The melanotic neuroectodermal tumor of infancy (MNTI) is a rare neoplasm that primarily affects the maxilla of infants during their first year of life. Complete resection is the conventional treatment and recurrence rates vary from 10% to 60%. The recurrent tumors grow more aggressively and can invade other anatomic structures, such as the nasal cavity, the orbit, and the skull base. The aggressive behavior of MNTIs may require radical resection, which may not be possible in some cases because of its rapid and invading growth together with invasion of vital structures. In these situations, adjunct radiotherapy or chemotherapy has been used. However, as there are no conclusive data regarding the molecular profile of this tumor, currently there is no targeted therapy that may be used in the treatment of selected aggressive cases. On the basis of MNTI similarities with melanomas, such as derivation from the neural crest cells and presence of large melanin-containing cells, we hypothesized that MNTIs also may harbor the BRAFV600E oncogenic mutation. We show for the first time that this important pediatric tumor may harbor the oncogenic BRAFV600E mutation, providing the first insights to their personalized treatment.
pathologic comprehension of the tumor and new treatment options emerged from this finding.\textsuperscript{6,7}

On the basis of MNTI similarities with melanomas, such as derivation from the neural crest cells\textsuperscript{8} and presence of large melanin-containing cells, we hypothesized that MNTIs also may harbor the BRAF\textsuperscript{V600E} mutation.

**CASE SERIES**

We studied 3 cases of MNTI. Details of these cases are listed in Table 1. Clinical and histologic images of case 3 are shown in Fig 1. The local human investigations committee approved this study and formalin-fixed paraffin-embedded (FFPE) tumor samples were retrieved from the files of the university.

We retrieved 4 cases from the files; however, only 3 had enough material for DNA extraction and were included in the study. None of the 3 patients had any medical condition or has been submitted to any relevant medical intervention. The main sign reported by the parents was presence of an expansion in the anterior maxilla of the child. The 3 tumors were surgically excised and did not recur after a 5-year follow-up period. All 3 tumors presented the biphasic cell population formed by large melanin-pigmented epithelioid cells and small, round neuroblastlike cells.

Genomic DNA was extracted from FFPE tissue samples by using QIamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). To access the BRAF\textsuperscript{V600E} mutation, TaqMan Mutation Detection Assays (Life Technologies, Carlsbad, CA) and Sanger sequencing with primers forward 3' TCATAATGCTTGCTCTGATAGGA 5' and reverse 3' CCAAAAATTTAATCAGTGGAG 5', were performed. We detected and confirmed BRAF\textsuperscript{V600E} mutation in 1 sample (Fig 1), another was wild-type, and the third was inconclusive (Table 1). We repeated the third case reactions, but as it was decalcified, this might have affected DNA quality/integrity.

**DISCUSSION**

Despite being a benign tumor, MNTI affects very young children and may be potentially lethal. The aggressive behavior of MNTIs may require

![Figure 1](https://example.com/figure1.png)

**TABLE 1** Clinical and Molecular Data of the MNTI Cases Included in the Study

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>BRAF Mutation (Codon 600)</th>
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<tbody>
<tr>
<td>1</td>
<td>75 d</td>
<td>Girl</td>
<td>V600E</td>
</tr>
<tr>
<td>2</td>
<td>5 mo</td>
<td>Girl</td>
<td>Wild-type</td>
</tr>
<tr>
<td>3</td>
<td>12 mo</td>
<td>Boy</td>
<td>Inconclusive\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The assays were repeated twice; however, as the tumor had been decalcified, DNA integrity might have been affected and results were not straightforward.
radical resection, which may be not possible in some cases because of its rapid and invading growth together with invasion of vital structures. In these situations, adjunct radiotherapy or chemotherapy has been used. However, as there are no conclusive data regarding the molecular profile of this tumor, there is no targeted therapy that may be used in the treatment of selected aggressive cases.

Attempts to find molecular alterations linking MNTIs to other pediatric small cell tumors with neuroectodermal features (ie, neuroblastoma, Ewing sarcoma/peripheral primitive neuroectodermal tumor, and desmoplastic small round cell tumor) have not succeeded. Based on the finding that the oncogenic BRAF mutation is an early and fundamental event in a group of melanocytic neoplasms, we searched for the most common oncogenic BRAF alteration, BRAFV600E, in MNTI. We show that some of the MNTIs are prone to harbor the BRAFV600E mutation (Table 1) and identify a possible new MNTI molecular target, especially to treat cases not amenable to surgical management or to minimize facial mutilation. It is interestingly that the case with the BRAF mutation is from a 75-day-old infant.

Small molecule drugs targeting the BRAF or MEK kinases have been approved for the treatment of BRAF-mutant melanoma, including the immune checkpoint inhibitor ipilimumab, the selective type 1 BRAF inhibitors vemurafenib and dabrafenib, and the MEK inhibitor trametinib. Treatment with these drugs has proven effective in decreasing tumor size, but development of resistance is pointed out as the major challenge to the success of melanoma treatment. Such drug resistance may be triggered by genomic instability leading to tumor heterogeneity, which is inherent of cancer progression. In this sense, as MNTI is a benign tumor, we hypothesize that the use of BRAF-targeted therapies has a higher chance of being successful and represent potential alternative treatments for aggressive tumors harboring BRAF mutations.

Our finding is important in terms of understanding MNTI tumor biology; however, caution must be exerted when bringing our results from bench to the clinics. There are scarce reports of pediatric patients with BRAFV600E-mutant tumors successfully treated with vemurafenib. Although vemurafenib has been proven safe in melanoma clinical trials, there are important side effects of its treatment, varying from rash, arthralgia, and nausea, to cutaneous squamous cell carcinoma and liver function abnormalities.

CONCLUSIONS

We show for the first time that this important pediatric tumor may harbor the oncogenic BRAFV600E mutation, providing the first insights to their personalized treatment.

ABBRIVATIONS

FFPE: formalin-fixed paraffin-embedded
MNTI: melanotic neuroectodermal tumor of infancy

REFERENCES

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Carolina C. Gomes, Marina G. Diniz, Grazielle Helena F. de Menezes, Wagner H. Castro and Ricardo S. Gomez

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