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Original Research Paper

Internal Medicine

Malignant Peripheral Nerve Sheath Tumor: A Case Report

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ABSTRACT Neurofibromatosis type 1 (NF-1) is classified as a neurocutaneous disorder caused by NF-1 gene mutations. This disorder presents with benign soft tissue tumors, neurofibromas, scattered throughout the body. They develop as a result of proliferation in all parts of the peripheral nervous system and can cause functional damage, deformities, pain, considerable mortality, morbidity and even an increased risk of malignant transformation in some critical cases. NF-1 is one of the most important risk factors for malignant peripheral nerve sheath tumors (MPNST). Malignant peripheral nerve sheath tumors (MPNSTs) have historically been referred to by a variety of names, including malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, and malignant neurilemmoma. Most MPNSTs are thought to arise from Schwann cells; however, the term MPNST is currently preferred to cover the possibility that some arise from other nerve sheath cells. They are rare, extremely aggressive soft tissue sarcomas and are tremendously challenging to manage. Recent advances in the understanding of the molecular pathogenesis of MPNST have been made, and offer promises for improving the management of these aggressive tumors. Surgery is the mainstay of therapy and represents the primary curative modality. Chemotherapy and radiation therapy have a role in the management of selected patients with MPNST. The goal of this review is to provide a detailed overview of the current understanding of the pathogenesis, risk factors, clinical management, and prognosis of patients with MPNST.

KEYWORDS : Neurofibromatosis, NF-1, MPNST

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is an autosomal dominant disorder caused by NF-1 gene mutation, which codes for a protein called neurofibromin. It presents with neurofibromas, optic nerve gliomas, pigmented nodules in the iris, and hyperpigmented cutaneous macules. (5)

Malignant peripheral nerve sheath tumours (MPNSTs) are rare soft tissue tumours that can arise from a pre-existing plexiform neurofibroma or a normal peripheral nerve. (1)

MPNSTs normally present as an enlarging mass. In patients with NF-1, unexplained changes in the size or development of new symptoms associated with neurofibromas should point towards a possibility of malignancy. The median size of MPNSTs at the time of diagnosis is 5–10 cm. They occur most commonly in the proximal upper and lower extremities and pelvis. (8)

MPNSTs are aggressive tumours with high rates of recurrence and distant metastasis, the most common site of metastasis is the lung followed by bone. (1)

CASE REPORT

We present a case of a 54-year-old African American man with a past medical history of Neurofibromatosis (Diagnosed in 1989) with multiple prior neurofibroma removal surgeries, and Sarcoidosis (primarily cutaneous in nature diagnosed at 40 years by skin Biopsy), Osteoarthritis, Glaucoma, benign prostatic hyperplasia, and hypertension.

He presented to the hospital with a mass in the left thigh, located laterally, with progressive enlargement for a month, and severe pain 10/10 in intensity, along with tenderness to palpation. The patient complained of blurry vision for the past year, intermittent hematuria for years, daily dizziness, trouble swallowing and regurgitation on and off for a year, pain in the right knee for a year, and myotonic episodes of the hand.

A punch biopsy of the thigh lesion was performed and it showed minute fragments of a spindle cell neoplasm with high cellularity and nuclear atypia, a small focus of necrosis (10%) and just a few mitoses are seen (Mitotic counts 28/10 HPF). The histologic findings are consistent with a malignant peripheral nerve sheath tumour arising in a background of plexiform neurofibromas, invading the nerve sheath. Neurofibromas are observed throughout the nerve chains but mainly at the proximal and distal ends. Staging of the tumour gives us pT2b.

A PET/CT scan was performed, showing multiple bilateral pulmonary nodules, the biggest ones were found in the right lower lobe, measuring 4.6 x 3.1 cm and 2cm respectively. The scan also showed left hilar lymphadenopathy, 4.6 x 3.1 cm in size.

A follow-up endoscopic bronchial ultrasound with transbronchial needle aspiration was performed on 2 sites, showing non-necrotizing epithelioid granulomas, anthracotic lymph nodes, CD 34 (-) and S100 (-) staining on subcarinal station 7 lymph nodes which suggest sarcoidosis. A left hilar mass showed a spindle cell neoplasm presumed to be neurogenic in origin with low-grade malignant features, CD34 (+) and S100 (-), Ki67 30-40%, which suggests metastatic Neurofibroma.

The patient underwent surgery for the thigh neurofibroma and a 12x8x6.5 cm mass was resected. The pathology report indicated negative margins and identical histologic features to the prior punch biopsy.

The Patient was referred to an outpatient clinic and reports

major improvement in pain levels, with postsurgical residual pain 4/10 in intensity, and is using a cane to ambulate. A Radiation regimen of 34 sessions for the affected site is planned along with physical therapy.

Several months later the patient reports a dry cough that wakes him from sleep, shortness of breath along with pleuritic pain and palpitations. On physical examination, there was dullness on percussion of the left hemithorax, darkened skin at the left lower extremities due to the radiation, and a healed surgical scar.

X-ray showed signs of a large left pleural effusion. A repeat PET-CT scan showed that the left hilar mass had increased in size to 9.4cm x 6.9 cm, uptake of 9.2 and is now extending into the aortopulmonary window and perivascular regions. The pulmonary metastatic nodules showed an increase in size, in the right lower lobe (3.1cm x 1.8 cm > 9.4cm x 6.3 cm).

Approximately 1.2 litres of bloody yellow fluid was drained from a small incision in the sixth rib anterolaterally. Pleural fluid analysis showed: RBCs 5250, LDH 221, pH 7.65, and Glucose 94.

Pericardial fluid cytology and biopsy were performed, they primarily showed blood with few inflammatory cells. It was negative for malignant cells. The pathology report indicates acute and chronic inflammatory findings with granulation tissue and fibrosis.

The patient was started on Imatinib as a result of NF1 positivity. After 2 cycles, therapy was discontinued due to the patient's worsening condition. A chemotherapy regimen (MAID) with Adriamycin (doxorubicin) 15mg/m2/d over 8 hours (4days), Ifosfamide 2g/m2/d Continuous IV infusion for 3 days (mesna started 1 hour prior to ifosfamide), Mesna 2.5 g/m2/d Continuous IV infusion, Dacarbazine 250 mg/m2/d over 8 hour, 6 cycles (4days) was started.

1 month after the start of therapy the patient reported severe shortness of breath and cough, X-ray showed a severe left pleural effusion. A pleurocentesis drained 2.4 litres of fluids, with similar characteristics as before. The patient underwent a Talc Pleurodesis due to recurrent left pleural effusion.

The patient's condition continued to worsen and he succumbed to the disease.

DISCUSSION

Neurofibromatosis (NF-1) is the most important known risk factor for MPNSTs. 50-60% of these tumours are found in patients with NF-1 mutations. The incidence and relative risk of MPNSTs in patients with NF-1 mutations is 10% and 113, respectively when compared to the rest of the population. Dermal neurofibromas are more frequently found but do not pose a higher risk for malignant transformation. The malignant transformation rate is higher with deeper plexiform neurofibromas. Radiation exposure is another risk factor for MPNSTs. Patients with NF-1 mutations tend to develop MPNSTs approximately 10 years earlier than non-NF-1 patients. These tumours may be associated with symptoms such as pain, paraesthesias, and neurological deficits. These symptoms may be misdiagnosed as disc herniation, carpal tunnel syndrome, or rotator cuff injuries. (8)

For a soft tissue tumour to be considered an MPNST, any of the following criteria should be met:

(i) The tumour arises within or from a peripheral nerve
(ii) It arises from a pre-existing benign or other malignant nerve sheath tumour
(iii) The tumour has the appearance of an MPNST and arises in a patient with NF1
(iv) Exhibits histologic, immunohistochemical, or ultrastructural features that suggest Schwann cell differentiation (8)

It is challenging to diagnose malignant transformation in a nerve sheath tumour, MRI is the preferred investigation for evaluation of these tumours. Four tumour markers (epidermal growth factor receptor, interferon-g, interleukin-6, and tumour necrosis factor-α) are being used to identify patients with NF-1 mutations. Insulin-like growth factor-binding protein 1 (IGFBP1) and regulated upon activation, normal T-cell expressed and secreted (RANTES) are two markers that can be used as early predictors of developing MPNSTs. These biomarkers can play a role in the screening of patients with NF-1 variants at a high risk of malignant transformation. (4,7)

Surgical resection is the primary treatment modality for MPNSTs. The management of MPNSTs is similar to the management of soft tissue sarcomas. Complete surgical tumour resection with negative margins in addition to adjuvant or neoadjuvant radiation and chemotherapy is the most common treatment option. Despite aggressive treatment of MPNSTs, local recurrences and distant metastasis are common. Lungs (nearly 65%) are the most common site of distant metastasis. Five-year survival is poor (20-50%) with high-grade MPNST. For large, unresectable, or metastatic MPNSTs, chemotherapy is the treatment of choice. Chemotherapy typically consists of a combination of Ifosfamide and Doxorubicin. NF1 patients respond less well to chemotherapy than sporadic MPNST patients. Signal pathway inhibitors are being investigated for the treatment of MPNSTs. (3,8)

CONCLUSION

- For patients with suspected MPNST, the medical evaluation must include a thorough history and physical examination. A core biopsy of the suspected tumour is the best diagnostic test. It provides enough tissue for histologic analysis and allows sampling from multiple areas of the tumour. Imaging of the primary tumour should be performed. Non-contrast CT chest should be performed on patients with MPNSTs to look for lung metastasis. (8)
- Many patients with MPNST already have distant metastasis at the time of presentation. Lungs are the most common site for metastasis followed by bone. Metastatic disease is a common cause of mortality in MPNST patients. The disease-free interval following treatment of the primary tumour is short in patients who develop metastatic MPNSTs. Size of the primary tumour, tumour grade, and locally recurrent presentation are some of the identified risk factors which play a role in the development of metastasis. (8)
- Due to the poor prognosis of MPNSTs, patients with NF-1 mutations should be educated about the possibility of malignant transformation of the neurofibromas. They should be asked to report signs of malignant transformation, such as rapid growth of a pre-existing lesion. (2)
- Local tumours should be controlled aggressively in patients with localised MPNST and regular follow-up should be scheduled for early detection of relapse and metastasis. (1)
- The prognosis of the MPNSTs is unpredictable because of the high risk of progression as well as its variable expressivity. (7)
- MPNSTs are a diagnostic as well as a therapeutic challenge. Newer treatment options with drugs that target the biological pathways involved in tumour growth are being actively investigated. (8)

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