Int J Clin Exp Med 2018;11(7):7471-7476
www.ijcem.com /ISSN:1940-5901/IJCEM0073850

Case Report

Intraspinal primary melanoma of intermediate grade: a case report and literature review

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Received July 25, 2017; Accepted May 24, 2018; Epub July 15, 2018; Published July 30, 2018

Abstract: The incidence of primary central nervous system (CNS) melanocytic neoplasms is relatively low compared to that of systemic melanocytic neoplasms. This type of tumor is rare, and its clinical, radiological, and histopathological characterization is therefore poor, presenting a challenge for its diagnosis and treatment. Amelanotic melanoma-particularly intraspinal primary melanoma of intermediate grade-is an especially rare subtype. Here, we report a case of intraspinal primary melanoma of intermediate grade. Preoperative assessment revealed a neurogenic tumor for which the patient underwent resection. Pathologic analysis determined that the tumor was a melanoma of intermediate grade. Upon admission to the hospital, neurological examination of the patient revealed hypoesthesia below the umbilical level and progressive weakness (grade IV) of the right lower limb. The patient's familial history was negative, with no neurocutaneous system disorders occurring in first-degree relatives. The tumor was completely resected using a standard posterior midline approach. The patient was discharged after surgery with improved motor capacity, and a follow-up MRI scan revealed no recurrence after two years. Cases of intraspinal primary melanoma of intermediate grade are very rare; although this case is diagnosed as intermediate grade, it may behave aggressively. Complete surgical resection is curative for most cases. Radiation therapy is important to prevent recurrence, especially in cases of incomplete surgical resection.

Keywords: Central nervous system, intraspinal, primary, melanoma of intermediate grade, surgical resection

Introduction

Primary melanocytic neoplasms originate from leptomeningeal melanoma cells. Rarely seen by neurosurgeons in clinical practice, they account for only 0.07-0.17% of intracranial tumors [1], Intraspinal primary melanocytic neoplasms are an even rarer subtype that manifests as a subdural or epidural lesion, causing spinal nerve root compression that results in the initial symptom of nerve root pain. Here, we report a case of intraspinal primary melanoma of intermediate grade in a 59-year-old male.

Case presentation

A 59-year-old man presented to our clinic on June 2, 2013, with a 3-month history of sensory loss below the umbilical level. A neurological examination revealed hypoesthesia below the umbilical level and progressive weakness (grade IV) of the right lower limb. Muscle tone was normal in both lower extremities. Positive pathological reflexes were absent bilaterally. The patient's familial history was negative, with no neurocutaneous system disorders reported among first-degree relatives. No obvious deposition of pigment was found in the skin or mucosa. There was no previous history of surgical procedure for the removal of melanoma.

Imaging studies

Between the third thoracic and fourth thoracic vertebrae, an oval space-occupying lesion was observed by sagittal magnetic resonance imaging (MRI; **Figure 1**), and enhancement was shown in a contrast-enhanced scan. The lesion appeared hypointense in T1-weighted images. Hypointense signals were noted in T2-weighted images. The tumor was primarily located at the subdural region with a spinal cord shift.

Cerebrospinal fluid (CSF) examination

Lumbar puncture revealed CSF pressure of 160 mmH_2O. The white blood cell count was 3 × 10^6/L, and the protein level was 0.31 g/L.

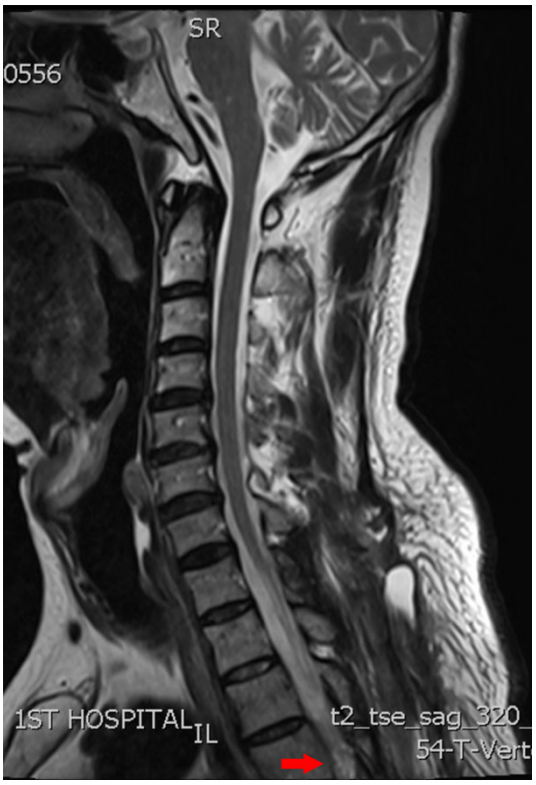

Figure 1. MR imaging of the spine of the patient upon initial diagnosis. A sagittal T2-weighted MR image revealed an oval space-occupying lesion between the third thoracic vertebrae and fourth thoracic vertebrae. Hypointense signals were noted on T2-weighted images. The tumor was primarily located at the subdural space with spinal cord shift (arrow).

Glucose levels and chloride content were normal.

Operation

Four days after admission, surgery was performed under general anesthesia using the posterior midline approach to remove the tumor. The tumor was solid, soft, tender, pale white, received a rich blood supply, and adhered to adjacent structures, including the underlying dura mater. The tumor was approximately 2.5 cm*1.5 cm*1.5 cm and was removed with the dura mater intact. After removal, the pulsatile motion of spinal cord was recovered. Gross total resection was achieved.

Pathologic examination revealed an amelanotic melanoma of intermediate grade. Under a light microscope (**Figure 2A**), nests of intermediate-grade tumor cells with intervening stroma were observed; the tumor cells contained clear eosinophilic cytoplasm with no obvious pigment. Examination of the tumor under higher magnification revealed prominent nuclear mitosis. Immunocytochemistry revealed Melan A (sparse), S-100 (**Figure 2B**) and SMA (sparse) positivity, while stains for HMB45, CK, EMA, CEA, TTF-1, SYN, CD56, CgA, Desmin, PAS, and PR were negative. The Ki67-positive rate was less than 5% (**Figure 2C**).

One day after the operation, sensory disturbances were markedly decreased. The patient's stitches were removed 12 days following the operation, at which time the surgical wound was largely healed. The patient was discharged 18 days after the operation with no complications. Follow-up MRI showed that the tumor had been completely resected (**Figure 3**). Over the course of 24 months of follow-up, the patient recovered well with no recurrence or related sequelae.

*Review of previous cases reported in the literature (**Tables 1** and S1)*

We queried the search engine PubMed with the keywords melanoma OR melanomatosis OR melanocytoma OR melanocytosis AND CNS AND primary and further searched with the keywords CNS OR brain OR cranial OR spinal.

The clinical manifestations of melanoma are non-specific, and its symptoms are associated with space-occupying compression related to the location and size of the tumor. Mohammed et al reported a case of melanocytic tumor located in the pituitary [2], and Jetschke et al reported a case of malignant melanocytic tumor located in the pineal region [3]. While these tumors are most commonly detected in adults with a male predominance, the age of onset ranges from 2 months to 79 years, with a median age of 41 years.

There were 104 males and 46 females reported in the literature, with a male-to-female ratio of 2.26:1. Gross total resection was achieved in 33 (48.53%) cases, subtotal resection was achieved in 13 (19.12%) cases, and biopsy was performed in 22 (32.35%) cases. Thirty of the 67 cases underwent radiotherapy, of which 16 patients (53.33%) experienced recurrence. However, due to limited clinical evidence, the definitive role of radiotherapy and the overall prognosis cannot be determined and requires

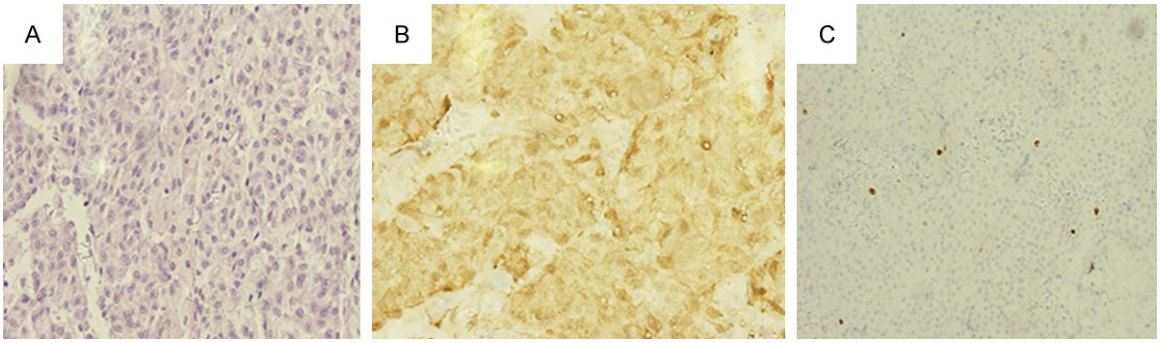

Figure 2. A. Pathology slice (hematoxylin-eosin stain, original magnification × 400) of the tumor. Nests of intermediate-grade tumor cells with intervening stroma can be seen. The tumor cells show clear to eosinophilic cytoplasm, with no obvious pigment. Higher magnification of the tumor, showing prominent nuclear mitosis and atypia. B. Higher magnification (original magnification × 200) of the tumor, showing S-100 positivity. C. Higher magnification (original magnification × 200) of the tumor, showing that the Ki67-positive rate was less than 5%.

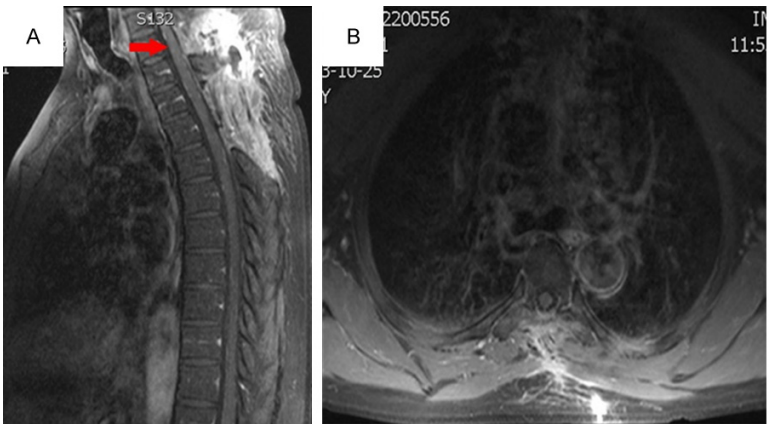

Figure 3. A. Sagittal T1-weighted MR image revealed the absence of the tumor. B. Post-operative gadolinium-enhanced MRI demonstrates the absence of the tumor.

further study of a much larger cohort. The mean follow-up period was 21.59 months.

Using magnetic resonance T1-weighted imaging, the tumor appeared isointense in 12.12% of cases, hyperintense in 66.67% of cases, hypointense in 15.15% of cases, and heterogeneously intense in 18.92% of cases. Using T2-weighted imaging, the tumor appeared isointense in 2.70% of cases, hyperintense in 18.92% of cases, hypointense in 59.46% of cases, and heterogeneously intense in 18.92% of cases. After administration of a gadolinium contrast agent, homogeneous and heterogeneous enhancement was noted in 60.61% and 30.30% of cases, respectively, while 9.09% of cases showed no enhancement. From our review of the literature, we found that melanoma was hyperintense in T1 and hypointense in T2. Immunohistochemical staining revealed that all amelanotic melanomas were negative for Melan A. The positive rates for S-100, HMB45, vimentin, and EMA were 91.84%, 93.62%, 80% and 5.88%, respectively. Primary cases were Ki67 ≤ 5%, while metastatic or malignant cases were Ki67 > 5%, indicating poor prognosis.

Discussion

Intraspinal primary melanoma is a rare tumor of the CNS. It originates from melanocytic cells located in the leptomeninges and is usually a solitary lesion, typically located in the posterior fossa and along the cervico-thoracic spinal cord [4]. Jun et al estimate that CNS melanoma accounts for 0.06-0.1% of all melanocytomas and 0.005/100,000 of melanomas, and other subtypes are rare. This tumor exhibits a slight female predisposition (F:M = 1.5:1). The age range of melanocytoma is 9 to 73 years (most often between 45 and 50 years) and that of primary nodular melanoma is 15 to 71 years (averaging 43 years) [5]. Brat classified melanocytic lesions of the CNS with respect to focal mass as low grade (melanocytoma), intermediate grade, and high grade (melanoma) [6]. Several authors consider melanocytoma to be a borderline tumor between cellular blue nevus

Table 1. Review of the literature of CNS amelanotic melanoma

Characteristics	Number (n)	Percentage (%)
Gender		
Male	104/150	69.33%
Female	46/150	30.67%
MRI T1-weighted imaging		
Hypointensity	5/33	15.15%
Isointensity	4/33	12.12%
Hyperintensity	22/33	66.67%
Heterogeneous intensity	2/33	6.06%
MRI T2-weighted imaging		
Hypointensity	22/37	59.46%
Isointensity	1/37	2.70%
Hyperintensity	7/37	18.92%
Heterogeneous intensity	7/37	18.92%
MRI enhancement		
Homogeneous	20/33	60.61%
Heterogeneous	10/33	30.30%
No	3/33	9.09%
Immunehistochemical staining		
S-100 diffuse positivity	45/49	91.84%
S-100 negativity	4/49	8.16%
HMB45 diffuse positivity	42/47	89.36%
HMB45 focal positivity	2/47	4.26%
HMB45 negativity	3/47	6.38%
GFAP negativity	16/16	100%
Vimentindiffuse positivity	8/10	80%
Vimentin negativity	2/10	20%
CK negativity	15/15	100%
EMA focal positivity	1/17	5.88%
EMA negativity	16/17	94.12%
Ki 67 0-5%	10/18	55.56%
Ki 67 > 5%	8/18	44.44%
Surgical resection extent		
Gross total resection	33/68	48.53%
Subtotal resection	13/68	19.12%
Biopsy	22/68	32.35%
Outcome		
No recurrence (no radiotherapy)	29/37	78.38%
Recurrence (no radiotherapy)	8/37	21.62%
No recurrence (radiotherapy)	14/30	46.67%
Recurrence (radiotherapy)	16/30	53.33%

and spindle cell melanoma. The present World Health Organization scheme classifies primary melanocytic lesions as diffuse melanocytosis, melanocytoma, malignant melanoma, and meningeal melanomatosis; of these types, only melanocytomas and malignant melanoma present as solitary lesions [7]. Thoracic cases were most common (42.3%), followed by cervical cases (34.6%), thoracolumbar cases (11.5%), cervicothoracic cases (7.7%), and lumbar cases (3.8%) [8].

MRI is the preferred imaging method for the diagnosis of spinal melanoma, but it is difficult to distinguish melanoma from other spinal tumors [9]. The accuracy of diagnosis by neuroimaging depends on the melanin content of the tumor. Isiklar et al [10] classified MRI performance into four groups: a) the melanotic group, with hyperintense T1 and hypointense T2; b) the amelanotic group, with iso-/hypointense T1 and iso-/hyperintense T2; c) the mixed group, fitting neither of the two criteria; and d) the hemorrhagic group, with characteristics of intra-/peri-tumoral hemorrhage. Gaviani et al reported that the T1 signal is positively correlated with the melanin content of the tumor, while T2 signal has no such correlation but is more sensitive to tiny loci. Unal and Castillo [11] reported a primary thoracic extradural spinal malignant melanoma with T2-hypointense and T1-hyperintense MRI signals. Lee et al [12] presented an MRI analysis of a patient with a primary intradural extramedullary melanoma of the cervical spinal cord, with decreased signal intensity on T2-weighted images and increased signal intensity on T1-weighted images. Lee et al [13] reported a case in which MRI revealed an enhanced mass in the intra- and extradural spaces, compressing the spinal cord at the left neural foramen at the C6-7 level. Unfortunately, the MRI appearance of melanocytic tumors can vary due to their heterogeneous pigmentation as well as the presence of other features, such as intratumoral hemorrhage [14]. Thus, classically reported neuro-imaging features cannot reliably distinguish melanocytic tumors from other tumors commonly found in similar dural locations (i.e., meningioma, schwannoma and

malignant melanoma) [14]. Therefore, as in the present case, the interpretation of the MRI pattern may easily lead to misdiagnosis. In the present case report, the lesion appeared hypointense on T1-weighted images, and hypointense signals were noted on T2-weighted images. Therefore, it is difficult to make a diagnosis of intraspinal primary melanoma based solely on imaging results. In the present case report, the final diagnosis of the patient required further investigation using methods other than MRI.

Intermediate grade melanocytic tumors typically invade the CNS. A rare example of malignant transformation of a melanocytoma has been reported [15]. Intraspinal primary melanoma of intermediate grade is rare and requires special techniques such as immunohistochemistry and electron microscopy for confirmation of the diagnosis. The diagnosis of melanocytic lesions relies on histopathological examination. Most benign and malignant melanocytic lesions display melanin pigment within tumor cells, tumor stroma, and the cytoplasm of tumoral macrophages (melanophages). Histologically, melanin-containing tumors, including melanocytosis, melanocytoma, malignant melanoma and meningeal melanomatosis, exhibit spindle or epithelioid cells arranged in sheets, bundles, nests or whorls containing variable quantities of melanin pigment in the cytoplasm. Tumors with CNS invasion or elevated mitotic activity are classified as intermediate grade melanocytic neoplasms. Malignant melanoma is more pleomorphic, contains more anaplastic nuclei, and exhibits higher cell density and unequivocal invasion or coagulative necrosis [5]. Anti-melanoma antibody (HMB-45) and S-100 protein staining may aid in the diagnosis of malignant melanoma. The immunohistochemistry profile of melanotic lesions (i.e., melanocytoma, malignant melanoma and melanocytosis) is similar: they are positive for HMB-45, Melan-A, S-100 and Vimentin. In addition, studies have shown that nuclear size is helpful for differentiating benign from malignant melanocytic lesions [15, 16].

Intraspinal primary melanoma is diagnosed using the following criteria: there is no malignant melanoma outside the central nervous system, and the lesion is confirmed pathologically [17]. The present case satisfied these criteria.

Surgical goals are to decompress the spinal cord and obtain a complete resection with a specimen for diagnosis. Complete surgical resection is the best treatment for melanocytic tumors [18].

Most intraspinal primary melanomas are malignant. Here, an extremely rare case of intraspinal primary melanoma intermediate grade is presented. We emphasize the importance of close post-operative monitoring and diligent follow-up, even in cases of radiographically gross total resection. Although this tumor was histopathologically defined as intermediate grade, it was treated by an aggressive clinical course due to its location and the mass effect imposed within the spinal cord. The patient was discharged with improved motor capacity, and a follow-up MRI scan showed no recurrence after two years.

Conclusion

A surgical approach for the resection of intraspinal primary melanoma must be carefully designed and thoroughly planned to ensure the functional preservation of the spinal cord; MRI provides valuable guidance in this respect. Furthermore, a strong understanding of the complicated anatomical structures involved is crucial for the complete tumor resection and nerve preservation.

Acknowledgements

Written informed consent was obtained from the patient for the publication of this case report and all accompanying images. We thank the patient and all of the physicians and staff who helped with this study.

Disclosure of conflict of interest

None.

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Table S1. Summary of EVN reported in literatures and the current case from 2002

Characteristics	Number (n)	Percentage (%)
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