Primary intramedullary malignant melanoma: can imaging lead to the correct diagnosis?

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Abstract
Melanoma is a malignant neoplasm of melanin-producing cells. Melanoma usually occurs in the skin, but can also arise in any anatomical site that contains melanocytes, such as mucous membranes, the eyes, and the central nervous system (CNS). Primary CNS malignant melanoma most often develops in the leptomeninges. We report a case of a rare intramedullary melanoma of the thoracic spinal cord. A 78-year-old man was treated with surgery, radiotherapy, and immunotherapy for leptomeningeal spread. We also discuss the role of imaging methods in diagnosis and follow-up. Medullary melanoma occurs more frequently in adults. The most common presenting symptoms are the insidious onset of lower extremity weakness and paresthesia. Magnetic resonance imaging is the method of choice for evaluation. Although there are no imaging features to accurately distinguish primary malignant melanoma from other melanocytic or hemorrhagic tumors, hyperintensity on T1-weighted magnetic resonance imaging should lead to inclusion of this neoplasm in differential diagnosis of spinal cord tumors. Positron emission tomography-computed tomography is a useful auxiliary examination to evaluate the extent of local and metastatic disease. Surgical resection is the primary treatment for intramedullary melanoma. However, the efficacy of adjunctive radiotherapy and chemotherapy for primary spinal cord malignant melanoma is still controversial.
Keywords
Spinal cord tumor, central nervous system, intramedullary melanoma, magnetic resonance imaging, positron emission tomography-computed tomography, leptomeninges

Introduction
Melanoma is a malignant neoplasm of melanin-producing cells. Melanoma usually occurs in the skin, but can also arise in any anatomical site that contains melanocytes, such as mucous membranes, the eyes, and the central nervous system (CNS). However, primary CNS melanomas accounts for only 1% of all melanomas, and the incidence of primary spinal cord lesions is even more rare. The diagnosis of primary CNS melanoma requires histological confirmation and exclusion of a melanoma outside the CNS. We present a case of a rare primary, intradural, intramedullary melanoma of the thoracic spinal cord and discuss the diagnostic utility of imaging studies.

Case report
A 78-year-old man presented with insidious onset of progressive weakness in both lower extremities over 6 months, followed by thoracic spinal pain that impaired ambulation. A neurological examination showed bilateral and symmetrical reduction of lower extremity strength to 3/5 grade bilaterally. Patellar tendon reflexes were brisk and bilateral extensor plantar reflexes were observed. Gross sensation was impaired distally to approximately the T10 level bilaterally. Spinal cord magnetic resonance imaging (MRI) showed an intradural, intramedullary, expansive lesion at the T9–T10 level. There was also a hyperintense signal on pre-contrast T1-weighted imaging and a predominantly hypointense signal on T2-weighted imaging, associated with discrete perilesional edema (Figure 1a–c). Because of the hyperintensity on T1-weighted imaging, a differential diagnosis of hemorrhagic neoplasms (e.g., ependymoma, astrocytoma, or hemangioblastoma) or pigmented lesions (e.g., metastatic or primary melanoma) was considered.

Further diagnostic investigations that included a thorough whole-body skin examination, ophthalmological and otolaryngological evaluations, and endoscopies of the pharyngolarynx, upper gastrointestinal tract, colon, and rectum did not show additional lesions. Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (18F-FDG PET-CT) was performed to diagnose disease outside the CNS. This examination showed intense 18F-FDG uptake by the spinal tumor, but did not show any other suspected lesions (Figure 1d).

The patient underwent T8–T10 laminectomy. After opening of the dura, a solid, dark, and hypervascular tumor was visualized. There were no clear margins between the lesion and the spinal cord. Myelotomy and gross total resection of the tumor were performed. Histological analysis showed a hyperplastic lesion composed of large atypical spindle cells arranged in sheets. There was an eosinophilic cytoplasm and a moderate grade of cellular and nuclear pleomorphism. Furthermore, prominent nucleoli and mitoses, with intracellular and extracellular melanin deposition were observed.
These findings suggested melanoma. Immunohistochemical assays for S-100 protein, Melan-A, and human melanoma black-45 confirmed the diagnosis of malignant melanoma. In histopathological analysis, there was no hemorrhagic component in the lesion.

Postoperatively, the patient had paraparesis, which impaired ambulation. Lower extremity strength was still 3/5 grade bilaterally and gross sensation continued to be impaired distal to the T10 level bilaterally. The patient received local postoperative adjuvant radiotherapy (50 gray, >30 fractions). A follow-up MRI showed only posttreatment changes (Figure 2). However, 6 months later, MRI showed recurrence in the tumor bed and leptomeningeal dissemination (Figure 3). Consequently, immunotherapy (imatinib) was initiated. One year later, the patient presented with severe headache and exacerbation of back pain. MRI showed major progression of the leptomeningeal spread, including intracranial metastasis (Figure 4). Currently, the patient is receiving palliative care.

Discussion

Primary CNS malignant melanoma usually develops in the leptomeninges, reflecting the common origin of melanocytes and meningotheelial cells in the neural crest. Neural crest cells are highly migratory and generate diverse structures that include the peripheral nervous system, skin melanocytes, adrenal neurosecretory chromaffin cells, and the pia mater and arachnoid of the spinal cord. Melanocytic cells arise in the neural crest by the sixth week of embryonic development and migrate to their destinations, reaching the skin by the tenth week and the meninges by the twentieth week. A hypothesis for development of primary intramedullary malignant melanoma suggests that a few neural crest cells fail to migrate during embryogenesis and they reside within the neural tube.
These cells are unable to establish normal signaling pathways with adjacent cells to mediate differentiation and maturation. Oncogenesis could be dependent on cellular migration-related anomalies. Additionally, primary CNS melanoma in atypical sites may originate from melanoblasts accompanying the pial sheaths of vascular bundles or from neuroectodermal cells with arrested migration during embryogenesis.

Primary CNS malignant melanomas are rare neoplasms, with an estimated incidence of 0.005 cases per 100,000 people. Most of these melanomas are solitary, intradural, extramedullary tumors of the cervical and thoracic spinal cord segments. The lesion found in our case is especially rare because of its intramedullary location. A review of 60 cases of spinal cord melanomas showed that 37.7% were intramedullary and 62.4% were extramedullary. The thoracic spinal cord segment is the most affected by these melanomas, followed by the cervical cord, and finally, by the lumbar segment. This lesion occurs most frequently in adults (mean age: approximately 50 years, ranging from 15–80 years), with a slight predominance in men. Symptoms of spinal cord melanomas depend on the location of the tumor, and a subacute or insidious onset is typical. However, acute onset or deterioration is possible owing to hemorrhage.
The most common presenting symptoms of spinal cord melanomas are the gradual onset of lower extremity weakness and paresthesia, but abnormal reflexes, sphincter incontinence, and pain can also occur.\textsuperscript{4,8,10} Hydrocephalus and/or signs of increased intracranial pressure, secondary to impaired cerebrospinal fluid circulation and absorption, may indicate leptomeningeal dissemination.\textsuperscript{12}

Radiological features of primary CNS melanoma depend on the degree of melanocytic content and the presence or absence of hemorrhage.\textsuperscript{7} On computed tomography, the tumor appears as a hyperdense lesion enhanced by intravenous contrast.\textsuperscript{13} PET-CT is useful for evaluating local and distant disease because malignant melanomas have increased function and metabolic activity of glucose transporter proteins and the glucose phosphorylating enzyme hexokinase.\textsuperscript{4,14} MRI of primary CNS melanoma shows hyperintense signals on T1-weighted imaging and hypointense signals on T2- and T2*-weighted imaging. This depends on the degree of pigment content, as well as homogenous enhancement on gadolinium postcontrast images. Enhancement patterns may also be inhomogeneous, peripheral, or nodular.\textsuperscript{7,15,16} Lesions secondary to

\textbf{Figure 4.} Recurrent melanoma and leptomeningeal spread. Magnetic resonance imaging performed 1 year after recurrence of the tumor and immunotherapy shows multiple leptomeningeal lesions. There is a hyperintense T1 signal in the interpeduncular cistern (arrow in a) and cervical (arrows in b) and thoracic (arrows in c) spinal cord segments, with contrast enhancement (arrows in d–f). These findings suggest advanced disease with progressive leptomeningeal dissemination.
leptomeningeal dissemination also display hyperintense signals on T1-weighted imaging, with gadolinium enhancement and hypointense signals on T2-weighted imaging. Similarly, in the present case, the primary lesion and leptomeningeal spread presented with a hyperintense signal on T1-weighted images and a hypointense signal on T2-weighted images owing to intratumoral pigment.

MRI is the imaging method of choice for diagnosing spinal cord tumors, including melanoma. However, unfortunately, there are no imaging characteristics that accurately distinguish primary malignant melanoma from other melanocytic lesions of the CNS, such as metastatic melanoma, and hemorrhagic neoplasms, such as ependymoma and astrocytoma.

Histopathology of malignant melanoma features hyperplastic sheets or nests of spindled or epithelioid cells, which may have considerable pleomorphism and prominent eosinophilic nucleoli. Cells may display variable amounts of cytoplasmic melanin. Atypical mitoses, invasion of adjacent structures, or necrosis may be observed. Human melanoma black-45 is a useful marker for melanocytic differentiation because it indicates active melanosome formation. Cells with melanocytic differentiation also express S-100. Melan-A is a melanocyte lineage-specific marker. In our patient, the neoplasm was composed of large atypical spindle cells arranged in sheets, with an eosinophilic cytoplasm and a moderate grade of pleomorphism, with intra- and extracellular melanin deposition. Furthermore, immunohistochemical assays for S-100 protein, Melan-A, and human melanoma black-45 indicated the diagnosis of malignant melanoma.

Because the MRI and histopathological characteristics of intramedullary primary and metastatic melanomas are indistinguishable, thorough examinations of the skin, squamous mucosa, and the eyes must always be performed. According to the Hayward criteria for the diagnosis of primary CNS melanoma, histological confirmation and exclusion of melanoma outside the CNS are required. Distinction between primary CNS and metastatic melanoma is essential. The median survival for metastatic CNS melanoma ranges from 3 to 6 months, in contrast to primary CNS melanoma, which may have a better prognosis. This difference may be related to the absence of a CNS lymphatic system, obviating distant metastasis.

Surgical resection is the primary treatment option for intramedullary melanoma. However, gross total resection is difficult, and most patients will require postoperative adjuvant treatment, such as radiotherapy. Additionally, the rarity of this tumor hinders evaluation of therapeutic options. Although the extent of resection is not related to mortality until 60 months after surgery, the overall survival after gross total resection is better than that after partial resection. However, the efficacy of radiotherapy and chemotherapy for primary spinal cord malignant melanoma is still controversial. Some studies have reported that postoperative adjuvant radiotherapy and chemotheraphy confer clinical benefits. However, other authors have reported favorable outcomes without adjuvant therapy, and have even concluded that primary CNS malignant melanoma is not radiosensitive.

In conclusion, awareness of primary intramedullary malignant melanoma is important and this neoplasm needs to be included in the differential diagnosis of spinal cord tumors when appropriate. While imaging plays a major role in the evaluation of this tumor, MRI alone cannot determine the final diagnosis. Therefore, histopathological analysis is fundamental for primary intramedullary malignant melanoma.
Ethics statement
Approval by an ethics committee was waived because the data were anonymized. The patient provided written informed consent for publication.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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References
1. Stedman. Stedman’s Medical Dictionary for the Health Professions and Nursing. 7th ed. Lippincott Williams & Wilkins, 2011.
2. Farrokh D, Fransen P and Faverly D. MR findings of a primary intramedullary malignant melanoma: case report and literature review. AJNR Am J Neuroradiol 2001; 22: 1864–1866.
3. Hayward RD. Malignant melanoma and the central nervous system. A guide for classification based on the clinical findings. J Neurol Neurosurg Psychiatry 1976; 39: 526–530.
4. Zhang M, Liu R, Xiang Y, et al. Primary spinal cord melanoma: a case report and a systemic review of overall survival. World Neurosurg 2018; 114: 408–420.
5. Unal B and Castillo M. MRI features of a primary thoracic epidural melanoma: a case report. Clin Imaging 2007; 31: 273–275.
6. Salpietro FM, Alafaci C, Gervasio O, et al. Primary intramedullary melanoma: Case report and histogenetic features. Neurosurgical Focus 1998; 4. DOI: https://doi.org/10.3171/foc.1998.4.5.7
7. Smith AB, Rushing EJ and Smirniotopoulos JG. Pigmented lesions of the central nervous system: radiologic-pathologic correlation. Radiographics 2009; 29: 1503–1524.
8. Liubinas SV, Maartens N and Drummond KJ. Primary melanocytic neoplasms of the central nervous system. J Clin Neurosci 2010; 17: 1227–1232.
9. Wuerdeman M, Douglass S, AbdA RB, et al. A rare case of primary spinal cord melanoma. Radiol Case Rep 2018; 13: 424–426.
10. Majeed K, Hussain I, Pisapia DJ, et al. Intradural intramedullary primary spinal melanoma: a case report and review of the literature. Sci J Neurol Neurosurg 2019; 5: 12–18.
11. Freudenstein D, Wagner A, Bornemann A, et al. Primary melanocytic lesions of the CNS: report of five cases. Zentralbl Neurochir 2004; 65: 146–153.
12. Jeong DH, Lee CK, You NK, et al. Primary spinal cord melanoma in thoracic spine with leptomeningeal dissemination and presenting hydrocephalus. Brain Tumor Res Treat 2013; 1: 116–120.
13. Fujimori K, Sakai K, Higashiyama F, et al. Primary central nervous system malignant melanoma with leptomeningeal melanomatosis: a case report and review of the literature. Neurosurg Rev 2018; 41: 333–339.
14. Fuster D, Chiang S, Johnson G, et al. Is 18F-FDG PET more accurate than standard diagnostic procedures in the detection of suspected recurrent melanoma? J Nucl Med 2004; 45: 1323–1327.
15. Fuld AD, Speck ME, Harris BT, et al. Primary melanoma of the spinal cord: a case report, molecular footprint, and review of the literature. J Clin Oncol 2011; 29: e499–e502.
16. Çetinalp NE, Yildirim AE, Divanlioglu D, et al. An uncommon intramedullary tumor: primary spinal cord melanoma. Asian Spine J 2014; 8: 512–515.
17. Koelsche C, Hovestadt V, Jones DT, et al. Melanotic tumors of the nervous system are characterized by distinct mutational, chromosomal and epigenomic profiles. Brain Pathol 2015; 25: 202–208.
18. Vij M, Jaiswal S, Jaiswal AK, et al. Primary spinal melanoma of the cervical
leptomeninges: report of a case with brief review of literature. *Neurol India* 2010; 58: 781–783.

19. Li MH and Holtas S. MR imaging of spinal intramedullary tumors. *Acta Radiol* 1991; 32: 505–513.

20. Kim MS, Yoon DH and Shin DA. Primary spinal cord melanoma. *J Korean Neurosurg Soc* 2010; 48: 157–161.

21. Tobin MK, Geraghty JR, Engelhard HH, et al. Intramedullary spinal cord tumors: a review of current and future treatment strategies. *Neurosurg Focus* 2015; 39: E14.

22. Ku A, Henry A, Tunkel R, et al. Lumbosacral radiculopathy secondary to L5 metastatic melanoma of unknown primary. *Arch Phys Med Rehabil* 1996; 77: 307–309.