CLINICAL VIGNETTE

Malignant Peripheral Nerve Sheath Tumor in Neurofibromatosis Type 1

Tejasvi Pasupneti, MD and Jesse Szatkowski, MD

Introduction

Neurofibromatoses are a set of autosomal dominant disorders that can be divided into three main forms: neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis. Neurofibromatosis type 1 (NF1) is the most common of these three disorders. This case highlights one of its most significant complications: the malignant peripheral nerve sheath tumor (MPNST).

Case Presentation

A 30-year-old male with history of NF1 and prior grade 3 malignant nerve sheath tumor status -post T12-L1 laminectomy with excision 3 years prior presented to the Emergency Department for shortness of breath. Physical examination revealed that he was febrile to 38.8°C, with heart rate of 108, respiratory rate of 26, blood pressure of 115/70, and oxygen saturation of 97% on room air. Exam demonstrated diminished breath sounds over the lower two-thirds of the right lung field. Laboratory studies demonstrated a white count of 21.8, hemoglobin of 10.4, and serum sodium level of 129. Chest x-ray showed a right pleural effusion, possible right lower lobe infiltrate, and concern for left upper lobe nodules. Chest CT with contrast revealed multiple right lower lobe enhancing masses measuring up to 14cm, bilateral upper lobe nodules, and a large loculated right pleural effusion. The right lower lobe mass is demonstrated in Figure 1.

He was admitted for further management with a differential diagnosis including infection and malignancy. A diagnostic thoracentesis was performed with return of grossly dark bloody fluid and laboratory results consistent with an exudative process. Cell count demonstrated a neutrophil predominance. Cytology of the pleural fluid showed reactive mesothelial cells, macrophages, lymphocytes, and numerous neutrophils in a background of blood. The patient was started on antibiotics for possible post-obstructive pneumonia. Given his history and imaging he underwent CT guided biopsy of his lung mass, with results consistent with metastatic malignant peripheral nerve sheath tumor.

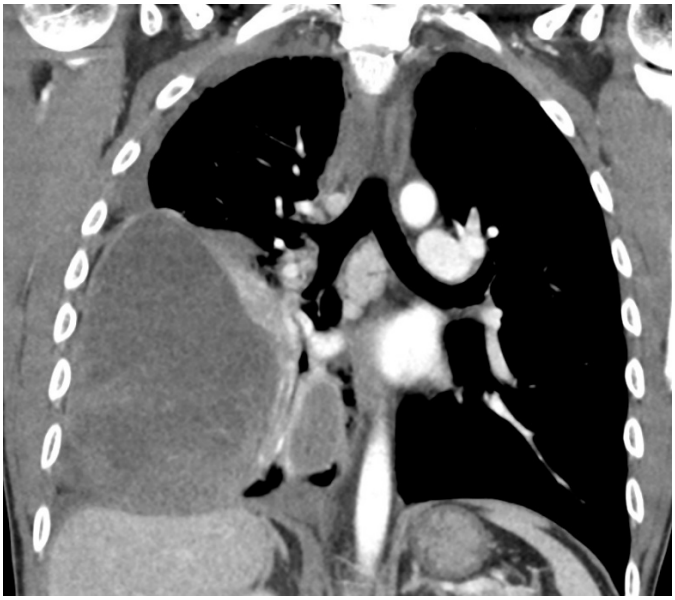

Figure 1: Large low-attenuation lesion in the right lower lobe measuring 14.5 x 9.7 x 13.5 cm with loss of fat plane between the mass and the liver.

Discussion

Fifty percent of all MPNSTs are associated with NF1, the complex autosomal dominant disorder that affects about 1 in 2500 individuals, regardless of gender or ethnic origin. MPNSTs are rare but represent a significant burden of disease within the NF1 syndrome. Discovered in 1990, the NF1 gene on chromosome 17q11.2 encodes for the neurofibromin protein, which plays a role in tumor suppression.[1] As a result, individuals with NF1 are at increased risk of both benign and malignant tumors over their lifespan. In addition, NF1 has a wide range of clinical heterogeneity with variable expression. In 1987 the National Institute of Health Consensus Development Conference developed the first set of diagnostic criteria for NF1.[2] Table 1 illustrates the most recent iteration of that criteria.[3] NF1 includes both tumor and nontumor manifestations across numerous organ systems which necessitates the need for ongoing surveillance and a multisystem approach to management. These manifestations can include CNS tumors, skeletal deformities, and learning disabilities.

Table 1: Diagnostic Criteria for Neurofibromatosis 1 [3]
A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present: • Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals • Freckling in the axillary or inguinal region • Two or more neurofibromas of any type or one plexiform neurofibroma • Optic pathway glioma • Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging • A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone • A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

The characteristic feature of NF1, however, is the neurofibroma which is a benign peripheral nerve sheath tumor that consists of mutations in mast cells, fibroblasts, or Schwann cells. Overall, there are three distinctive types of neurofibromas: cutaneous, nodular, and plexiform. Benign cutaneous neurofibromas are common and are restricted to the dermis. Nodular neurofibromas may develop within any peripheral nerve and can grow large enough to compress surrounding structures. Plexiform neurofibromas are multinodular lesions arising from multiple nerves or nerve roots that can invade surrounding structures. Studies show that 8% to 13% of patients with NF1 will develop a MPNST[4], most of which arise from nodular and plexiform neurofibromas.[5] MPNSTs can also occur sporadically or due to radiation exposure but the overall lifetime risk in NF1 individuals is significantly higher. Our patient's initial MPNST occurred in the spinal nerve roots and likely resulted from previous plexiform neurofibroma that transformed and invaded other structures. The most common sites of involvement include the nerve roots in the extremities and pelvis, particularly the sciatic nerve. Close surveillance is essential in NF1 patients. Patients may initially present with an enlarging mass that may be painful or cause local neurological symptoms such as weakness or paresthesia. The development of new, worsening, or persistent pain in a neurofibroma is an important symptom that should warrant further investigation.

Although clinical features of rapid growth and pain associated with a neurofibroma are concerning for malignancy, a biopsy is necessary for definitive diagnosis. As discussed above, MPNSTs arise from either a peripheral nerve or from an existing neurofibroma. As a result, the cells involved may appear similar to Schwann cells, perineurial cells, or fibroblasts. Minimal criteria to distinguish malignant from benign includes cell crowding, nuclear enlargement, nuclear hyperchromasia, and a mitotic rate greater than 10 per high power field.[6] Furthermore, MPNST cells can appear as monomorphic spindle cells arranged in long fascicles. The appearance is often described as "marble-like" due to the alternating cellular superstructure. The cellular nuclei are often wavy or buckled and the cytoplasm is unremarkable. Figure 2 and 3 are histology images from our patient's lung biopsy which demonstrate these features. Immunohistochemistry analysis has an important role in the diagnosis and is best used for ruling out alternative diagnoses. Incomplete staining for S100 and SOX10, is common, however the lack of these stains does not rule out MPNST.[7]

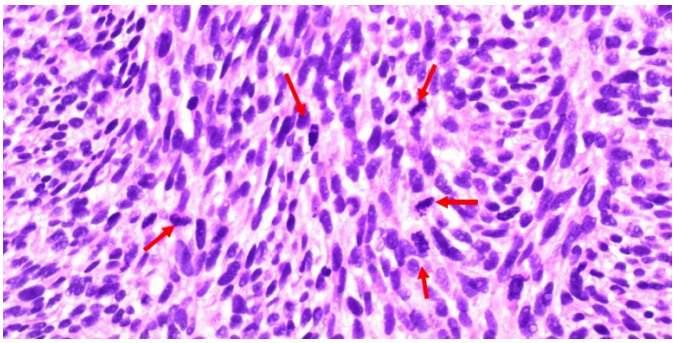

Figure 2: Spindled cells display mild to moderate anisonucleosis, nuclear hyperchromasia, and increased mitotic activity (>10 per high powered field) indicating malignancy.

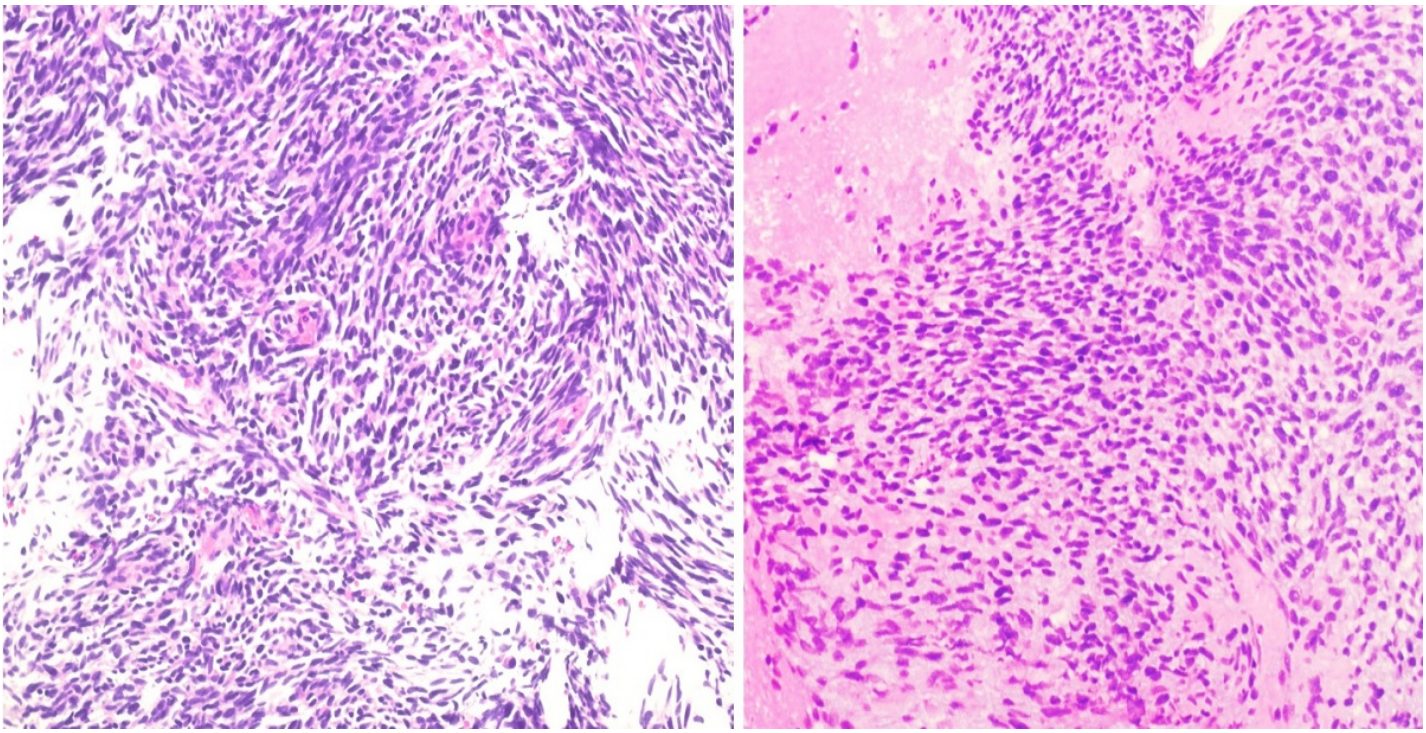

Figure 3: Malignant peripheral sheath tumor cells organized into storiform, whorled and intersecting fascicles of proliferating spindled cells are separated by fibrocollagenous to fibrovascular tissue.

Biopsy may be challenging with risk of persistent nerve damage because of the tumor's proximity to nerve roots. Imaging may be helpful in the evaluation of a growing soft tissue mass, but cannot definitively distinguish between benign and malignant tumors. For example, magnetic resonance imaging is frequently used for surgical planning, but is not specific enough to differentiate between benign and malignant nerve sheath tumors.[8] Positron emission tomography/computed tomography (PET/CT) has also been studied as a method to assess risk of MPNST. However, an ideal threshold for PET/CT maximum standardized uptake values have not been established.[9] Several serum biomarkers have also been studied, however they have low sensitivities and specificities.[10]

The prognosis for MPNST tends to be poor as it is an aggressive malignancy. When associated with NF1, MPNSTs tend to occur at significantly younger ages compared to sporadic cases, with a peak incidence in the third and fourth decade of life. In addition, patients are more often male, have shorter survival times, shorter times to local recurrence, and greater risk of metastasis.[11] Studies report recurrence rates up to 40%, and approximately two-thirds metastasize, most frequently to the lungs. Among individuals who develop metastatic MPSNT, the disease-free interval after management of the primary tumor is usually short, with a median of 13-24 months.[12] In addition, poorer prognosis is associated with large tumors (>5cm), higher grade, truncal location, positive margins, and recurrence. Our patient had recurrence of his MPNST with metastases to the lungs, all within 3 years of his initial diagnosis. He was in his late twenties at time of the diagnosis with a large high-grade tumor.

The mainstay of treatment for localized MPNST is wide surgical excision with negative margins. Resection along major nerve roots and plexus may result in a potential loss of function, depending on which structures are excised. In addition to surgery, standard of care also includes radiation to control local disease and reduce recurrence. However, this does not appear to affect long-term survival. Chemotherapy similarly does not improve survival rate but is used to treat metastatic MPNST. For those with high-grade MPNST like our patient, overall, 5-year survival rate ranges from 20% to 50%.[13] Thus, early care coordination from a multidisciplinary team of oncology, neurosurgery, and palliative care is essential.

Conclusion

MPNSTs are a significant cause of morbidity and mortality in patients' with NF1. These tumors can be clinically similar to benign neurofibromas and biopsy is essential to confirm the diagnosis of any painful or rapidly growing lesions. Treatment is wide surgical excision with negative margins, however, recurrence is common. Our patient experienced recurrence of his MPNST with metastatic spread to the lungs. In the setting of lung metastasis, treatment options included chemotherapy and radiation. Overall, however, our patient had a poor prognosis given his recurrence and high-grade nature of the tumor. He is followed closely by multidisciplinary team with a low threshold for biopsy.

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