Malignant Peripheral Nerve Sheath Tumor in Neurofibromatosis Type 1 Patient

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Abstract: Malignant peripheral nerve sheath tumor (MPNST) is rare and highly aggressive neoplasm. Approximately half of MPNST cases occur in association with neurofibromatosis type 1 (NF1). MPNST contribute significantly in reducing life-span of neurofibromatosis type 1 patients. The only known definitive therapy for MPNST is surgical resection with wide negative margins which may not be feasible in certain conditions involving tumor size, location, and/or metastases. Therefore, early diagnosis of MPNST is mandatory to increase the rate of successful surgical resection. We present a 36-year-old female with NF1, who had a giant MPNST on the right arm. She died six months after diagnosis in spite of a surgical resection and chemotherapy. This case report aimed to highlight the signs and symptoms of malignant peripheral nerve sheath tumor and examinations that are needed to make an early diagnosis of MPNST especially in patients with neurofibromatosis type 1.

1 INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder characterized by neurofibromas, cafe-au-lait spots, intertriginous freckling, bone malformations, learning disabilities and iris hamartomas. It is associated with mutation in NF1, a tumor suppressor located on chromosome 17q11.2. NF1 encodes neurofibromin, a protein of the ras-signal transduction pathway (Zehou et al., 2013). NF1 represents a major risk factor for development of malignancy, particularly malignant peripheral nerve sheath tumors (MPNST), optic gliomas, other gliomas, and leukemias (Korf, 2005).

MPNST is a rare disease with an incidence of 1 in 1.000.000 in the general population. The incidence of MPNST in patients with NF1 has been estimated to be 2% to 5%. MPNST is considered aggressive and is associated with a low survival rate (Hwang et al., 2017). MPNST contribute significantly in reducing life-span of NF1-patients (Freidrich, 2007). We present a rare case of giant MPNST with lung metastases in a patient with NF1.

2 CASE

A 36-year-old female presented with painful huge mass on her right arm, which rapidly increased in size within a four-year period. The mass had restricted movement of the extremity without neurological deficits. She also had multiple nodular masses of different sizes almost covering her entire body. These masses were initially seen in the head, neck and upper extremities when she was 7 years old. She also had multiple hyperpigmented macules on her axilla and trunk when she was 3 months old. None of her close relatives had similar signs and symptoms.

Upon physical examination, a firm, tender soft tissue mass with small necrotic area in right arm was found. Size of the mass was about 13 cm x 9 cm x 9 cm (Figure 1). “Bag of worm” sensation was negative on palpation. Multiple soft dome-shaped, flesh-colored nodules with diameters ranging from 0,5 cm to 5 cm covering almost her entire body (Figure 1). Multiple small to large cafe-au-lait macules, more than six in number, with irregular margins were seen on trunk. She also had multiple

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tiny hyperpigmented macules in her both axilla. Eye examination revealed multiple Lisch nodules on the iris of both eyes and the visual acuity were 6/12. Chest x-ray examination was normal.

Based on anamnesis and physical examination, the differential diagnosis of the enlarging mass were MPNST and plexiform neurofibroma (PN). The patient underwent wide excision under general anesthesia. Histopathology evaluation revealed overall features of MPNST composed of pleomorphic spindle cells with hyperchromatic nuclei and mitotic activity (more than 20 mitoses per 10 high-power field) arranged curlicue and whorls (Figure 2). Infiltration of the tumor cells into the surrounding soft tissue and area of necrosis was noted. Immunohistochemical analysis revealed a scattered positive staining uptake in the cells with S-100 antibody.

During follow-up, three months later, she presented with enlarging mass of 6 cm x 8 cm in her right axilla. Fine needle aspiration biopsy of the mass revealed disease progression presence of mitotic cells dominance, including some pleomorphic malignant spindle cell proliferation. CT-scan examination of axilla and lung revealed solid mass of 6,2 cm x 8,3 cm x 6,1 cm on axilla and multiple nodules on lung suggestive lung metastases. We referred the patient to oncology surgeon and she received two cycles of chemotherapy (ifosfamide) without any improvement. She died six months after diagnosis.

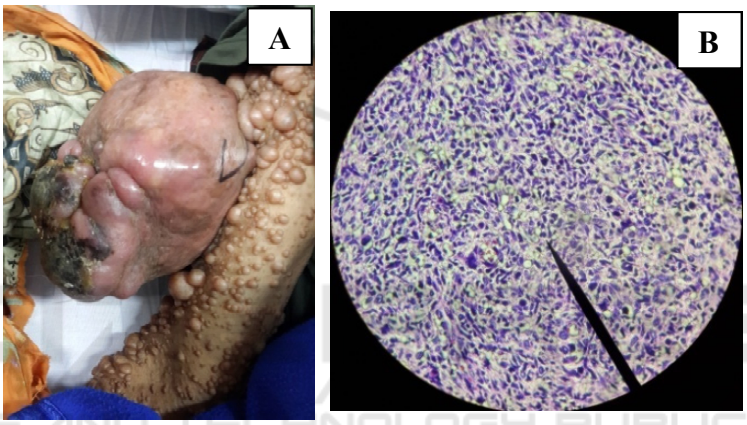

Figure 1: (A) A huge soft tissue mass with multiple neurofibromas in right arm. (B) Leomorphic spindle cells with hyperchromatic nuclei and mitotic activity.

3 DISCUSSION

The term MPNST currently describes a heterogeneous group of malignant tumors that possibly arise from cells of the nerve sheath (Freidrich et al., 2007). MPNST may appear *de novo* or develop from the malignant transformation of a benign neural neoplasm, generally a PN. Approximately half of MPNST cases occur in association with NF1 (Cunha et al., 2012).Leroy et al (2001) reported the prevalence of MPNST was approximately 4% in patients with NF1.In our patient, MPNST occurred in association with NF1. A diagnosis of NF1 was confirmed by the presence of four clinical manifestations that met the National Institutes of Health (NIH) consensus criteria.

In NF1 patients, one allele of Nf1 is inactivcated. PN is initiated when a second-hit mutation inactivates the remaining functional Nf1 gene, resulting in a loss of neurofibromin expression and Ras hyperactivation. This enhanced Ras signalling promotes the proliferation and invasive behavior of the neoplastic cells and their production of factors that recruit other Nf1 haploinsufficient cell types into the nascent neurofibroma. The subsequent loss of additional tumor suppressor genes (p53, cyclin D1-cyclin-dependent kinase (CDKN2A), phosphate and tensin homologue (PTEN), retinoblastoma (Rb)), amplification of key growth factor receptor genes (epidermal growth factor receptor (EGFR), ErbB2, C-Met, platelet-derived growth factor receptor (PDGFRα), KIT), mutation of polycomb repressive complex 2 (PRC2) components and alteration of key cytoplasmic signaling pathways then leads to the development of MPNST derived from the the neoplastic Schwann cells within the neurofibroma (Carroll, 2016).

MNPST may arise at any age with no gender predilection (Farid et al., 2014).Patients with NF1

usually present at a slightly earlier age than those with sporadic MPNST (Goldblum et al., 2014). The median age for sporadic MPNST is between 30 and 60 years, and that for NF1- associated MPNST is between 20 and 40 years (Farid et al., 2014). Our case was a 36-year-old female.

MPNST usually presents as a progressively enlarging mass with pain and, later neurological symptoms such as weakness and paresthesias. Symptoms are present for months before the malignant neoplasm is identified correctly (Farid et al., 2014; Leroy et al., 2001).Most MPNST arise in association with major nerve trunks, including the sciatic nerve, brachial plexus, and sacral plexus. Consequently, the most common anatomic sites include the proximal portions of the upper and lower extremities and the trunk. Few MPNST arise in the head and neck (Goldblum et al., 2014). de Vasconcelos et al. (2017) reported the extremities (58%) as the most common affected sites, followed by trunk (32%) and head and neck (10%) (de Vasconcelos et al., 2017). MPNST is usually large, averaging more than 5 cm in diameter and has a fleshy, opaque, white-tan surface marked by areas of secondary hemorrhage and necrosis (Goldblum et al., 2014).de Vasconcelos et al. (2017) reported the mean tumor sizes were 15,8±8,2 cm (range, 3-47 cm).[10] Our case presented with painful huge mass (13 cm x 9 cm x 9 cm) on proximal portion of the upper extremity without neurological symptoms.

Most MPNST are aggressive with a high likehood of local recurrence and distant metastases. The local recurrence rate varies from 40% to 65% and the metastatic rate from 40% to 68%. They frequently metastasize to the lung followed by bone, liver, brain, soft tissue, skin and retroperitoneum.[11] Three months after surgical resection, our patient developed local recurrence in the axilla and lung metastases.

Fluorodeoxyglucose positron emission tomography (PET-CT) is of great value in monitoring lesions with the potential for malignant transformation in NF1 (Batista et al., 2015). Increased uptake was found to be characteristic of MPNST (Korf, 2005). Due to the frequency and severity of MPNST associated to NF1, PET-CT scan could be useful in the following situations: a) when the plexiform tumor growth is inconsistent with the child's growth track; b) in the presence of neurological deficit, c) changes in tumor texture; and finally d) when patient reports an inexplicable and progressive pain (Batista et al., 2015).

Histologic features of MPNST are composed of monotonous spindle cells arranged in intersecting fascicles. Pleomorphic variants also exist. At low power, alternating hyper- and hypocellular areas may be present, often with hypercellular areas localized in close proximity to blood vessels. Compared with benign neurofibromas, MPNST usually demonstrate a marked increase in tumor cellularity, pleomorphism, and mitotic activity and show a more organized cellular growth pattern, with less extracellular matrix material (Farid et al., 2014). S-100 protein has been the classic and the most widely used antigen for documenting nerve sheath differentiation. Between 50% and 90% of MPNST express the antigen but usually focally only (Goldblum et al., 2014).Our patient had histopathological and immunochemical findings similar to the earlier findings and diagnosis of MPNST was made.

Current treatment of MPNST is similar to treatment of soft tissue sarcomas as a whole and relies primarily on local control measures. The only known definitive therapy for MPNST is surgical resection with wide negative margins, which may not feasible due to variables such as tumor size, location, and/or metastases. The role of adjuvant radiation and chemotherapy is not defined (Kim et al., 2017). Chemotherapy is usually preferred for metastatic disease and may be also useful in the preoperative management in order to decrease the size in patients with inoperable tumors. Radiation therapy is recommended for positive microscopic margins providing local control and delaying the onset of recurrence (Pourtsidis et al., 2014). Our patient underwent excision and chemotherapy was given after local recurrence and distant metastases of the tumor to the lung.

MPNST are very aggressive tumors and all current treatments have shown poor results. The five-year overall survival rate of patients with MPNST ranges between 34% and 58%, with several studies suggesting that prognosis in the setting of NF1 may be worse (Dunn et al., 2013).A meta-analysis testing the effect of NF1 status on MPNST by Kolberg et al. (2012) showed a significantly worse outcome in NF1 patients (Kolberg et al., 2013). de Vasconcelos et al. (2017) showed the presence of NF1 and tumor size (greater than 10 cm) had a significant negative impact on overall survival. The five-year overall survival was 18% for NF1 associated and 40% for sporadic MPNST (de Vasconcelos, et al., 2017). Our patient died six months after diagnosis in spite of a surgical resection and chemotherapy. She had NF1 status and huge tumor size (13 cm x 9 cm x 9 cm) that associated with poor prognostic.

4 CONCLUSION

Patients with NF1 need careful follow up because of the possibility of hidden carcinomas such as MPNST underneath the neurofibromas. Clinicians should be alert to unexpected growth of a pre-existing neurofibroma, particulary a plexiform neurofibroma, or the occurrence of unexplained pain with/without neurological symptoms such as weakness and paresthesias. Fluorodeoxyglucose PET-CT should be used in suspicious lesion with the potential for malignant transformation in NF1. Early diagnosis of MPNST is mandatory to increasing the successful of surgical resection

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