location for these tumors as described on the pathological findings and review in the literature.

1.4. Conclusion: MPNSTs are very rare sheath tumors that must be suspected in patients with NF1, especially with a previous diagnosis or another benign lesion, because this is very aggressive and rapidly growing disease.

2. Case Presentation

A 50-year-old man with a previous diagnosis of NF1 and a pathological diagnosis of plexiform Neuro Fibroma (NF) in the right ankle in 2016. He had no co-morbid illness, no relevant surgical history, only the previous partial resection in the ankle, and no family history of neurofibromatosis. He had followed up with the dermatologist until he presented a hot lump for a month in the same area of the previous resection with minimal response to antibiotic treatment. The radiological study showed a 18x13x12 cm mass in the posterior distal third of the right leg and ankle without identifying areas of necrosis. Biopsy was taken for study of this new lesion.

Histologic features showed a tumor composed of monotonous spindle cells arranged in intersecting fascicles. At low power, alternating hyper- and hypo cellular areas were focally present with enlarged nuclei and variable degrees of nuclear pleomorphism (Figure 1A, B, C). There were no elements of pre-existent neuro fibroma, zonal necrosis, or glomeruloid vascular proliferation but there was a high proliferation activity with more than 10 mitosis/10HPF (Figure 1D). Heterologous rhabdomyosarcoma-like or

osseocartilaginous differentiation was not present in this case.

Immunohistochemically, the tumor was negative for S100 and SOX10 (Figure 2A and 2B). The tumor cells showed loss of p16 expression and CD34 (Figure 2C). Proliferation index (ki67) was very high estimated at 80% (Figure 2D). The diagnosis of high-grade MPNST was made and the patient was remitted to the reference hospital for extension study and treatment decision.

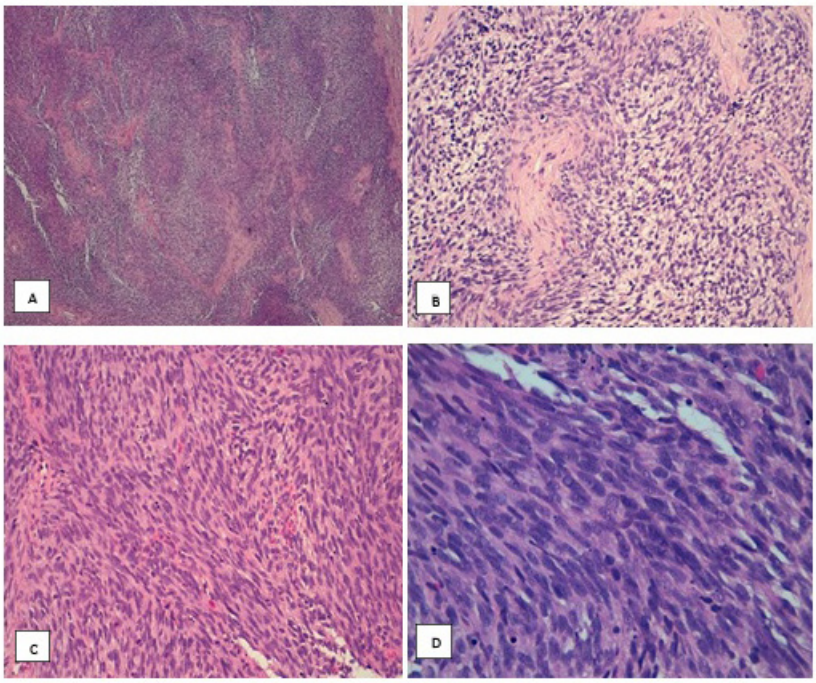

Figure 1: Histological findings of the high-grade MPNST.

A. Panoramic view of the lesion alternating hypercellular areas with hypocellular in a fascicular pattern.

B. High power of the hypocellular areas possibly corresponding to residual Schwann cells of the pre-existing neurofibroma.

C. Fibrosarcoma-like highly cellular spindled tumor with mitotic activity.

D. Nuclear pleomorphism with spindled cells with hyperchromatic nuclei and eosinophilic cytoplasm in a fascicular pattern of growth.

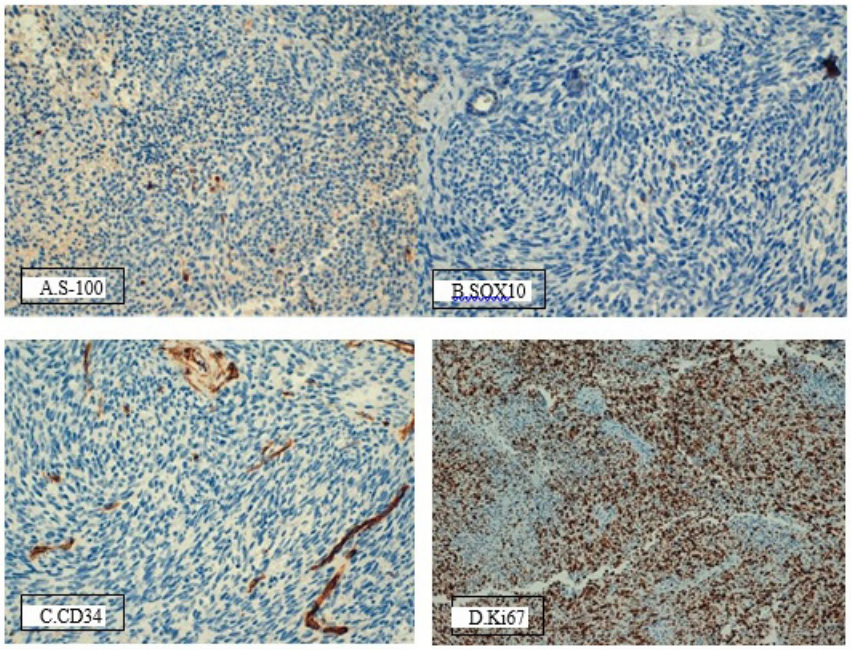

Figure 2: Immunohistochemically findings of high-grade MPNST. A and B (upper view): S100 and SOX10 were negative as well as CD34 (C) with positive internal control.

D. Tumor cells showed a high proliferation index that was view in HE preparations (Fig.1C) counting more than 10 mitosis /10HPF.

3. Introduction

Malignant Peripheral Nerve Sheath Tumor (MPNST) is derived from Schwann cells or pluripotent cells of the neural crest [4-7, 12, 13]. Epithelioid or other heterologous components can be observed in 15% of cases; the latter include rhabdomyoblasts, cartilaginous, osseous differentiation and, rarely, smooth muscle, glandular or liposarcomatous components have been reported. It is rare that there are two or more heterologous components in a single MPNST [4, 5, 14-19]. They account for between 3-5% of malignant soft tissue tumors and often arise from association with NF or in the setting of NF1 where reported incidences range from 2% to 29% [20]. NF1-associated neuro fibromas have an estimated 10%–15% risk of malignant transformation, with internal plexiform tumors at the highest risk of transformation [21]. MPNSTs occur in up to 10% of NF1 patients over their lifetimes; conversely, half of all MPNSTs are seen in NF1 patients [22, 23]. MPNST is generally characterized by alternating hypo- and hyper-cell areas or a diffuse growth pattern of spindle-shaped cells which are usually fusiform with wavy or comma-shaped hyperchromatic nuclei [4, 6, 7, 24]. In about 15% of MPNSTs, epithelioid or heterologous differentiation can be found [4]; the latter includes rhabdomyoblasts, smooth muscle, bone, cartilage, and neuroendocrine component [4-18]. The most common heterologous component in MPNST is rhabdomyoblast differentiation [4, 7, 24] known as malignant triton tumor. Additionally, differentiation into cartilage or bone is also not uncommon [14-16], while liposarcomatous differentiation is very rare [14, 15]. In most cases, the above-mentioned differentiation can be focally observed on the background of typical spindle-shaped tumor cells.

4. Histopathological and Immune histochemical Findings

Most of the MPNSTs (61%) demonstrated a coexisting neurofibromatosis component [8]. However, being our case a biopsy, only a small percentage of tumor was represented. Most sarcomas exhibit variability in cytology and histologic pattern. In these cases, low-grade tumors are characterized by mild to moderate hyper cellularity, significant nuclear atypia, and a mild increased mitotic index (3-9/10HPF) and high-grade neoplasms show pronounced hyper cellularity, variable cellular pleomorphic, and brisk mitotic activity index (10 or more/10HPF with or without necrosis). Additional features often encountered are microvascular proliferation and geographic necrosis with pseudo palisading. This characteristic pattern of necrosis results from the persistence of viable perivascular cuffs of tumor cells. These findings were not found in our case. The tumor cells are usually monotonous spindle cells arranged in intersecting fascicles. Pleomorphic variants also exist. At low power, alternating hyper- and hypo cellular areas may be present, often with hyper cellular areas localized near blood vessels. Compared with benign neuro fibromas, MPNST

usually demonstrates a marked increase in tumor cellularity, pleomorphic, and mitotic activity and shows a more organized cellular growth pattern, with a less extracellular matrix material. Occasionally, a spectrum of changes may be seen, ranging from atypical neuro fibromas to high-grade MPNST [25]. As mentioned above, heterologous elements, such as skeletal muscle, bone, cartilage, and blood vessels, are present in approximately 15% of tumors. Heterologous elements may confer an even poorer prognosis; MPNSTs demonstrating skeletal muscle differentiation (malignant Triton tumors) are particularly aggressive and associated with poor prognosis.

There is no pathognomonic molecular or immune histochemical study for MPNST. Most MPNSTs are negative for all nerve sheath stains, while others are positive for S100 protein and/or SOX10 in only a small subset of the tumor cells. It is also likely that residual Schwann cells of the pre-existing neuro fibroma contribute to the S100 protein/SOX10 positivity of MPNSTs [11]. Loss of the CD34-positive fibroblastic network encountered in neuro fibromas can be a helpful clue to the diagnosis of MPNST [26]. Loss of p16 expression related to losses in the CDKN2A genes is also a typical finding. However, because this change can predate morphologic transformation into MPNST, it cannot be used as a sole marker of malignancy. Recent studies showed the inactivation of polycomb repressive complex 2 (PRC2) in a large subset of MPNST, due to loss-of-function mutations in PRC2 subunits EED or SUZ [26, 27, 28]. These co-occur with somatic mutations of CDKN2A and NF1 and are associated with a distinct DNA methylation profile [27]. In addition to its DNA-wide effects on methylation, PRC2 inactivation specifically leads to loss of trimethylation at lysine 27 of histone-H3 (H3K27me3). The loss of methylation can be demonstrated by highly specific immunohistochemistry. Moreover, this is an important finding given that monophasic synovial sarcoma and fibrosarcomatous dermatofibrosarcoma protuberans are usually monomorphic, hyper cellular spindle cell sarcomas with fascicular growth patterns, they represent some of the best morphologic mimics of malignant peripheral nerve sheath tumors. Consequently, H3K27me3 specificity is vital to the diagnostic utility of the stain when attempting to exclude synovial sarcoma and fibrosarcomatous dermatofibrosarcoma protuberans. Such trimethylation is typically ubiquitous in neuro fibroma and atypical neuro fibromatous neoplasm with uncertain biologic potential (ANNUBP) but is often lost in MPNST. The frequency of H3K27me3-loss has varied between 30–90%, and by some studies, has been more frequent in sporadic and radiation-associated MPNSTs than NF1-associated MPNSTs [29–31]. Genetic data suggest that loss of H3K27me3 does not occur in cellular schwannoma, and therefore this marker may also be useful in the differential diagnosis between cellular schwannoma and those MPNSTs that have lost this marker.

5. Treatment and Prognosis

Surgical excision remains the primary treatment modality for MPNSTs. MPNSTs are treated best with wide surgical margins,

followed by chemotherapy and local radiation; unfortunately, metastases are common, with poor long-term survival [23]. MPNST is a tumor-associated with aggressive behavior and poor prognosis [13]. There are some prognostic factors such as their truncal location, tumor size >5cm, local recurrence, and high-grade morphology are all adverse prognostic factors a patient with NF1-associated MPNST appear to have a worse prognosis than patients with sporadic tumors [4].

6. Conclusion

MPNSTs are difficult to manage because of their aggressive nature and the limitations in early diagnosis and management, hence the importance of keeping in mind these tumors when dealing with a patient with NF-1 and a previous diagnosis neuro fibroma, especially NF with a prolonged history of a mass, all of which support the concept of a sarcoma arising upon neuro fibroma. Molecularly targeted therapies following surgery for MPNST should be developed to render a patient disease-free.

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