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Malignant Transformation and Leptomeningeal Melanomatosis in a Primary Meningeal Melanocytoma: A Case Report and Review of Literature

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Abstract

Meningeal melanocytomas of the central nervous system, although typically benign, rarely undergo malignant transformations. A 46-year-old man presented with headache and nausea 4 years after gross total resection of a craniovertebral junction meningeal melanocytoma at another hospital. The initial clinical course was previously reported.[1)] Computed tomography revealed the presence of multiple intracranial mass lesions. Furthermore, magnetic resonance imaging showed multiple intracranial lesions and meningeal dissemination. A biopsy was performed for a circumflex lesion located in the right frontal lobe. Pathological examination showed anaplastic changes and a Ki-67 index of 33%. Based on the pleomorphic changes and high mitotic activity, the patient was diagnosed with primary cerebral malignant melanoma. The patient received four cycles of nivolumab (80 mg) and ipilimumab (165 mg), followed by whole-brain radiotherapy (37.5 Gy). However, the disease progressed after the third cycle. Genome analysis revealed *GNAQ* Q209P and *SF3B1* R625C mutations, but no treatments related to these gene mutations were available. Despite the seven cycles of nivolumab therapy, the patient eventually passed away 9 months after surgery. This case was a rare example of malignant transformation and leptomeningeal melanomatosis in a meningeal melanocytoma. It highlights the importance of careful follow up after gross total resection. Identification of molecular alterations can lead to better detection of melanocytic melanomas with poor prognosis and high risk of recurrence and metastasis. It can also facilitate the development of novel therapeutic options for these patients.

Keywords: malignant transformation, meningeal melanocytoma, melanoma

Introduction

Meningeal melanocytomas, a rare variant of melanoma that accounts for <0.1% of all brain tumors, are characterized by their benign nature and potential for cure through complete surgical excision.[2)] However, meningeal melanocytomas rarely undergo malignant transformation or exhibit a metastatic behavior. To date, the incidence of malignant transformation and the ideal treatment approach for meningeal melanocytomas remain unclear. We herein present a case of malignant transformation and leptomeningeal melanomatosis in a craniovertebral junction (CVJ) meningeal melanocytoma and review relevant literature.

Case Report

History and examination

A 46-year-old man underwent gross total resection (GTR) for a CVJ meningeal melanocytoma at another hospital 4 years ago. The initial clinical course was previously reported.[1)] He presented to our hospital with acute severe

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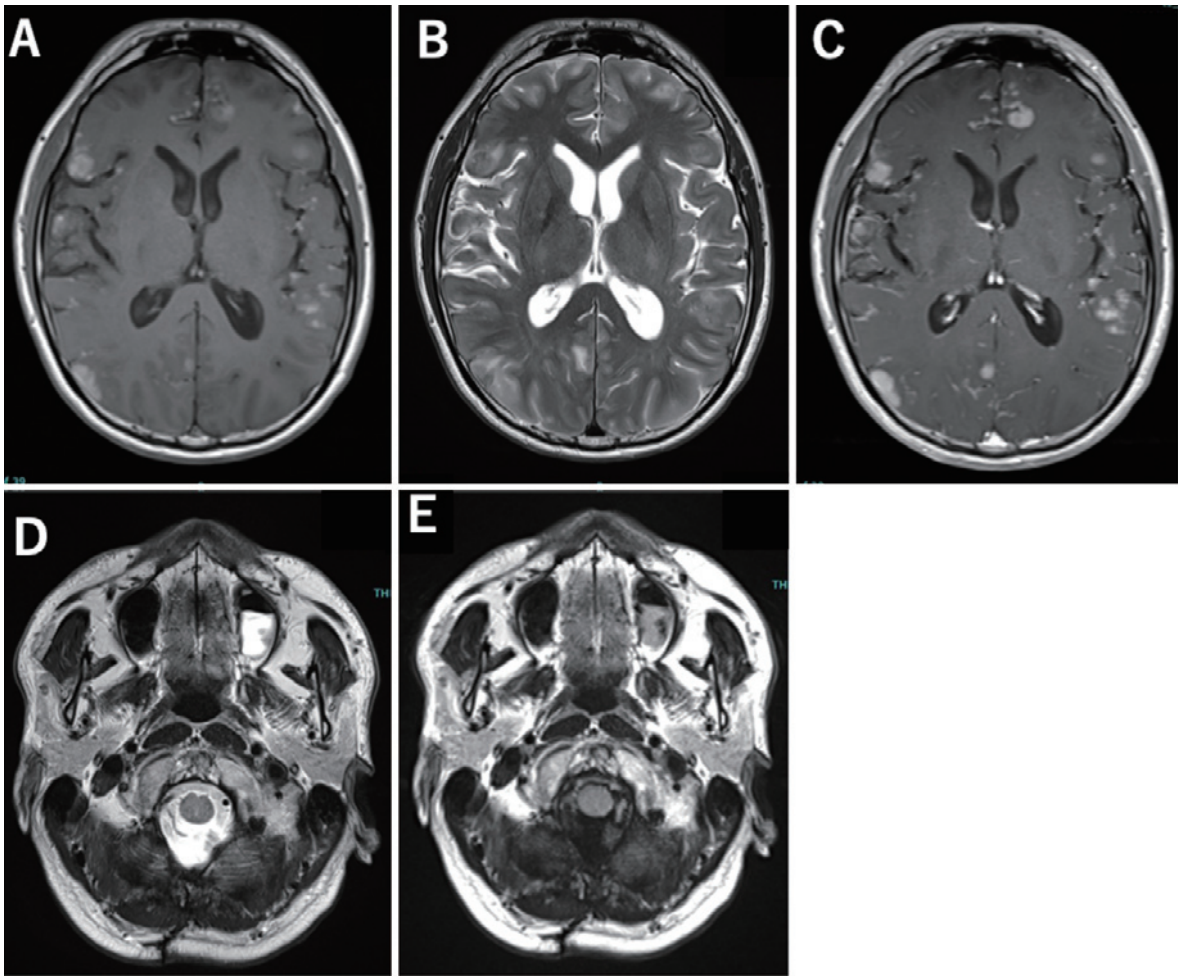

Fig. 1 MRI showing multiple lesions and meningeal dissemination. The lesions were hyperintense on axial T1-weighted images (A) and hypointense on axial T2-weighted images (B). (C) Contrast-enhanced T1-weighted image showing no obvious enhancement. (D, E) Axial T2-weighted and gadolinium-enhanced T1-weighted images showing no evidence of recurrence at the site of previous surgery.

headache and nausea. He was then referred to our department after computed tomography revealed multiple intracranial mass lesions. Magnetic resonance imaging (MRI) revealed multiple intracranial lesions and meningeal dissemination, exhibiting hyperintensity on T1-weighted images, hypointensity on T2-weighted images, and no enhancement following gadolinium administration (Fig. 1A-C). Furthermore, MRI showed no evidence of recurrence at the initial surgical site (Fig. 1D, E). A biopsy was performed for a circumflex lesion in the right frontal lobe (Fig. 2).

Pathological findings

Histopathological analysis revealed that the tumor cells were significantly pleomorphic with abundant eosinophilic cytoplasm. Most of the tumor cells contained melanin. The nuclei were irregular in shape and had prominent nucleoli. A high mitotic rate of 15 per 10 HPF was recorded. Necrosis and hemorrhage were also observed. Immunohistochemical studies were positive for S-100, human melanoma black-45. The Ki-67 labeling index was approximately 33%, compared with 4% in the initial pathology (Fig. 3). Based on these findings, the patient was diagnosed with melanoma. There was no evidence of metastases outside the central nervous system.

Postoperative course

Two weeks after biopsy, the patient received four cycles of nivolumab (80 mg) and ipilimumab (165 mg). Whole-brain radiation therapy was administered, with a planned dose of 37.5 Gy in 15 fractions. However, disease progression occurred after the third treatment cycle. FoundationOne CDx (F1CDx) (Foundation Medicine, Inc., Cambridge, MA, USA) genetic analysis revealed alternations in the guanine nucleotide-binding protein G subunit alpha q (*GNAQ*) Q209P and *SF3B1* R625C genes, but no anticancer drugs related to these mutations were available. The F1CDx test also designed the tumor as microsatellite-stable and revealed an intermediate tumor mutation bur-

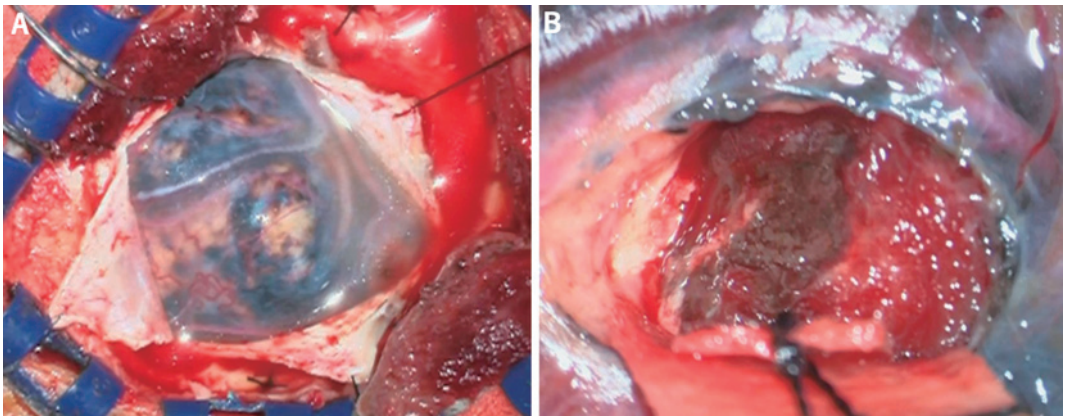

Fig. 2 Intraoperative findings. (A) Melanin pigmentation can be observed on the cerebral surface. (B) A blackish-gray tumor was identified at the time of central removal, and a biopsy was performed.

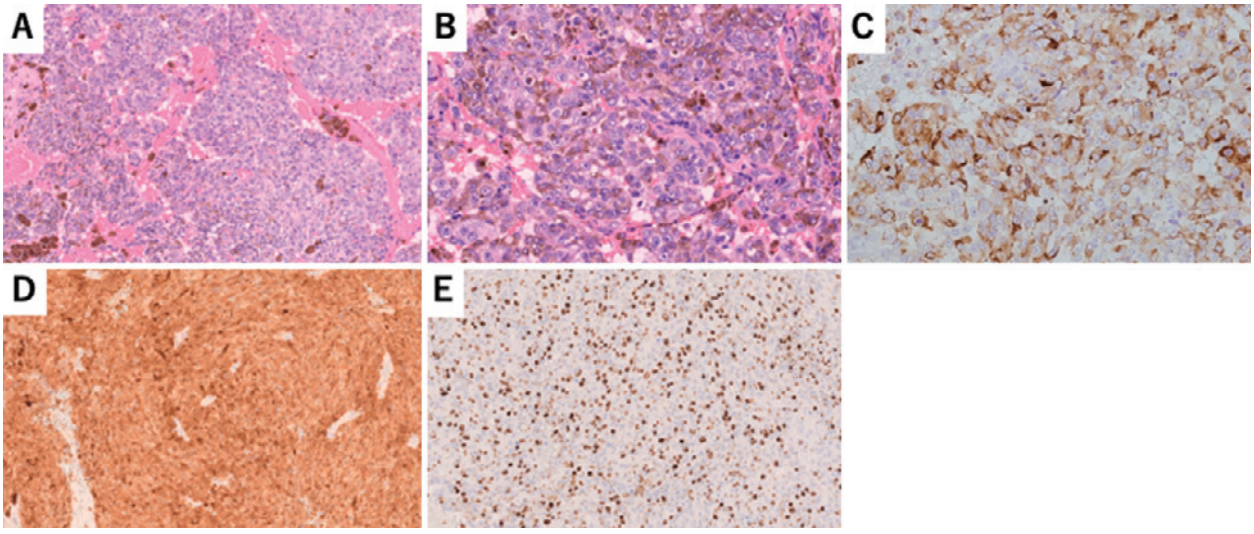

Fig. 3 Malignant transformation in meningeal melanocytoma; histopathological and immunohistochemical findings. (A) Proliferation of large, severely dysplastic cells with prominent nucleoli. Some of the cells are spindle-shaped and prominently pleomorphic. Most of the tumor cells contain melanin (hematoxylin and eosin staining, 100×). (B) Pleomorphic tumor cells and numerous multinucleated cells (hematoxylin and eosin staining, 400×). (C) Most tumor cells react with HMB-45. (D) S-100 positive of tumor cells. (E) High Ki-67 labeling index (33%).

den of 9 mutations per megabase. Despite the seven cycles of nivolumab (240 mg), the disease progressed, and the patient eventually passed away 9 months after surgery.

Discussion

Meningeal melanocytomas are rare and typically benign neoplasms that arise from neuroectodermal melanocytes derived from the neural crest.[3] First reported by Limas and Tio in 1972, melanocytomas are derived from leptomeningeal melanocytes, not from meningothelial cells.[4] Meckel's cave and the cerebellopontine angle are the most common locations of melanocytomas.[5]

Malignant transformation

Meningeal melanocytoma rarely undergo malignant transformation, with only nine cases reported in literature (Table 1).[6-13] Six of these cases, including our case, underwent GTR. This indicates the possibility of malignant transformation even after GTR. The time to malignant transformation ranges from 6 months to 5 years. Wang et al. reported that the initial Ki-67 index for melanocytomas was 1%-2%, which increased to 20% at the time of recurrence.[10] Roser et al. demonstrated a shorter disease course, with an increase in the Ki-67 index of 10% in 9 months.[7] It is unknown whether the cases with faster malignant transformation differed from those with longer disease courses. Although the factors associated with malignant transformation remain unknown, San-Miguel et al. recently re-

Table 1 Reported cases of meningeal melanocytoma with malignant transformation

Reference	Age (years)/ Sex	Location of primary tumor	Surgery of primary tumor	Primary pathology/Ki-67	Duration between the last confirmed benign pathology to the confirmed malignant transformation	Recurrence	Ki-67 of secondaty pathology	Adjuvant therapy	Outcome
Uozumi et al. (2003)[6]	49/M	Lt. frontal lobe	PR	Meningeal melanocytoma/0-1%	60 months	Lt. frontal lobe Leptomeningeal melanomatosis	5%-10%	-	Died 6 months after confirmed malignant transformation
Roser et al. (2004)[7]	37/F	Petroclival area	STR	Meningeal melanocytoma/5%	7 months	Petroclival area Leptomeningeal melanomatosis	25%	WBRT (40.8 Gy)/ TMZ 200 mg/m^2	Died 4 months after confirmed malignant transformation
Wang et al. (2008)[8]	57/M	An intradural extramedullary lesion (L5-S1 level)	GTR	Meningeal melanocytoma/ NA	12 months	L5-S1 level Leptomeningeal melanomatosis distant metastases (liver, left 9th rib)	NA	RT (50 Gy)	Still alive 5 months after confirmed malignant transformation
Perrini et al. (2010)[9]	79/F	An intramedullary lesion (Th10-11 level)	GTR	Intermediate-grade meningeal melanocytoma/1-4%	24 months	Th11 level	15%	-	Still alive 6 months after confirmed malignant transformation
Wang et al. (2011)[10]	32/M	Rt. temporal lobe	GTR	Meningeal melanocytoma/1-2%	36 months	Rt. temporal lobe	20%	-	Still alive 12 months after confirmed malignant transformation
Gempt et al. (2011)[11]	71/F	Rt. frontal lobe	PR	Meningeal melanocytoma/2% melanoma/12%	-	Rt. frontal lobe Leptomeningeal melanomatosis	-	WBRT	Still alive 18 months after confirmed malignant transformation
Küsters-Vandevelde et al. (2017)[12]	43/F	Rt. parietal lobe	GTR	Intermediate-grade meningeal melanocytoma/5%	32 months	1st: Rt. frontal lobe 2nd: Rt.temporal lobe 3rd: Distant metastases (liver, pancreas) 4th: Rt.temporal lobe Leptomeningeal melanomatosis	10%	1st: RT 2nd: RS 3rd: TMZ 200 mg/m^2 4th: RS/Ipi	Died 31 months after confirmed malignant transformation
Deng et al. (2022)[13]	19/F	A dumbell-shaped lesion (C1-2 level)	GTR	Meningeal melanocytoma/1-2%	6 months	1st: C2 level 2nd: Intracranial multiple metastases Leptomeningeal melanomatosis	5%-10%	1st: Pemb+Bev+TMZ 2nd: CSI (30 Gy)/ Pemb+Bev+Ipi/ Intrathecal Ipi	Died 2months after the last chemotherapy
Our case	44/M	Craniovertebral Junction	GTR	Meningeal melanocytoma/4%	45 months	Intracranial multiple metastases Leptomeningeal melanomatosis	33%	WBRT (37.5 Gy)/ Niv+Ipi	Died 9 months after confirmed malignant transformation

Bev, bevacizumab; C, cervical vertebra; GTR, gross total resection; Ipi, ipilimumab; NA, not available; Niv, nivolumab; Pemb, pembrolizumab; PR, partial resection; RS, radiosurgery; RT, radiotherapy; S, sacral; STR, subtotal resection; Th, thoracic; TMZ, temozolomide; WBRT, whole-brain radiotherapy

ported that loss of heterozygosity for the *BRCA1* gene was associated with an increased proliferative index in the case of cerebellopontine angle meningeal melanocytoma that recurred thrice despite GTR.[14] Seven cases had leptomeningeal melanomatosis. Furthermore, five of the reported patients with malignant transformation eventually died, whereas four developed tumor progression. In some cases, the tumor can metastasize to other organs, including the liver, pancreas, and bones.[8,12]

Primary therapeutic approach

As previously discussed, malignant transformation and recurrence can occur despite GTR. Thus, previous studies have also demonstrated the role of adjuvant radiotherapy in these cases. Prasad et al. reported that a combination of GTR and radiotherapy led to very low recurrence rates, but the difference was not significant.[15] They also reported that GTR and CVJ or posterior fossa tumors were significantly associated with low recurrence rates. Ricchizzi et al. reported that the combination of GTR and adjuvant radiotherapy may be considered only for cases with high mitotic activity.[16] In the present case, because GTR was achieved and the Ki-67 index was low, it was appropriate to follow up the patient without radiotherapy.

Adjuvant therapy for malignant meningeal melanocytomas

Recurrence and malignant meningeal melanocytomas poorly respond to adjuvant therapy and have a poor prognosis. Chemotherapeutic and immunotherapeutic agents, including temozolomide,[17] cisplatin-fotemustine,[14] methotrexate,[18] nivolumab,[5] ipilimumab,[12] and pembrolizumab-bevacizumab-ipilimumab,[13] have previously been used with radiotherapy. However, tumor progression was observed in all but one patient. In our case, nivolumab and ipilimumab were administered in combination with radiotherapy, but the patient did not respond.

Molecular features of meningeal melanocytomas

Several genetic mutations, including *GNAQ*, *GNA11*, *BRAF*, and *NRAS*, have recently been identified in meningeal melanocytomas.[15,19,20] The molecular profile of primary leptomeningeal melanocytic neoplasms differs from that of cutaneous melanomas and is more similar to that of uveal melanomas (UMs) and blue nevi.[21] This indicates that *GNAQ* and *GNA11* are typically mutated in leptomeningeal melanocytic neoplasms, although *BRAF* and the *TERT* promoter mutations are uncommon. A previously published series showed that *GNAQ* mutations are thought to be present in 39% of melanocytomas and 17% of primary leptomeningeal melanomas, whereas *GNA11* mutations are thought to be present in 17% of melanocytomas and 19% of primary leptomeningeal melanomas.[22] Thus, *GNAQ* and *GNA11* have been identified as promising therapeutic targets. These genes cause constitutive activation of the MAPK and PI3K/AKT pathways, leading to the use of downstream targeted therapies against effector proteins, including MEK and AKT. Selumetinib, an oral selective MEK1/2 inhibitor, was compared with temozolomide and dacarbazine chemotherapy, but it exhibited limited clinical activity (objective response rates of 14% and 3%, respectively). Trametinib, an MEK inhibitor, was tested alone and in combination with the AKT inhibitor, GSK2141795.[23] The objective response rates for trametinib-alone (n = 18) and combination (n = 21) groups were 5.5% and 4.8%, respectively, suggesting that the combination did not improve clinical outcomes. The median progression-free survival was 3.6 months for both groups. Existing anticancer drugs and novel targeted therapies based on genetic mutations have not proven to be effective, and there is an urgent need for newer treatments.

In our case, we were also able to find a mutation in *SF3B1*. *SF3B1* is the largest subunit of the *SF3B* complex promoting efficient mRNA splicing.[24] Previous studies reported that the *GNAQ*, *GNA11*, and *NRAS* genes contribute to the early stages of carcinogenesis, whereas *SF3B1* mutations occur later in the oncogenic process.[25] These mutations impact hotspot codons, which are linked to certain cancer types. For instance, codon 700 alterations are typically observed in chronic lymphocytic leukemia and myelodysplastic syndromes, but the involvement of codon 625 in UMs is substantially more common.[25,26] *SF3B1* codon 625 mutations can be found in 20% of UMs.[27] Griewank et al. suggested that *SF3B1*-mutant tumors should be considered as intermediate-risk tumors owing to their potential for metastasis.[28] Melanie et al. reported that all patients with the *SF3B1* mutation displayed aggressive behaviors and leptomeningeal seeding immediately after diagnosis despite one case being identified as melanocytoma.[21] To date, it remains unclear how this mutation may affect the course and prognosis of the disease. However, as more unique therapies emerge, knowledge of the mutational status of meningeal melanoma is necessary. Splicing modulators are becoming more popular because of the role of *SF3B1* in splicing. Furthermore, protein arginine methyltransferase 5 inhibitors and nonsense-mediated mRNA degradation inhibitors may be effective against *SF3B1* mutations.[29,30]

In summary, we demonstrated the first case of *GNAQ* and *SF3B1* double mutation that has malignant transformation and leptomeningeal melanomatosis in CVJ meningeal melanocytoma. A careful follow up after GTR is crucial, and knowledge of the mutational status of meningeal melanoma like *GNAQ* and *SF3B1* is necessary to understand molecular features and to consider the treatment for individual cases.

Informed Consent

The patient provided written informed consent.

Conflicts of Interest Disclosure

The authors have no conflicts of interest to report regarding the materials, methods, and findings of this study.

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