BRAF Mutation in Neuroblastoma: A Rare Finding

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Title: *BRAF*Mutation in Neuroblastoma: A Rare Finding

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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

To the Editor:

We report the rare finding of a MS neuroblastoma harboring a mutation in*BRAF* . Briefly, a healthy 5 month old female presented with fever, tachycardia and Escherichia coli bacteremia. Imaging evaluation revealed a right-sided adrenal mass and liver lesions (Fig. 1A). Homovanillic acid (HVA) was mildly elevated to 34.1 mg/g creatinine and vanillylmandelic acid (VMA) was increased to 82.2 mg/g creatinine. She underwent right adrenalectomy, liver biopsy, and bone marrow aspirates. Pathology of the adrenal mass was consistent with poorly differentiated neuroblastoma with favorable histology, liver biopsy revealed metastatic neuroblastoma, and bone marrow aspirates revealed minimal marrow involvement (Fig. 1B). She was diagnosed with Stage MS neuroblastoma and was managed with observation. Six months later, follow-up imaging revealed a left adrenal mass, stable liver lesions, and bony disease (Fig. 2A). Bone marrow aspirates showed increased marrow disease (5%, previously <1%) (Fig. 2B), Curie score was 7 and HVA and VMA were elevated (59.6 and 90.6 mg/g creatinine, respectively). Molecular genetic testing 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. End of therapy disease evaluation showed resolution of the adrenal mass, decreased liver lesions, negative bone marrows, normal VMA and HVA, and Curie score of 0. She is currently fifteen months out from therapy without evidence of recurrence.

A unique subset of neuroblastoma patients diagnosed in infancy is categorized as Stage MS according to the International Neuroblastoma Risk Group (INRG) Staging System using diagnostic criteria that include age less than 18 months at the time of diagnosis and metastatic disease confined to liver, skin and/or bone marrow (<10%) [1]. Most children with MS disease will have spontaneous regression, but 10-15% will experience disease progression [2].

Multiple genetic mutations occur in neuroblastoma. Amplification of the*MYCN* gene is the most common mutation in patients with poor prognosis [3]. Segmental chromosome abnormalities including deletions of 1p and 11q and gain of 17q are common in high-risk neuroblastoma, while whole chromosomal gains are found in low-risk disease [4, 5]. The most frequently mutated gene is anaplastic lymphoma kinase (*ALK*) [6].

The *BRAF* V600E 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 [7, 8]. *BRAF* mutations are rare in pediatric solid tumors and are not thought to play a role in the development of these neoplasms [9]. Recent studies have identified *BRAF* mutations in neuroblastoma. Shahid et al. identified *BRAF* V600E mutations in two patients with high-risk neuroblastoma that developed vasoactive intestinal peptide (VIP)-induced diarrhea during induction therapy [10]. In another study, investigators found a *BRAF* V600E mutation to be present in 1 of 192 neuroblastoma cases, revealing its occurrence in less than 1% of cases [11]. 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 [11]. These findings suggest *BRAF* mutations may play an oncogenic role in a small group of neuroblastomas pediatric sarcomas.

BRAF inhibitors have been developed to target tumors harboring*BRAF* mutations. Vemurafenib was one of the first inhibitors specific for *BRAF* V600E mutations. Other BRAF inhibitors are now available [12]. Shahid et al. combined dabrafenib with trametinib, a MEK inhibitor, as an adjunct to conventional high-risk therapy to treat VIP-induced diarrhea in two children with *BRAF* V600E mutations. They concluded that this targeted therapy was compatible with conventional high-risk neuroblastoma therapy and yielded minimal additional toxicities [10]. For the patient in the current report, BRAF inhibition was reserved for the treatment of relapsed disease.

We present a case of an infant with Stage MS neuroblastoma with*BRAF* V600E mutation, which, to our knowledge has not been reported previously in the literature. 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 oncogenic drivers in some pediatric tumors, and highlights the importance of sequencing for tumors that do not respond to standard therapies.

Fig 1: CT and MIBG scans and bone marrow aspirates at presentation. (**A**) CT scan demon-

strating 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.

The authors have nothing to disclose.

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