Primary Melanoma of the Spinal Cord: A Case Report, Molecular Footprint, and Review of the Literature

Introduction

Primary melanoma of the spinal cord is a rare entity with fewer than 60 cases reported in the literature since the first report in 1906.\(^1\)\(^-\)\(^^6\) The diagnosis requires exclusion of a primary cutaneous or ocular lesion, as in rare instances melanoma may metastasize to the spinal cord.\(^7\) Prognosis is generally better, with a slower rate of progression, than for cutaneous melanoma with CNS metastases.\(^8\) We report a case of this uncommon tumor and also describe the molecular footprint that characterizes it.

Case

A 62-year-old man with limited past medical history presented with several months of progressive right-sided weakness with ipsilateral ataxia and gait disturbance. On examination, the patient demonstrated mildly decreased strength throughout his right side without loss of sensation or atrophy. The patient’s left side was unaffected and his cranial nerves were intact. Magnetic resonance imaging (MRI) of the cervical spine showed an enhancing intramedullary spinal cord lesion at the C2 and C3 level on T1-weighted, gadolinium-enhanced images (Fig 1A, sagittal; 1B, axial). The mass was isointense to the spinal cord on the T2-weighted image with areas of signal hyperintensity centrally, likely representing necrosis. Associated spinal cord edema extended from the craniocervical junction down to the level of C5 (Fig 1C, sagittal). Differential diagnosis for the mass included astrocytoma, ependymoma, and metastasis, with ependymoma favored because of the well-circumscribed appearance with areas of cystic/necrotic change.

The patient was referred to our institution for neurosurgical consultation. Intraoperative monitoring with somatosensory and motor evoked potentials was planned. Preincisional neuromonitoring suggested a delay in the patient’s right sided responses. The patient underwent an uncomplicated C1 to C3 laminectomy. On opening the dura, a visibly swollen area of the spinal cord was identified asymmetrically right at C2. A linear paramedian incision was made revealing a moderately vascular, soft, and darkened mass. Ultrasonic aspiration of the mass was performed and planes were reached inferiorly and medially. Superiorly and laterally the lesion was debulked down to a thin area of remaining tumor as no safe planes were observed. The patient’s somatosensory and motor evoked potentials profile showed a slight reduction of amplitude on the right and no change on the left.

At the time of resection, pigmentation of the specimen was noted grossly. An intraoperative consultation smear displayed relatively uniform spindled tumor cells with moderate cytoplasm and round to oval nuclei with prominent nucleoli (Fig 2A, smear ×600). Permanent sections similarly showed densely packed spindle-shaped tumor cells with uniform nuclei and occasional mitotic figures (Fig 2B, paraffin section, hematoxylin and eosin ×400). Both smear and cut section preparations revealed many of the tumor cells to have abundant melanin granules either finely
dispersed or in clumps. Immunohistochemical analysis of the sections produced strong immunoreactivity of the tumor cells for antibodies to S-100 and HMB45 (Fig 2C, S-100 immunohistochemistry ×400; Fig 2D, HMB45 immunohistochemistry ×400). The histological and immunohistochemical features were diagnostic for melanoma.

Subsequent fundoscopic and skin examinations did not reveal a primary lesion, nor the presence of vitiligo-like depigmentation or halos that would suggest a primary that had regressed. Total body positron emission tomography did not detect other sites of disease and MRI of the brain did not show intracranial tumor. Therefore, a diagnosis of primary intramedullary spinal malignant melanoma was made.

The patient’s postoperative recovery was uncomplicated. He received external-beam radiation therapy to the C2 and C3 spinal levels with 30 Gy delivered in 10 fractions. He did not receive chemotherapy. The patient slowly recovered strength and coordination in his right side although he continues to have some mild residual weakness of the right upper extremity, with associated spasticity. Follow-up positron emission tomography and MRI scan of the spine have not revealed disease recurrence. He is currently 11 months out from his surgery.

To further characterize this rare tumor, gene analysis was performed on genomic DNA from the tumor to determine the presence of possible common melanoma oncogenic somatic mutations using the Sequenom MassARRAY (Sequenom, San Diego, CA) system. In brief, this system involves polymerase chain reaction amplification of sequences of interest, followed by primer extension and mass spectrometry as previously detailed. Assays were derived from the Sequenom OncoCarta panel (Sequenom) and were validated in the laboratory. The gene panel did not demonstrate the presence of the most common oncogenic mutations in melanoma, including mutations in BRAF, NRAS, and KIT, but did reveal the presence of the mutation GNAQ 209.

**Discussion**

Primary melanoma of the spinal cord is a rare diagnosis, although there is some debate as to the exact number of reports due to variable definitions, inclusion of melanocytomas in some reports, lack of autopsy to rule out other lesions, and advancement of imaging techniques, which may now be able to reveal primary lesions that previously would have been missed. Although the overwhelming majority of melanocytic tumors arise from a skin primary, noncutaneous primary sites are well-described, including ocular and gastrointestinal locations. While the origins are not fully understood, noncutaneous melanomas including primary melanoma of the spinal cord are thought to originate from melanoblasts. Melanoblasts are derived from neural crest early in embryonic development and are found in the normal leptomeninges. The melanoblasts accompany the pial sheaths of vascular bundles. Another hypothesis is that the melanoma arises from neuroectodermal rest cells that migrate to reside within the neural tube and its coverings.

Based on our examination of the literature, the thoracic spine is the most frequent site of primary spinal melanoma (> 60%), with lesions confined to the cervical and lumbar spine being much less common. In terms of the spinal compartment, we found 21 cases that were intramedullary and an additional six that involved both intramedullary and extramedullary areas. Sixteen cases were considered extramedullary and intradural with at least five additional cases arising from the dura. Thus, our case is unusual in its cervical location.
There are no highly specific signs or symptoms for the diagnosis. The majority of patients will have back pain, and typically there may be weeks or months of progressive, asymmetric myelopathic symptoms before the diagnosis. MRI can be helpful in diagnosis in that spinal cord melanoma is typically characterized by high signal intensity on T1-weighted images relative to that of the spinal cord, likely due to the melanin present or associated hemorrhage. On T2-weighted images, spinal cord melanoma may show equal or low signal intensity as compared to the normal cord. Typically, the administration of gadolinium will cause mild and homogenous enhancement of the lesion. Given the rarity of the tumor, and nonspecificity of these findings, diagnosis often requires pathologic confirmation.

Treatment is not standardized, but most authors recommend surgical resection followed by postoperative radiation therapy, an approach similar to that for the management of metastases to the spine. Chemotherapy, including intrathecal administration, and immunotherapy are not usually employed but have been tried in some cases. One series of five patients reported an average survival of longer than 6 years. However, it is unclear if treatment is curative as late recurrences have been seen.

Characteristic mutations in BRAF (50% to 70% of melanomas), NRAS (15% to 30% of melanomas), and CDKN2A (30% to 70% of melanomas) are frequently seen in cutaneous melanoma. In this case, mutation of GNAQ 209 was identified. This is an activating somatic mutation in the ras-like domain of the heterotrimeric G-protein α-subunit (GNAQ), leading to BRAF- and NRAS-independent activation of the MAP kinase pathway. GNAQ 209 is mutated with high frequency (46%) in uveal melanoma, as well as 83% of blue nevi. It has been suggested that this tissue specificity is linked with the involvement of GNAQ with endothelial signaling, which is important in the development of melanocytes and the migration of melanoblasts. A recent case series examining pigmented brain neoplasms demonstrated that primary melanocytic brain lesions also appear to have a high rate of the GNAQ 209 mutation, and thus may share a genetic profile distinct from epithelial-derived melanoma. This mutation is thought to occur early in the malignant transformation of uveal melanomas, but has not been significantly associated with disease-free survival.

Our report is unique in that, to the best of our knowledge, it is the first case of a primary melanoma of the cervical spinal cord that was analyzed for common oncogenic somatic mutations seen in melanoma and which demonstrated a mutation in the GNAQ 209 oncogene. Given the increasingly evident molecular heterogeneity of malignant cells, characterizing the molecular profile of a given tumor, even rare ones such as ours, will hopefully help guide future investigations and treatments.

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