An Unusual Case of Late Recurrence of MS Neuroblastoma in a Young Adult

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Abstract

This case describes an unusual presentation of a young adult with very late recurrence of stage MS neuroblastoma over 20 years after initial diagnosis. Tumor histology at relapse demonstrated ganglioneuromatous foci within her undifferentiated tumor. In combination with evidence of altered catecholamine metabolism, it proposes a case for dedifferentiation of unresected ganglioneuromatous lesions as the etiology of her recurrence of disease. An additional, compelling component of the case is the overall positive treatment response of the patient with relapsed neuroblastoma despite the poor prognostic factors of late relapse and adult age.

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– Abbreviation key:

INRGSS	International Neuroblastoma Risk Group Staging System
INSS	International Neuroblastoma Staging System
VMA	Vanillylmandelic acid
HMA	Homovanillic acid
^{123}I-MIBG	^{123}I-meta-iodobenzylguanidine
VZV	Varicella zoster virus

– No previously published papers

Abstract

This case describes an unusual presentation of a young adult with very late recurrence of stage MS neuroblastoma over 20 years after initial diagnosis. Tumor histology at relapse demonstrated ganglioneuromatous foci within her undifferentiated tumor. In combination with evidence of altered catecholamine metabolism, it proposes a case for dedifferentiation of unresected ganglioneuromatous lesions as the etiology of her recurrence of disease. An additional, compelling component of the case is the overall positive treatment response of the patient with relapsed neuroblastoma despite the poor prognostic factors of late relapse and adult age.

Introduction

Neuroblastomas are neuroendocrine tumors which arise from neural crest cells in the developing sympathetic nervous system.[1]Neuroblastoma is the most common extracranial solid tumor in pediatric populations and the most common malignancy in infancy.[2] The patient described was staged IV-S by the INSS definition and MS by the INRGSS definition. Stage MS is a distinct pattern of disease in infants less than 18 months of age and characterized by metastatic spread to the liver, skin, and limited bone marrow involvement.[3] Stage MS generally infers a good prognosis with survival approximated at 70-90% depending on clinical and genetic favorability and frequently with the outcome of spontaneous regression.[4, 5] Late recurrence of neuroblastoma, defined as recurrence greater than five years after diagnosis, is rare occurring in 3.1% of all cases and is associated with poor survival outcomes.[6,7] This case was compelling due to the unusual presentation of a very late recurrence of neuroblastoma in a young adult patient with history of stage MS disease and the overall favorable treatment response of her relapsed disease.

Results

A 20-year-old female with history of stage MS neuroblastoma presented with three weeks of progressive mid-epigastric abdominal pain. Her medical history was notable for stage MS neuroblastoma diagnosed at 7 weeks of age with clinical findings of abdominal distension and skin nodules. At initial diagnosis, she had elevated VMA and HVA levels (291 mg/g and 212 mg/g) and ^{123}I-MIBG avid disease. She was staged MS with palpable skin nodules, right adrenal mass, and <10% marrow disease. The patient underwent 90% resection of retroperitoneal mass at 20 months with pathology demonstrating favorable histology, N-MYC nonamplified and DNA index 1.2. She received isotretinoin for 44 months due to multiple progressions with gradually increasing size of residual retroperitoneal mass and delayed catecholamine normalization. Stabilization of mass was achieved, but catecholamines did not normalize until 175 months after diagnosis. She had subsequently been followed in survivor clinic until presentation.

Computerized tomography imaging demonstrated an abnormal portacaval node, a retroperitoneal mass with periportal extension, and a proximal right femoral lesion. Fine-needle aspirate of the periportal mass confirmed recurrent neuroblastoma. FISH showed N-MYC nonamplification, and ^{123}I-MIBG scan demonstrated avidity in tumor bed, portocaval and paraaortic lymph nodes, T8 vertebra, and proximal right femur. Urine VMA and HMA were 3.3 mg/g and 3.4 mg/g respectively. Bone marrow biopsy was negative for disease. The patient was diagnosed with stage M or stage IV neuroblastoma 20.5 years after initial diagnosis, a very late recurrence.

She was initiated on high-risk neuroblastoma therapy per ANBL0532 protocol. Aggressive biopsy of retroperitoneal mass demonstrated neuroblastic tumor with histologic evidence of early treatment response versus ganglioneuromatous stroma with foci of maturing ganglions. She underwent tandem autologous stem cell transplant and radiation with a total of 2160 cGy to the vertebral bodies, right femoral head, and right adrenal gland. Patient tolerated treatment well with reimaging demonstrating stable ^{123}I-MIBG uptake. Due to severe VZV-esophagitis, TPN initiation was indicated, ultimately delaying immunotherapy initiation. After stabilization of nutritional status, she was treated per ANBL0032 with clearance of bone disease on immunotherapy. End of treatment scans demonstrated no evidence of metastatic disease and stabilization of retroperitoneal mass with minimal ^{123}I-MIBG positivity.

Patient's clinical course was complicated by severe liver fibrosis secondary to transfusion-related iron over-

load. She endured recurrent episodes of abdominal pain and ascitic fluid accumulation with eventual peritoneovenous shunt placement. She unfortunately passed due to septic shock and peritonitis suspected to be due to shunt dysfunction. This was 23 months and 19 days from achieved clinical remission of neuroblastoma without evidence of disease progression.

Discussion

This case represented an uncommonly late relapse of neuroblastoma, 20.5 years after initial diagnosis. Interestingly, she had a recurrence of stage MS neuroblastoma, a stage which overall portends a good prognosis with event-free survival reported between 85-90%.[5, 8]Relapse occurs in these patients but almost exclusively within the first two years of diagnosis.[8] To our knowledge, there have been only two previously reported cases of late recurrence of MS disease. *Cervera et al.* described a patient with MS disease whose course complicated by interval development of several skin metastases with ganglioneuromatous histology at 3 and 19 years of age followed by eventual development of a bone metastasis at 23 years of age.[9] The second case presented by *Kato et al.* [10] described a 12-year-old female eleven years after complete remission. This patient had a history of stage MS disease with primary adrenal tumor and diffuse liver metastases who developed recurrent tumor in the liver. As in this case, the patient presented at relapse with normal urinary catecholamines, ^{123}I-MIBG avidity, and N-MYC nonamplified tumor. She underwent chemotherapy and ASCT but experienced local recurrence 11 months after myeloablative therapy and died of progressive disease. Notably ganglioneuromatous lesions were found within the periphery of the patient's undifferentiated hepatic tumor on autopsy pathology. Literature does report additional cases of IV-S with late recurrence; however, based on their clinical descriptions and revised staging definitions, they would be reclassified as stage IV or M.[11,12]

Similar to the case presented by *Kato et al* , our patient's histopathologic findings demonstrated ganglioneuromatous foci within the undifferentiated mass. A suggested hypothesis for late relapses after apparent clinical remission proposes that neuroblastoma development occurs after malignant conversion via dedifferentiation of unresected ganglioneuromatous lesions.[13] The discrepancy in the described patient's urinary catecholamine status from initial diagnosis to relapse suggests a change in predominant catecholamine metabolism.*In vitro* studies have demonstrated that negative catecholamine excretion signal less differentiated tumor secondary to decreased tyrosine hydroxylase expression.[14] Perhaps, the change in catecholamine metabolism strengthens the dedifferentiation theory over the alternate explanation of late activation of primary disease. Further study of catecholamine metabolism patterns in relapsed patients may provide better insight into the biologic differences in relapsed disease and could improve monitoring mechanisms to increase clinical ability to predict recurrence of disease.

Another intriguing component of the case was the relapse in adulthood at 20 years of age. There is a relative paucity of data regarding neuroblastoma in adolescent and young adult populations largely driven by the skewed age distribution of the disease in infancy and early childhood. Adolescents and young adults make up less than 5% of all neuroblastoma cases.[15] Studies of tumors in these older patients demonstrate significantly lower rates of N-MYC amplification and catecholamine elevation and higher rates of ATRX mutations, suggesting alternative cancer biology.[16]The described patient's N-MYC nonamplified status and normal catecholamine levels were consistent with the general patterns of neuroblastoma in adolescents and young adults; however, she was negative for ATRX mutations. Further highlighting an intrinsic difference of neuroblastoma in these older populations is the poorer health outcomes in adolescents who have decreased event-free and overall survival for all stages of neuroblastoma as well as a more indolent, protracted course.[15-17] This patient did well from an oncologic perspective on high-risk, aggressive therapy with 23 months of event-free-survival until she unfortunately passed prematurely due to complications from comorbid conditions. At the same time, her apparent positive response to therapy may represent the more indolent nature of neuroblastoma in older populations as long-term follow-up was not possible. Further research into tumor biology and characteristics is needed to better elucidate and guide treatment of adolescents and young adults with neuroblastoma

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