BRAF Mutation in Neuroblastoma: A Case Report of a Rare Finding

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Abstract

Neuroblastoma is the most common extracranial solid tumor in children. Approximately half of the patients with Stage MS disease have tumor regression, but 10-15% will have progression of disease. *BRAF* mutations are common in some cancers, such as melanoma and pediatric astrocytoma, but are rare in pediatric extracranial solid tumors, including neuroblastoma. Here we report the case of an infant with Stage MS neuroblastoma with a rare *BRAF* V600E mutation and subsequent progression to Stage M disease.

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Abbreviations key:

ALK; anaplastic lymphoma kinase

HVA; homovanillic acid

INRG; International Neuroblastoma Risk Group

LOH; loss of heterozygosity

MIBG; meta-iodobenzylguanidine

VMA; vanillylmandelic acid

Abstract

Neuroblastoma is the most common extracranial solid tumor in children. Approximately half of the patients with Stage MS disease have tumor regression, but 10-15% will have progression of disease. *BRAF*mutations are common in some cancers, such as melanoma and pediatric astrocytoma, but are rare in pediatric extracranial solid tumors, including neuroblastoma. Here we report the case of an infant with Stage MS neuroblastoma with a rare *BRAF* V600E mutation and subsequent progression to Stage M disease.

Case Report

A 5 month old female with no significant past medical history presented with fever and tachycardia and was found to have Escherichia coli bacteremia. Imaging evaluation for source of bacteremia revealed a right-sided adrenal mass and liver lesions (Fig. 1A). Homovanillic acid (HVA) was mildly elevated to 34.1, while vanillylmandelic acid (VMA) was increased to 82.2. She underwent right adrenalectomy and biopsy of liver lesions. Pathology of the adrenal mass was consistent with poorly differentiated neuroblastoma with favorable histology, and liver biopsy specimen revealed metastatic neuroblastoma. Further workup revealed minimal bone marrow involvement (Fig. 1B). Given confinement of disease to the adrenal gland, liver, and bone marrow, and patient's age, she was diagnosed with Stage MS neuroblastoma and was managed with observation alone. Approximately six months after her initial diagnosis, routine follow-up imaging revealed a new left adrenal mass and new disease bilaterally in the pelvis and in the proximal femurs (Fig. 2A). Bone marrow aspirates showed increased bone marrow disease on the left side (5%, previously <1%) (Fig. 2B). Liver lesions remained stable. HVA and VMA were elevated at 59.6 and 90.6, respectively, and the Curie score was 7. Molecular genetic testing was performed, which revealed *BRAF V600E* mutation and loss of heterozygosity (LOH) at 1p and copy number gain at 17q. She was treated with 6 cycles of intermediate risk therapy per Children's Oncology Group, ANBL0531. Her end of therapy disease evaluation showed improved to stable liver lesions, resolution of the left adrenal mass and negative bilateral bone marrows. VMA and HVA were no longer elevated, and MIBG scan had Curie score of 0. She is currently fifteen months out from therapy without evidence of recurrence.

Discussion

Neuroblastoma is the most common extracranial solid tumor in children and presents almost exclusively in childhood [1]. Neuroblastoma accounts for 12-15% of all childhood cancer-related deaths. The median age at diagnosis is about 18 months with nearly all cases being diagnosed by 10 years of age. Disease prognosis is variable, with survival ranging from 80-90% in children with very low and intermediate risk tumors to less than 50% in children diagnosed with high risk tumors [2]. A unique subset of neuroblastoma patients diagnosed in infancy may experience spontaneous tumor regression, and this group of patients is categorized as Stage MS according to the International Neuroblastoma Risk Group (INRG) Staging System. Diagnostic criteria for MS disease includes age less than 18 months at the time of diagnosis and metastatic disease limited to liver, skin and/or bone marrow (<10%) [3]. Many children with MS disease will have tumor regression, but approximately 10-15% of them will experience disease progression, usually in the liver or bone [4].

Although the pathogenesis of neuroblastoma is poorly understood, multiple genetic mutations have been found to occur frequently in neuroblastoma. Amplification of the *MYCN* gene, a transcription factor involved in cell proliferation and apoptosis, is the most common mutation in patients with poor prognosis [5]. Other chromosomal changes that have been linked to poor prognosis in neuroblastoma include deletions of 1p and 11q and gain of 17q. Segmental chromosome abnormalities such as these are more common in high risk neuroblastoma, while whole chromosomal gains are frequently found in low risk disease [6, 7]. The most frequently mutated gene in primary neuroblastoma is the anaplastic lymphoma kinase (*ALK*) gene, which is present in nearly all cases of familial neuroblastoma and in 7-10% of sporadic cases [8].

The *BRAF* V600E mutation is a known neoplastic producing mutation. This mutation is a hyper-activating missense mutation in codon 600 of exon 15 of the *BRAF* gene that allows BRAF to function in a Ras dispensable manner [9, 10]. It was previously reported that*BRAF* mutations are extremely rare in pediatric solid tumors and were not thought to play a role in the development of these neoplasms [11]. However, recent studies have identified *BRAF* mutations in the pathogenesis of neuroblastoma. In one study using Sequenom-based genetic profiling of pediatric solid tumors, investigators found that the *BRAF* V600E mutation was present in 1 out of 192 neuroblastoma cases, revealing its occurrence in less than 1% of cases. An alternate*BRAF* F595L mutation was discovered in another neuroblastoma sample. *BRAF* mutations were identified in 1.7% of embryonal rhabdomyosarcoma samples and 1.3% of Ewing sarcomas. The patient linked to the neuroblastoma sample with *BRAF* V600E mutation in this study was alive at the time of the review, while the child with the reported F595L mutation died of disease. Furthermore, the patient with embryonal rhabdomyosarcoma with *BRAF* V600E mutation also died of disease [12]. These findings suggest *BRAF* mutations may play an oncogenic role in a small group of pediatric sarcomas and neuroblastomas.

As molecular profiling of tumors has evolved, cancer treatments have followed suit. BRAF inhibitors have been developed to target tumors harboring *BRAF* gene mutations. Vemurafenib (Zelboraf) was one of the first mutant-specific BRAF inhibitors specific for *BRAF* V600E mutations. Other BRAF inhibitors are now available, such as dabrafenib (Tafinlar), and encorafenib (Braftovi) [13]. Shahid et al reported on the use of dabrafenib with and without trametinib, a commonly used MEK inhibitor, in two pediatric patients with *BRAF* -mutated high risk neuroblastoma. In both cases, these therapeutic agents were used in conjunction with conventional high risk therapy. The authors concluded that this targeted therapy was compatible with conventional high risk neuroblastoma therapy and yielded minimal additional toxicities [14]. For the patient in the current report, BRAF inhibition was reserved for the treatment of relapsed disease.

In conclusion, we present the rare case of an infant with Stage MS neuroblastoma with *BRAF* V600E mutation, which has been reported to occur in less than 1% of neuroblastoma cases. Furthermore, the patient progressed from Stage MS to Stage M disease, a phenomenon that occurs in only 10-15% of patients diagnosed with MS disease. This case offers further evidence for *BRAF* mutations as an oncogenic driver in some pediatric solid tumors, and highlights the importance of tumor sequencing for tumors that do not respond to standard of care therapies.

Figure legends

Fig 1: CT and MIBG scans and bone marrow aspirates at presentation. (**A**) CT scan demonstrating right adrenal mass (*open arrow, left panel*) with MIBG avidity (*closed arrow, right panel*). (**B**) Immunohistochemistry of right (*left panel*) and left (*right panel*) iliac bone marrow aspirates demonstrating large atypical cells (*star*) and clumps of atypical cells *(star*), consistent with neuroblastoma constituting less than 10% of the specimen. Scale bars represent 10 µm.

Fig 2: MIBG scan and bone marrow aspirates at relapse.(**A**) MIBG scan showing left adrenal mass (*open arrows*) and bilateral pelvic and femur bony disease (*closed arrows*). (**B**) Bilateral right (*left panel*) and left (*right panel*) iliac bone marrow aspirates with large atypical cells*(star*) consistent with neuroblastoma. Scale bars represent 10 µm.

Disclosures

The authors have nothing to disclose.

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