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BRAF V600E Mutation in Two Distinct Meningeal Melanocytomas Associated With a Nevus of Ota

Introduction

Meningeal melanocytomas are rare tumors of the CNS that develop from melanocytes that are present in leptomeninges, with differing pigmented appearance. They generally occur in the posterior fossa and the spinal cord. This lesion may manifest at any age, but most patients are in the fifth decade of life.[1,2] Occasionally, these tumors appear in a complex neurocutaneous grouping with other melanocytic lesions. The nevus of Ota (oculodermal melanocytosis) is a blue hyperpigmented dermal lesion that affects the trigeminal dermatome. The association of a meningeal melanocytoma with an ipsilateral nevus of Ota is extremely rare; to our knowledge, only eight cases have been reported in the literature to date.[3,4] In these cases, the melanocytomas were located in the supratentorial area.

We present a patient with neurocutaneous melanosis showing a highly pigmented meningeal melanocytoma and a less pigmented meningeal melanocytoma in association with a meningeal melanocytosis and a congenital nevus of Ota. We have analyzed the histopathologic and molecular characteristics of these lesions. To our knowledge, this is the first report of melanocytomas with mutations in BRAF, PTEN, and NF2, genes that are involved in the melanomagenesis process.

Case Report

The patient, a 15-year-old boy, presented with a severe headache, nausea, and vomiting, symptoms consistent with increased intracranial pressure. The neurologic examination showed no other alterations. A physical examination revealed an oculodermal macula in the right frontoparietal area that was diagnosed as congenital nevus of Ota (Fig 1A). Magnetic resonance imaging revealed the presence of two lesions in the right temporal region. One lesion was large (Fig 1B, double asterisks), hyperintense in T1, and hypointense in T2. The other lesion was smaller (Fig 1B, single asterisk), isointense in T1, and hypointense in T2. The tumors were removed, as was the entire exposed dura. Macroscopically, the two lesions were identified as attached to the dura mater, corresponding to magnetic resonance imaging observations: a large tumor with a maximal diameter of 5.5 cm and brown in color (Fig 1C, double asterisks), and another, smaller tumor with a maximal diameter of 1.5 cm and pinkish in color (Fig 1C, single asterisk). The patient progressed favorably and showed no signs of recurrence after 3 years of follow-up.

Microscopically, the large tumor did not invade the surrounding structures; it was composed of large epithelioid cells organized in an organoid pattern. Cells were arranged in nests around blood vessels, separated by scarce stroma (Figs 2A and 2B). The cells had a well-delineated cytoplasm and round or ovoid nuclei with prominent nucleoli. A significant number of cells presented abundant cytoplas-
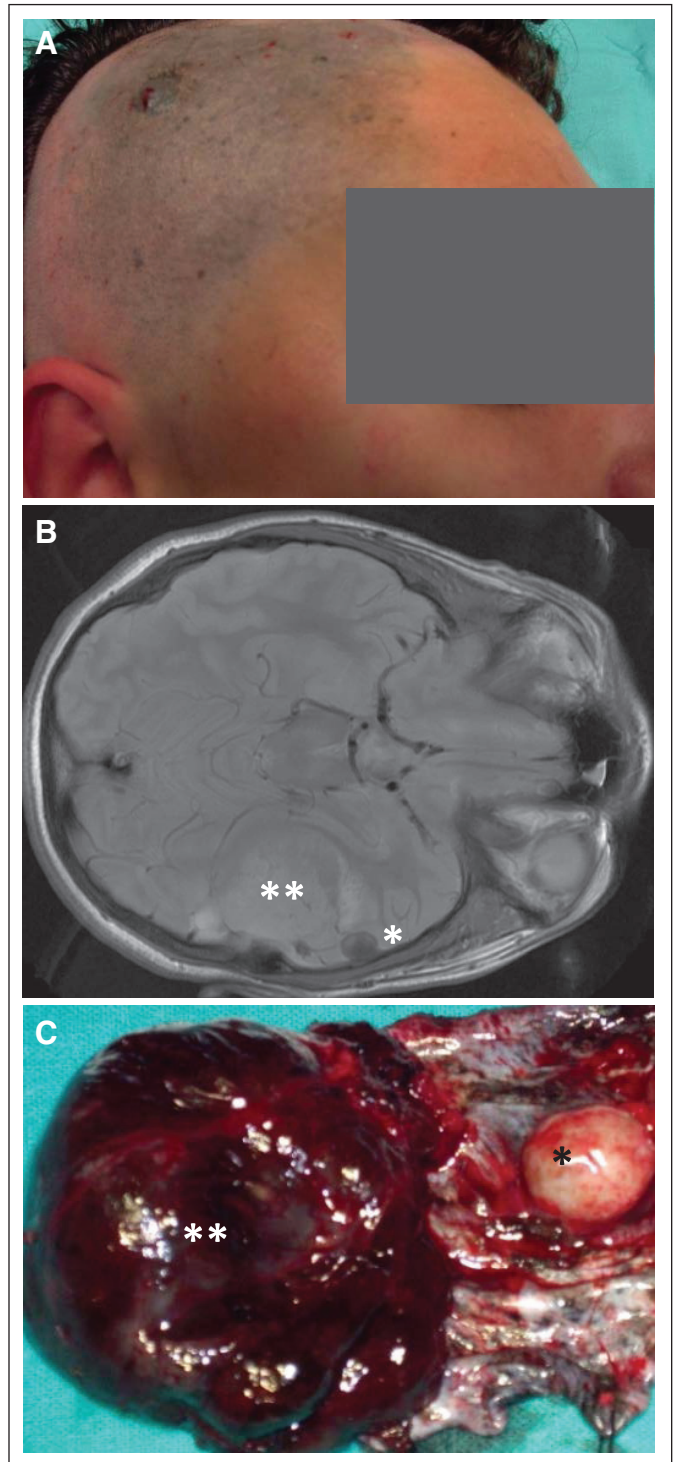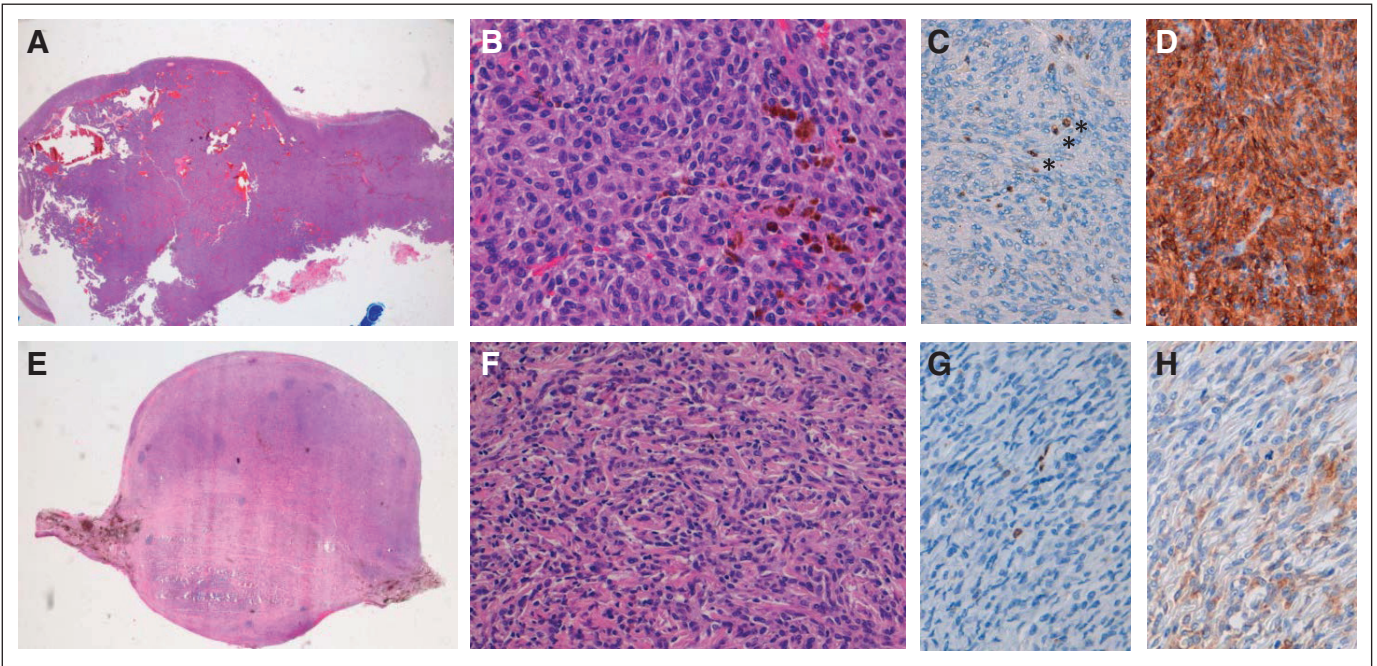

Fig 1.

Fig 2.

mic pigmented melanin granules. Isolated mitotic figures, a MIB-1 proliferation index of 3% (Fig 2C, asterisks), and no necrosis were observed. The immunohistochemical study showed strong positivity to vimentin, HMB-45, Melan-A (Fig 2D) and S-100 protein, and negativity to epithelial membrane antigen. The smaller tumor was composed of cells with a fusiform or epithelioid structure. The nuclei were irregular, and the stroma between cells showed abundant collagen (Figs 2E and 2F). Pigmented melanin granules were present in the cytoplasm of some cells. No necrosis, no mitosis, and a MIB-1 proliferation index of ≤ 1% (Fig 2G) were observed. The immunohistochemical study showed positivity to vimentin, HMB-45, Melan-A, and S-100 protein, and negativity to epithelial membrane antigen. Melan-A (Fig 2H), HMB-45, and S-100 were expressed in fewer cells than in the larger tumor. The histologic diagnosis of both tumors was consistent with meningeal melanocytoma; the larger tumor was con-

sidered to be highly pigmented (HPMM), and the smaller tumor as less pigmented (LPMM).

The nevus of Ota presented abundant pigmented fusiform cells in the dermis (Fig 3A), without mitosis and with a MIB-1 proliferation index of ≤ 1%. Meningeal melanocytosis in the dura and arachnoid showed an increase in melanocytic pigmentation (Fig 3B). No mitosis and a low MIB-1 proliferation index (≤ 1%) were observed.

In the molecular study, using multiplex ligation-dependent probe amplification (MLPA), we determined deletions in *PTEN* and *NF2*. The MLPA study used the MS-MLPA probe sets P105-C2 and PO44-B1 (MRC-Holland, Amsterdam, the Netherlands). The P105-C2 probemix contains probes for each exon of *PTEN*. The P044-B1 *NF2* probemix contains probes for each of the exons of *NF2*. In addition, two probes for the promotor region of *NF2* were included. For the mutational analysis, *BRAF* and *GNAQ* were amplified
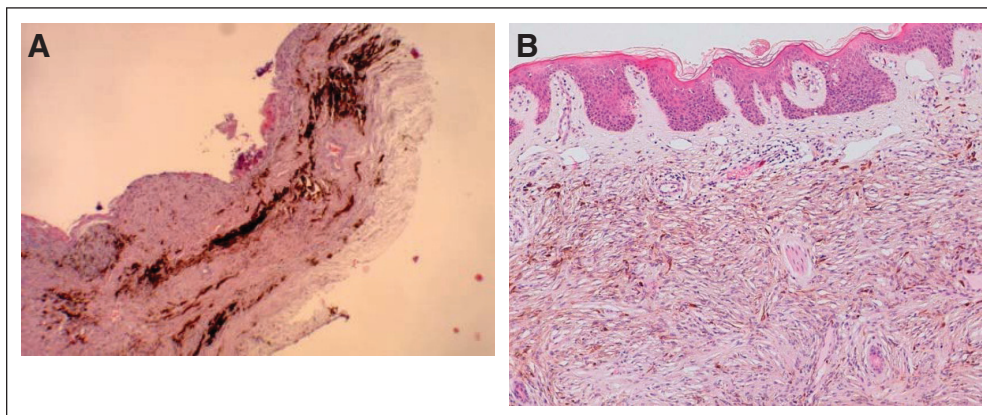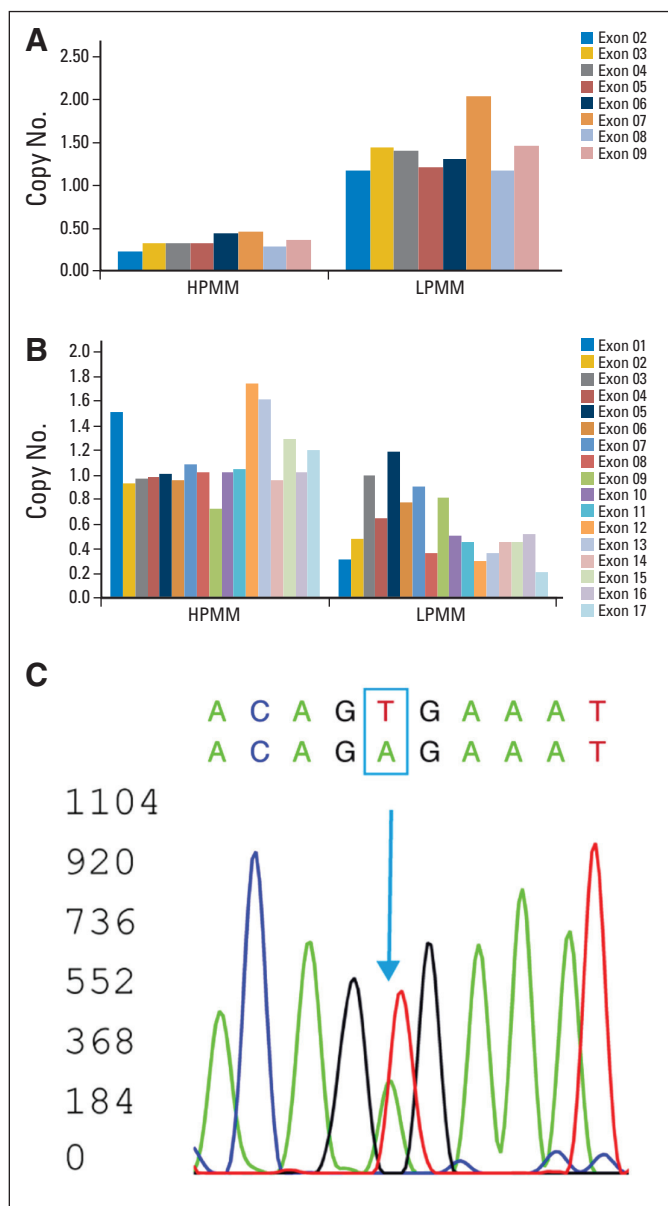

Fig 3.

Fig 4.

and may give rise to primary leptomeningeal pigmented tumors, a group of uncommon pathologic entities that includes meningeal melanocytoma, pigmented meningioma, melanotic schwannoma, melanoblastosis, and malignant melanoma.

Meningeal melanocytoma is an infrequent and benign pigmented neoplasm, although malignant transformation to melanoma can occur.[5] Meningeal melanocytosis, which represents an excess of benign melanocytic cells in the leptomeninges, is thought to be the precursor of intracranial melanocytomas.[1] However, the extremely rare association between ipsilateral melanocytoma and nevus of Ota has been regarded as an alteration in the melanocytes derived from the neural crest, probably in the trigeminal dermatome.[6,7] This association of lesions known as neurocutaneous melanosis constitutes a form of neurocristopathy.

The primary molecular engine that drives melanomagenesis is the activation of the extracellular regulated kinase pathway, mainly as a result of the oncogenic mutation of *BRAF* (V600E) or *NRAS*.[8] Moreover, and of interest, the concurrent mutation in *BRAF* and diminished expression of *PTEN* are common in melanomas.[9,10] Less common is the appearance of an altered *NF2* gene associated with melanomas, although recently it has been found that merlin protein, encoded by this gene, is a negative regulator of the growth of human melanoma cell lines.[11] Frequently, loss of function in the *NF2* gene results in neurofibromatosis type 2 and in the development of tumors of the central and peripheral nervous system, predominantly meningiomas, benign schwannomas, and ependymomas.[12,13] Interestingly, melanocytes and meningeal and Schwann cells are derived from the neural crest.[7,14]

The molecular characteristics of melanocytomas are largely unknown. Some studies have reported the presence of activating mutations in the *GNAQ* at codon 209 in 50% of primary leptomeningeal melanocytomas.[15] In our patient, none of the lesions that were examined had the *GNAQ* mutation. Nevertheless, to our knowledge, this is the first report describing a *BRAF* mutation in meningeal melanocytomas in association with either *PTEN* or *NF2* deletions. These alterations could be related to the presence of the tumors within a neurocutaneous melanosis syndrome or with their particular location in the supratentorial area.

The results point to the involvement of different signaling pathways in the tumorigenesis of meningeal melanocytomas. The finding of *BRAF* mutations in meningeal melanocytomas points to a potential initiating role of *BRAF* in transformation toward malignancy and could have therapeutic implications in these specific melanocytomas.

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by polymerase chain reaction, and the reaction products were separated and analyzed using the ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA) automated sequencer.

The HPMM showed a deletion in *PTEN* (exon 2 to exon 9) that was not found in the LPMM (Fig 4A). In contrast, an *NF2* deletion (principally exon 10 to exon 17) was found only in the LPMM (Fig 4B). These two genes were neither altered in the meningeal melanocytosis nor in the nevus of Ota. With respect to *BRAF*, only the meningeal melanocytomas presented a mutation that led to a substitution of valine by glutamic acid at position 600 (V600E) of the protein (Fig 4C). Finally, *GNAQ* was normal in all of the analyzed specimens.

Discussion

Melanocytes derive from the neural crest during early embryonic development. These cells are present in the leptomeninges of adults

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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