Neuroblastoma in an Adult: Case Presentation and Literature Review

Laura Smith¹, Steve Minter¹, Paul O’Brien¹, Jacqueline M Kraveka², Ana Maria Medina³, John Lazarchick³

¹Department of Medicine, ²Pediatrics, and ³Pathology and Laboratory Medicine, Medical University of South Carolina, SC, USA

Abstract. Neuroblastoma is the most common malignancy in children less than one year of age, but is rare in adults. Adult neuroblastoma differs from pediatric cases by lacking classical features including low incidence of \textit{MYCN} amplification, elevated urinary catecholamimes, and MIBG avidity. The diagnosis may not be initially considered because of the rarity, which emphasizes the importance of immunohistochemical staining and cytogenetic testing in aiding the diagnosis. We present a case of neuroblastoma in a 39-year-old woman who failed to respond to intensive therapy for this malignancy and died within a year after diagnosis.

Introduction

Neuroblastoma is an embryonal neural crest tumor involving the peripheral sympathetic nervous system. It can arise anywhere in the sympathetic nervous system and frequently occurs in the adrenal gland or sympathetic ganglia in a paraspinal location in retroperitoneum or chest. It metastasizes to regional lymph nodes, liver, skin, brain, bone, and bone marrow. It is the most common malignancy in children younger than age 1, but rarely presents in adolescent or adult patients. Neuroblastomas are biologically heterogeneous tumors, with some tumors undergoing spontaneous differentiation and other being highly resistant to multi-modal therapy [1-3].

Approximately 45% of neuroblastomas are classified as high risk. According to SEER data from 1973-2002, only 6.1% of those diagnosed with neuroblastoma were over 20 years of age [4]. In patients ages 30-39, the incidence rate is under 0.3 cases per million years. Because neuroblastoma is exceedingly uncommon in adult patients, immunohistochemical (IHC) staining and cytogenetic testing are often vital diagnostic tools. Growing evidence suggests that adult neuroblastoma differs from pediatric cases by lacking classic features, including low incidence of \textit{MYCN} amplification, urine catecholamine elevation, and MIBG (iodine-131-meta-iodobenzylguanidine, an analog of nor epinephrine) avidity [4-7]. Currently, there are no standard recommendations for treatment of adult neuroblastoma. We report a case of neuroblastoma in a 39 year old female to emphasize diagnostic awareness and discuss our experience following induction chemotherapy.

Case Presentation.

A 39-year-old woman presented to an outside hospital with lower back pain of 3 months duration. The pain was gradual in onset, sharp in character, radiated to the hips, and had minimal response to pain medications. A computed tomography (CT) scan of her lumbar spine showed pathologic fracture of L1, a paravertebral mass, and retroperitoneal lymphadenopathy. The paravertebral mass was biopsied but the pathology was in question, so she was referred to our hospital. Physical examination
on admission was unremarkable. Laboratory test results were notable for a CBC with differential showing a microcytic, hypochromic anemia (hemoglobin, 7.8gm/dl, MCV 77FL, MCH 23.6 pg), thrombocytopenia (40,000/CUMM), and presence of numerous nucleated-RBCs (32/100WC). LDH and ferritin were elevated (2148IU/L and 5199ng/ml respectively). Results of all other laboratory tests were within the normal range. A magnetic resonance imaging (MRI) of the lumbar spine showed a large anterior paravertebral mass at T12-L1 with extension into the neural foramen and epidural space, without spinal cord signal abnormality. Whole body PET/CT scan showed diffuse metastatic disease, including osseous metastases throughout the axial and appendicular skeleton, multiple levels of paraspinal masses, liver metastases, and supraclavicular and retroperitoneal lymph nodes. A bone marrow biopsy revealed hyperchromatic tumor cells and Homer-Wright pseudorosette formation. Immunohistochemical (IHC) staining showed tumor cells positive for synaptophysin and CD56 (Figure 1). Cytokeratin AE1/AE3, CD3, CD20, CD43, CD45, CD79a, CD138, MPO, chromogranin, and CD99 were negative. Based on the morphologic and IHC findings, we made a diagnosis of poorly differentiated neuroblastoma. A MIBG scan was performed to assess potential response to therapy but no MIBG-avid lesions were demonstrated. Urinary catecholamines showed elevated norepinephrine (139/ug/g crr, reference values 0-45) 3 times normal limit concerning neuroendocrine tumor. Dopamine, epinephrine, vanillylmandelic acid, and homovanillic acid levels were not elevated.

She completed six cycles of induction chemotherapy (2 cycles of cyclophosphamide and topotecan, followed by 1 cycle cisplatin and etoposide, 2 cycles of cyclophosphamide, doxorubicin, and vincristine,
and 1 cycle cisplatin/etoposide) over six months. Bilateral bone marrow biopsies performed then showed no signs of residual disease. The plan was for her to undergo consolidation chemotherapy with HSC autologous stem cell rescue, and subsequent radiation therapy, followed by maintenance therapy with isotretinion. However, her GFR post-induction chemotherapy did not recover adequately for transplantation.

After 9 months of progression-free survival, the patient developed right cerebellar, right frontal, and left frontal lesions suspicious for brain metastases. She underwent gamma knife stereotactic radiosurgery to the lesions. Two months later she was noted to have new right cerebellar, right temporal, and right frontal metastases on brain MRI. In Jan 2012, her MRI showed progressive diffuse osseous metastases, spinal intramedullary, and leptomeningeal metastases. In March 2012 her performance status continued to worsen, with increasing pain, and she decided to forgo chemotherapy. The patient was referred to hospice care and died shortly thereafter.

**Discussion**

We present a woman with neuroblastoma, a pediatric malignancy that uncommonly affects the adult population. Neuroblastoma exhibits a wide spectrum of clinical and histopathologic heterogeneity, with poor outcomes in older patients and/or patients with advanced disease, but also uniquely has the propensity to spontaneously differentiate in young patients with low-risk, localized disease [2,3,6,7]. Growing evidence suggests that adult neuroblastoma may have distinct biologic features, including low frequency of MYCN amplification, urine catecholamine elevation, and MIBG avidity. Multiple studies have shown that prognosis of neuroblastoma worsens with increasing age. Because of the rarity of this disease in adults, survival data is limited to single institution case reports and small case series. Retrospective case series show variable, but consistently poor outcomes [4-6]. In our case, despite a vigorous initial response to induction chemotherapy, the patient developed progressive disease and her survival was 1.5 years.

Amplification of the MYCN oncogene occurs in ~20% of patients under 13, and in the pediatric setting confers a worse prognosis [2-5,7,8]. MYCN amplification occurs in ~40% of high risk tumors. Interestingly, while adults with neuroblastoma have a worse outcome, this particular mutation appears to be rare [5,7,8]. Patients with neuroblastoma may have elevated urinary catecholamines, such as homovanillic acid/vanillylmandelic acid, which is another way to further characterize this malignancy. However, the literature is inconsistent on the frequency of catecholamine elevation in adults with neuroblastoma. Case series report urine catecholamine elevation rates from 46% to 90%, and thus while the test can be a useful aid, its negative predictive value is not high [4-7]. Our patient had an excess level of norepinephrine, over three times the normal value, which is suggestive of a neuroendocrine tumor, but also could be secondary to other complicating factors.

While neuroblastoma is rare in adult patients, it is important to consider in the differential diagnosis of small round blue cell tumors. This is especially relevant given the poor prognosis and lack of treatment strategies. The differential diagnosis for our case included lymphoma, Ewing sarcoma/primary neuroectodermal tumor (PNET), rhabdomyosarcoma, osteosarcoma, and neuroblastoma. Lymphoma was initially suspected at the outside hospital due to the morphology of the initial biopsy, anatomic location, and age of the patient. It was subsequently excluded based on morphology on bone marrow biopsy and with IHC. Ewing sarcoma/PNET is generally not associated with the presence of neuropil and ganglionic differentiation is rare, but can occur. PNET can express neuroendocrine markers, but can be differentiated from neuroblastoma by positive CD99 and cytokeratin staining [9].

Neuroblastoma may be diagnosed by morphology, and has been shown to express CD56, chromogranin A, synaptophysin, neurofilament, and neuron-specific enolase [9]. In addition to MYCN amplification, these tumors can also have loss of heterozygosity at 11q and 1p. Cytogenetics and
MYCN amplification were not performed in our patient, but may have contributed to the diagnosis. Neuroblastoma’s histology is classified according to International Neuroblastoma Pathologic Committee Classification (INPCC), which ranks tumor histology as favorable or unfavorable based on differentiation of tumor cells, as characterization of stroma and mitosis-karyorrhexis index [10-12]. Unfavorable histology has been shown to confer a worse prognosis [2-3]. Our patient had a highly undifferentiated tumor consistent with unfavorable histology.

In conclusion, while neuroblastoma is a rare malignancy in adults, it is a documented occurrence and can have grave implications for patients. The infrequency with which it occurs may delay time to diagnosis, and therefore it is important to consider in the differential diagnosis of small round blue cell tumors, especially when such tumors lie in the distribution of sympathetic ganglia. Treatment with high dose chemotherapy and myeloablative therapy with HSC rescue may be beneficial in the pediatric setting, but may not be tolerated by adults.

References