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A rare case of leptomeningeal carcinomatosis in a patient with uveal melanoma: case report and review of literature

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Abstract

Uveal melanoma is a rare subtype of melanoma, accounting for only 3–5% of all melanoma cases in the USA. Although fewer than 4% of uveal melanoma patients present with metastasis at diagnosis, approximately half will develop metastasis, more than 90% of which disseminate to the liver. Infrequently, a number of malignancies can lead to leptomeningeal metastases, a devastating and terminal complication. In this case report, we present an exceedingly rare case of a patient with uveal melanoma who developed leptomeningeal carcinomatosis as the sole site of metastasis. After conventional methods to diagnose leptomeningeal carcinomatosis fell short, a diagnosis was confirmed on the basis of identification and genomic analysis of melanoma circulating tumor cells in the cerebrospinal fluid.

Keywords

circulating tumor cells; leptomeningeal carcinomatosis; metastasis; uveal melanoma

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Conflicts of interest

There are no conflicts of interest.

Introduction

Uveal melanoma is a rare subtype of melanoma that can arise from melanocytes of the uveal tract, representing ~ 3–5% of all melanoma cases in the USA [1]. Uveal melanoma is divided into distinct anatomic subtypes: anterior (iris) and posterior (ciliary body and choroid) uveal melanoma [2]. The individual subtypes are associated with differences in prognosis. Although fewer than 4% of uveal melanoma patients present with detectable metastasis at diagnosis, an analysis of 8033 uveal melanoma patients showed the rate of metastasis at 5 and 10 years to be 4 and 7% for iris melanoma, 19 and 33% for ciliary body melanoma, and 15 and 25% for choroidal melanoma [3,4]. Patients typically present with visual symptoms and, unlike many other tumor types, uveal melanoma can be frequently diagnosed through examination without the need for histopathological analysis [5]. The prognosis for uveal melanoma is typically good, with a 5-year survival rate of 81.6% [1]. However, once the tumor has metastasized, the median overall survival (OS) is only 4–15 months [6]. Uveal melanoma spreads hematogenously, and ~50% of patients will develop metastatic disease over a median duration of 5 years [5]. Previous work has shown that both uveal melanoma and primary leptomeningeal melanocytic neoplasms frequently harbor activating mutations in the G-protein coding genes, *GNAQ* and *GNAI1*, which behave in a manner similar to activating RAS mutations [7–10]. More recently, a study has shown that uveal melanomas and leptomeningeal melanocytic neoplasms also share mutations in *SF3B1*, a mediator of mRNA splicing, and *EIF1A*, a component of the translation machinery [8]. However, despite the molecular similarities, geographical proximity, and the presence of a neural pathway into the brain through the optic nerve/tract, the metastatic spread of uveal melanoma seldom results in leptomeningeal carcinomatosis (leptomeningeal metastasis; LMM) and metastases instead seed to the liver – which is observed in more than 90% of patients [11]. A recent retrospective analysis of 2365 uveal melanoma cases reported central nervous system (CNS) metastasis to occur in ~ 0.7% of cases, and none of these showed dissemination to the leptomeninges [12]. Here, we present a rare case of a patient with uveal melanoma with leptomeningeal carcinomatosis as the sole site of metastasis whose diagnosis was made on the basis of a molecular analysis of the circulating tumor cells (CTCs) in the cerebrospinal fluid (CSF).

Leptomeningeal carcinomatosis

Leptomeningeal carcinomatosis is a disease in which the tumor cells spread to the CSF and the meninges (the membranes that line the CNS). It may also involve the invasion of the tumor into the parenchyma of the brain, spinal cord, and cranial or peripheral nerves [13]. LMM is an aggressive terminal complication in cancer patients, typically characterized with poor OS and debilitating symptoms. The OS of patients with untreated LMM is ~6–8 weeks [14]. Because of the rapid progression of the disease and difficulties in diagnosis, many cases of LMMs are diagnosed after death. Reports of the overall frequency of LMM have varied from 0.8 to 8%, and may be as high as 20% or more if including undiagnosed or asymptomatic cases [13,15]. Even at autopsy, evidence of LMM may be microscopic and not apparent during gross inspection.

Although any systemic cancer can seed the leptomeninges, the most common primary tumors to metastasize to the leptomeninges include breast cancer (12–35%), lung cancer (10–26%), melanoma (5–25%), leukemia, and lymphoma [13,15–19]. Not all leptomeningeal tumors arise as a result of metastatic disease at other sites. Primary leptomeningeal lymphomas, melanomas, and rhabdosarcomas have been reported previously [13,20–22]. To our knowledge, this is the first ever report of leptomeningeal carcinomatosis in a patient with primary uveal melanoma.

Leptomeningeal carcinomatosis typically arises at later stages of systemic disease, commonly detected years after initial diagnosis, coupled with relapse at other sites [13,23]. Leptomeningeal carcinomatosis patients typically present with symptoms of CNS dysfunction. In 40–60% of patients, the tumor causes an accumulation of CSF in the brain, leading to an increase intracranial pressure (hydrocephalus), a symptom that also marks a poor prognosis and makes treatment of LMM a challenge because of impaired CSF flow and the uneven distribution of injected drugs [14,24]. Patients may experience seizures, cognitive changes, headache, gait difficulty, and pain in the neck or back [13]. Radiation therapy (RT), delivered as external-beam RT or intrathecal RT, is currently the most effective way to reduce symptoms [25]. However, treatment of the entire neuroaxis with RT can result in significant adverse events for the patient; therefore, RT of symptomatic sites coupled with chemotherapy is a more favorable approach [13,25,26]. When the blood–brain barrier has been significantly disrupted, systemic chemotherapy can be beneficial; in other instances, intrathecal chemotherapy through a ventricular cannula with a subcutaneous reservoir (Ommaya reservoir) is utilized to deliver a higher concentration of the therapeutic agent directly at the tumor site for a superior effect [13]. One recent study reported intrathecal chemotherapy to improve survival and symptom control in patients with LMM from non-small-cell lung cancer, leading to a median OS of 3 months [24]. Although treatment outcomes for leukemia and lymphoma are exceptional, most patients with LMM from solid tumors (especially lung and melanoma) deteriorate rapidly irrespective of treatment [13]. With the help of the proper prophylactic treatments, the incidence of LMM has been reduced successfully in acute lymphoblastic leukemia from 66 to 2–10% [27,28]. The identification of the drivers of LMM in patients with melanoma or other solid tumors will hold a key to developing similarly efficacious treatments.

Case report

A 48-year-old woman was diagnosed with uveal melanoma in her right eye in 2013. The tumor was confined to the posterior uveal tract of her eye and was not in proximity to the optic nerve. Gene-expression analysis of a panel of 15 genes using DecisionDx-UM (Castle Biosciences Incorporated, Friendswood, Texas, USA) showed a molecular signature consistent with class 1A uveal melanoma associated with the lowest metastatic risk [29,30]. Intraocular pressure was normal. The patient was treated with ocular radiation and monthly intraocular bevacizumab [31,32]. She continued to receive monthly injections up until May 2015 and remained well.

In June 2015, the patient presented with symptoms of painless left leg weakness, some gait instability, frequent falls, and mild headaches. On examination, she had an atrophied and

blind right eye. Her neck was supple and she had no papilledema in the left eye. Her gait was complex and she had difficulty moving both her legs, with the right leg movement being worse. She had a subtle upper motor neuron pattern of weakness in her right leg and a lower motor weakness in her left leg, characterized by weakness of the iliopsoas and quadriceps. The patient was hyporeflexive throughout, but her reflexes were obtainable. An MRI of her brain and spine showed significant leptomeningeal enhancement of her brain and spine (Fig. 1) on a T1-weighted MRI with gadolinium. Importantly, her MRI brain showed enhancing tumor extending posteriorly from the right optic nerve into the right optic tract (Fig. 1b). The enhancement was diffuse and intense. No solid metastases were observed in her brain nor spine. A lumbar puncture showed an opening pressure of 19.4 cm of H₂O, an elevated white blood cell of 21/mm³, red blood cell of 1/mm³, an elevated protein of 138 mg/dl, and a low glucose of 43 mg/dl. The cytology was diagnostic for malignancy, showing intact cellularity consisting of small reactive lymphocytes admixed with macrophages. A few large atypical cells were observed.

Aware that LMM from uveal melanoma is exceedingly rare, we attempted to rule out other systemic causes of the leptomeningeal MRI enhancement, such as a systemic lymphoma or perhaps a systemic inflammatory disorder (e.g. sarcoidosis, etc.). Her examination and blood work were negative for systemic inflammatory disorders (erythrocyte sedimentation rate 3.0 mm/h, C-reactive protein 0.17 mg/dl) and serum angiotensin-converting enzyme was low (14 U/l). A PET-computed tomography of her body showed a right retrobulbar hypermetabolic mass with extraocular extension and no metastases elsewhere (and specifically none in the liver). A small meningeal biopsy was performed during the insertion of an Ommaya reservoir and showed atypical cells, but was nondiagnostic for neoplasia.

We performed another lumbar puncture and analyzed the cells using the CellSearch CTC test (Janssen Diagnostics, LLC, Raritan, New Jersey, USA) adopted for use in melanoma [33–39]. The test uses a ferrofluid-based capture technology, enriching for cells using antibodies targeting the CD146 antigen. Enriched cells are then stained and counted as circulating melanoma cells if the cells were intact, had a DAPI-positive nucleus, were positive for anti-high-molecular-weight melanoma-associated antigen (MEL-PE), and negative for both endothelial cell marker CD34 and leukocyte marker CD45. We found 136 CTCs per milliliter of CSF from lumbar puncture and no CTCs in her serum (Fig. 2, Table 1). Rather than perform another meningeal biopsy or brain biopsy, we next sought to determine whether the CSF CTCs had a *GNAQ* or *GNAI1* mutations, both commonly found in uveal melanomas [7]. DNA was isolated from CSF precipitate and sequenced with TruSight Tumor 26 panel (Illumina, San Diego, California, USA). Genes analyzed included *AKT1*, *ALK*, *APC*, *BRAF*, *CDH1*, *CTNNB1*, *EGFR*, *ERBB2*, *FBXW7*, *FGFR2*, *FOXL2*, *GNAQ*, *GNAS*, *KIT*, *KRAS*, *MAP2K1*, *MET*, *MSH6*, *NRAS*, *PDGFRA*, *PIK3CA*, *PTEN*, *SMAD4*, *SRC*, *STK11*, and *TP53*. The sequencing indicated a Q209P mutation in *GNAQ* at an allelic frequency of 4%. The analysis also found two additional nonsynonymous mutations: *MET*N373S and *TP53*P72R; however, these were polymorphic and in all likelihood are germline alterations without a well-defined clinical significance. As mentioned earlier, both uveal melanoma and primary melanocytic leptomeningeal neoplasms commonly harbor *GNAQ* Q209P mutations; therefore, it should be noted that, on a mutational basis, the possibility of co-occurrence of these two rare diseases cannot be

ruled out. However, given the clear extension of the enhancing tumor from the eye, and the fact that it is unilateral, unlike primary melanocytosis (which is usually symmetric), strongly supports the proposal that the tumor arose in the eye and migrated to the leptomeninges.

Intrathecal thiotepea was administered through the Ommaya reservoir. Unfortunately, the patient progressed neurologically in her legs and had further enhancement in her lumbosacral spine. Accordingly, she was treated with 2000 cGy in five fractions over 5 days to her lumbosacral spine. By July 2015, she had worsening headaches, nausea, vomiting, confusion, and bilateral arm weakness. An MRI showed increasing hydrocephalus with persistent enhancement and whole brain radiotherapy was administered to a total dose of 3000 cGy in 10 fractions. Intrathecal chemotherapy resumed. Since the placement of the Ommaya reservoir, three consecutive analyses of the CSF were carried out to analyze the numbers of CTCs, showing a decrease in the number of melanoma CTCs in the CSF over time (Table 1). The CSF from the Ommaya reservoir showed 76 melanoma CTCs 3 days after Ommaya placement, decreasing to 63 CTCs after 23 days and finally to 21 CTCs on day 125. The patient was stable until August 2015, during which time her corticosteroids were tapered and then discontinued. Accordingly, she was started on ipilimumab and received three cycles (3 mg/kg intravenously every 21 days). Unfortunately, this proved ineffective. The patient deteriorated further and then died in December 2015.

Discussion

This report highlights the opportunity to make a diagnosis with a molecular phenotype in a patient with leptomeningeal disease by examining the CTCs from the CSF. This was achieved when conventional methods, including an invasive meningeal biopsy, were unsuccessful. The CellSearch analysis identified the cells as melanoma cells, and then a focused mutational analysis was used to confirm the tumor cells' origin as uveal and to interrogate for therapeutically relevant targets. As no targeted agents were predicted to be useful (such as Braf or cKit inhibitors) because of the absence of therapeutically relevant mutations, we began immunotherapy with the anti-CTLA-4 antibody ipilimumab. It is possible that the therapy may not have been administered long enough to have an effect. We are expanding this approach to render a more rapid molecular diagnosis on patients with LMM to help direct treatment and monitor resistance to therapy. It should be noted that the CellSearch test is still in early development for the detection of melanoma CTCs and is currently only being used for research purposes. Additional testing is still required to determine the sensitivity, specificity, negative predictive values, and positive predictive values of the assay.

Uveal melanoma is the most common primary intraocular malignancy in adults, making up 85–95% of all ocular melanomas, but only accounts for a small fraction of all melanoma cases [1,5,40]. The molecular biology and pathogenesis of uveal melanoma are distinct from that of cutaneous melanoma. Although mutations in *BRAF*, *NRAS*, or *NF1* account for the majority of driver mutations in cutaneous melanomas, these are rarely detected in uveal tumors [41]. Instead, ~ 80% of uveal melanomas harbor activating mutations in *GNA11* or *GNAQ*, leading to constitutive signaling to the MAPK and phosphatidylinositol 3-kinase/Akt (PI3K/Akt) pathway [5,9,10,42]. Only recently has it been discovered that both

uveal melanomas and primary melanocytic leptomeningeal neoplasms share driving mutations in *GNAQ*, *GNA11*, *SF3B1*, and *EIF1A* [7,8]. Even so, reports of uveal melanoma leading to leptomeningeal carcinomatosis are almost unknown. Although there is a small possibility that the melanoma cells identified in the leptomeninges resulted from regional spread of the orbital recurrence, without clear evidence of tunneling of the tumor cells within the dural (optic nerve) sheath and contiguous spread into the suprasellar region, we believe that this manifestation can be classified as LMM. At this time, it is unclear what drives uveal melanoma to spread to the leptomeninges, but some of the shared molecular biology underlying both uveal melanoma and primary leptomeningeal neoplasms suggests a targetable common signaling axis: the MAPK pathway. A number of clinical trials have been initiated to investigate the use of MEK inhibitors in uveal melanoma; however, to date, the results have been disappointing (NCT01143402) [5,43,44]. It is possible that this small subset of uveal melanomas that preferentially metastasize to the leptomeninges may be more sensitive to therapies targeting the MAPK or AKT pathways (perhaps administered intrathecally to ensure local drug availability), underlying the importance of the shared molecular pathogenesis. Preclinical studies have provided the rationale for targeting both the MEK/ERK and PI3K/AKT pathways simultaneously in uveal melanoma, abrogating the two major transduction cascades downstream of constitutively active GNAQ [45]. A clinical trial designed to investigate the efficacy of targeting both MAPK and PI3K/AKT pathways in metastatic uveal melanoma has finished accrual and results are expected soon (NCT01979523). Currently, there is no standard of care therapy for disseminated uveal melanoma. At this time, it is unclear why the CellSearch test detected a decrease in melanoma CTCs as the patient progressed, but certainly supports the need for further study. A more in-depth understanding of the molecular mechanisms that drive the metastatic spread of this devastating disease is urgently required for treatment strategies to be improved.

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Fig. 1.

MRI shows spread of uveal melanoma to the leptomeninges. (a) Axial MRI brain with gadolinium contrast shows diffuse leptomeningeal enhancement without any tumor masses nor other focal abnormalities. The diffuse enhancement is present on the surface of the brain (dark gray arrows) and extends deep into many of the sulci (light gray arrows). (b) A coronal MRI with contrast shows linear enhancement in the right optic nerve and tract (gray oval) that is contiguous with the right eye that was affected by uveal melanoma.

Fig. 2.

CellSearch platform detects circulating melanoma cells in the cerebrospinal fluid. The figure includes a set of representative images exemplifying melanoma CTCs identified using the CellSearch platform (Janssen Diagnostics, Raritan, New Jersey, USA) following CD146 enrichment. Cells are identified as circulating melanoma cells when the images show an intact cell with a positive nuclear stain (DAPI), positive staining for anti-high-molecular-weight melanoma-associated antigen (Mel), and negative for CD45 (leukocyte marker) and CD34 (endothelial marker). The top two rows show cells identified as melanoma CTCs and the bottom row shows an example of a cell that is not identified as a melanoma CTC. CTC, circulating tumor cell.

Table 1

Circulating tumor cell counts

Sample date	Number of CTCs in blood	Number of CTCs in CSF from LP	Number of CTCs in CSF from Ommaya	p75NTR positive (%)
Day 1	0	136	–	–
Day 3	–	–	76	–
Day 23	–	–	63	–
Day 125	–	–	21	36

The number of CTCs detected from patient blood and CSF over time, starting at lumbar puncture showing melanoma cytology. Ommaya reservoir placed on day 3. CSF, cerebrospinal fluid; CTC, circulating tumor cell; LP, lumbar puncture.