Atypical primary malignant melanoma originating in the spinal canal: A case report and literature review

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Abstract. Central nervous system (CNS) malignant melanomas are rare tumors of the CNS that are thought to arise from aberrant changes in melanocytes of the neural crest or melanocytic elements of the pia mater during early embryonic development. As a rare type of CNS malignant melanoma, only a few cases of primary malignant melanoma in the spinal canal have been reported thus far. The majority of these studies have reported on the diagnosis, radiographic features and gross total resection of primary spinal canal malignant melanoma; however, the prognosis and ideal treatment of patients with residual tumors remain elusive. The current study presented the rare case of a patient with primary malignant melanoma originating from the thoracic spinal canal, without any history of irradiation exposure and with an incompletely resected tumor. Disease-free survival of >2.5 years was observed in this patient who was treated with concurrent chemoradiotherapy followed by adjuvant chemotherapy with temozolomide and bevacizumab.

Introduction

Malignant melanoma is a tumor derived from melanocytes that is normally located in the basal layer of the epidermis and dermis of the skin where DNA is protected from ultraviolet light-induced damage. Malignant melanoma accounted for ~3% of all tumors in the United States in 1998 (1) and may be caused by the malignant transformation of dysplastic nevi, junctional nevi and benign melanocytic nevi (2,3). Based on their location, malignant melanomas are generally classified into cutaneous malignant melanomas (skin and acra; 90%), mucosal malignant melanomas (mucosa of head, neck, gastrointestinal, conjunctiva and genital areas; 8-15%), uveal malignant melanomas (uvea and ciliary body; 3-5%) and central nervous system (CNS) malignant melanomas (dopaminergic neurons in the substantia nigra and locus coeruleus; 1%) (4-6). Although CNS melanomas are rare, primary malignant melanomas in the spinal canal are even more rare, with only a few cases reported thus far (7,8). The majority of previous studies have reported the diagnosis, radiographic features and gross total resection of primary malignant melanomas originating in the spinal canal, however, the prognosis and ideal treatment of patients with residual tumors remain elusive and the efficacy of postoperative radiotherapy or chemotherapy is controversial (7,8). The present study reported an unusual case of primary malignant melanoma originating from the thoracic spinal canal in a patient without a history of irradiation exposure. Furthermore, this patient had an incompletely resected tumor. To our knowledge, the patient described in this report appears to represent the first case of primary malignant melanoma originating from the spinal canal with a residual tumor and a good prognosis.

Case report

A 21-year-old female attended First Affiliated Hospital of Kunming Medical University in Kunming, China on June 2020 for gradually aggravated lower back pain for 3 months and progressive numbness in both lower limbs over 2 weeks. These symptoms were associated with activity and abated after rest. There was no significant past medical history, no history of tumors or any previous radiation exposure and no positive family history of tumors. Neurological examination indicated that the pain and numbness were accompanied by a muscle strength of grade 4 in the right lower limb and grade 4 in the left lower limb. A general examination of the patient, including physical and radiological examinations, did not find any subcutaneous nodules or skin lesions. In addition, no mental status, motor or sensory impairments were detected in the patient.

The following descriptions of the imaging examinations were based on reports by 2 or 3 independent radiologists. Magnetic resonance imaging (MRI) examination demonstrated an oval mass (~1.7x2.1x4.0 cm^3; front-back x left-right x up-down) in the extraspinal subdural space and the right side

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of the intervertebral foramen in the T6-8 spinal canal. The mass exhibited high signal intensity on T2-weighted images and isointensity on T1-weighted images. The signal intensity demonstrated uneven enhancement in the lesion after contrast enhancement. At the same level, spinal stenosis and intervertebral foramen enlargement were observed and the spinal cord appeared significantly compressed and displaced to the left side (Fig. 1). An MRI diagnosis of neurogenic tumor was considered. Non-contrast CT imaging demonstrated a mass ~1.5x2.3x3.4 cm^3 in the T6-8 plane with intervertebral foramen enlargement and the spinal cord appeared significantly compressed and displaced to the left side (Fig. 2). Neurogenic tumors were considered based on CT examination. No obvious abnormalities were demonstrated upon hematological examination of the patient.

Due to the difficulty of intraspinal diagnostic biopsy and the possibility of tumor spread and metastasis, surgery to remove as much of the lesion as possible was considered the best option for the patient. The surgery was performed by orthopedic surgeons and neurosurgeons and the description of the operation in the present report was based on the operation records written by the surgeons. After imaging and hematology tests, the patient underwent thoracolumbar posterior focal lesion exploration and excisional biopsy, laminectomy and orthopedic internal fixation under general anesthesia. The tumor was located in both the epidural and subdural regions and appeared red and black because of the plentiful supply of blood. In addition, the tumor demonstrated aggressive and invasive growth and indistinct borders from the surrounding tissues. After piecemeal resection of the epidural tumor tissue, the subdural object was excised following cutting of the retrodural space of Okada and release of the cerebrospinal fluid (CSF). Postoperative MRI demonstrated a poorly defined, residual T2 hyperintense mass and a T1 isointense or hypointense mass in the T6-8 spinal canal, and the signal intensity demonstrated obvious enhancement in the lesion after contrast enhancement (Fig. 3).

Histology is critical for the differential diagnosis of atypical primary malignant melanoma and neurogenic tumors originating in the spinal canal. The descriptions of the pathological findings were based on the pathological records written by 2 independent pathologists. Intraoperatively, biopsies of the lesion from the T6-8 spinal canal were taken for frozen and permanent pathology samples. Histopathological examination after hematoxylin and eosin staining according to standard procedures (9) of the surgical specimen demonstrated spindle cell features and melanin pigmentation (Fig. 4). Immunohistochemistry staining according to standard procedures (9) demonstrated that the positive rate of the Ki-67 (marker of proliferation) index was >5%, and positivity for Vimentin, S-100 (S100 calcium binding protein A1), HMB45 (premelanosome protein), MelanA and SOX-10 was observed. However, staining for P53, CK (cytokeratin), EMA (mucin 1), PR (progesterone receptor), MBP (myelin basic protein), CD34, GFAP (glial fibrillary acidic protein) and CD57 were negative (data not shown) (the above antibodies were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., LTD.). Thus, the histological diagnosis was primary malignant melanoma of the T6-8 spinal canal. Currently, there is no test available for tumor-infiltrating lymphocytes (TILs).

The surgeons and physicians agreed that the patient had residual tumor and was at high risk for tumor dissemination along the CSF; therefore, postoperative treatment was necessary. Concurrent chemoradiotherapy was performed for four weeks post-surgery with a dose of 40 Gy in 20 fractions at the T5-9 spinal canal level using volumetric modulated arc therapy plus continuous daily temozolomide [75 mg/m^2 of body surface area (BSA)/day for 42 days]. Subsequently, the patient received five cycles of adjuvant temozolomide (150-200 mg/m^2 BSA for five days during each 28-day cycle of treatment) plus bevacizumab every three weeks (7.5 mg/kg of body weight) for six cycles and then entered the follow-up phase of treatment. Throughout chemotherapy plus bevacizumab, the patient experienced mild gastrointestinal events and no grade 3-4 adverse events were reported.

Follow-up was performed every three months in the first two years following completion of adjuvant chemotherapy. At each follow-up, the patient underwent clinical examination, quality of life test, hematological and imaging examination including tumor markers, chest CT, and head and pyramidal MRI. A whole-body bone scan was performed every six months. To date, the patient has demonstrated no evidence of progression or tumor recurrence for >2.5 years, has reported having no issues and has been studying and working normally. Further follow-up will continue.

Discussion

All types of cancer have the potential to invade the CNS as primary or metastatic tumors (2,3). Clinically, the most common type of cancer to invade the CNS is malignant melanoma metastatic to the CNS, whilst primary malignant melanoma of the CNS is rare (10). Primary melanoma of the CNS originates from aberrant changes in melanocytes of the neural crest or melanocytic elements of the pia mater during early embryonic development (7,11,12). Primary spinal malignant melanomas are also rare, with only several cases reported to date (7,8).

Primary melanoma of the CNS is diagnosed using the criteria devised by Hayward (13) as follows: No malignant melanoma outside the CNS, no presence of the lesion in any other region of the CNS and histological confirmation of the melanoma (8). Regarding the symptoms of primary spinal malignant melanoma, patients often present with intracranial hypertension and focal neurological deficits due to spinal blocking; thus, the diagnosis of spinal malignant melanomas is difficult and requires imaging examinations, pathological examination and exclusion of other CNS diseases and systemic melanoma (14,15). A diagnosis of cutaneous melanoma should also be ruled out, as cutaneous melanoma have a higher incidence rate combined with a high propensity to metastasize to the CNS, with CNS involvement reported in ~10% of patients with cutaneous melanoma in previous clinical studies (16,17). In addition to the skin, primary melanomas may originate from less visible locations, such as nail beds, mucosal surfaces of the genitals, sinonasal cavity and gastrointestinal tract and the uveal tract (4-6). Therefore, before concluding that spinal melanoma is a primary tumor, a thorough clinical examination, as well as histological revision of previously removed melanocytic tumors, should be performed.

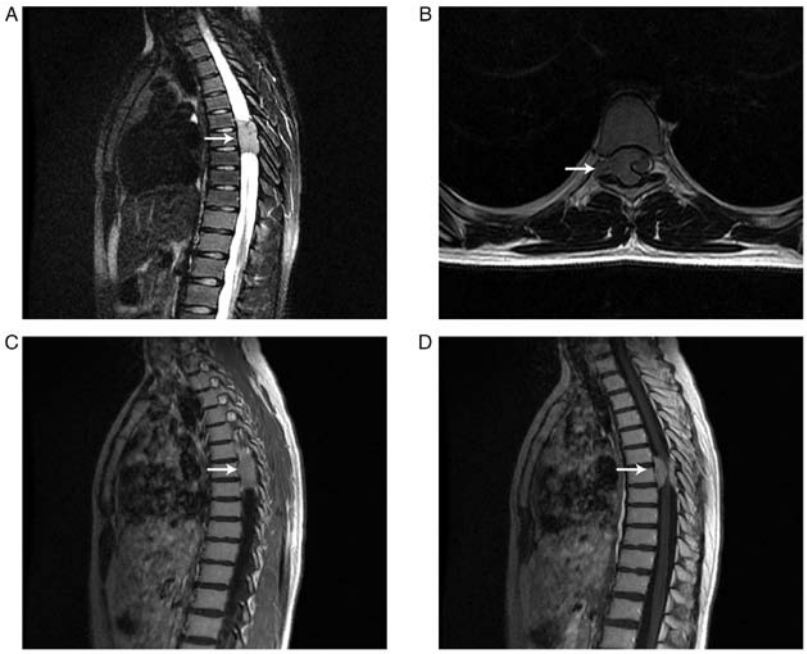

Figure 1. MRI examination of an oval mass in the T6-8 spinal canal (white arrows). (A) T2-weighted image showed mass from median sagittal section. (B) T2-weighted image demonstrated that the tumor grew out of the spinal canal through the intervertebral foramen from transverse sections. (C) T1-weighted image demonstrated an indistinct tumor boundary. (D) T1-weighted image demonstrated that the spinal cord was significantly compressed and displaced to the left side.

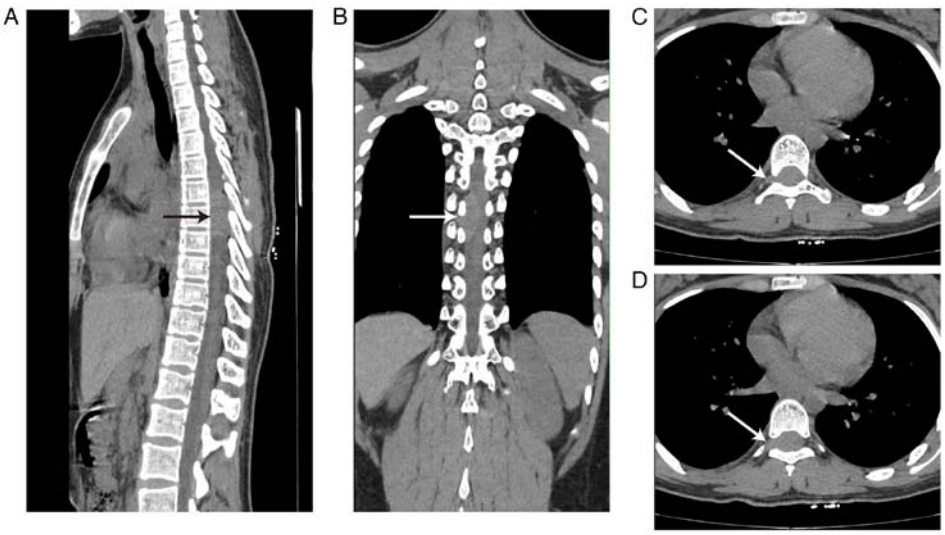

Figure 2. Non-contrast CT images of a mass in the T6-8 plane (arrows). (A) Median sagittal section demonstrated aggressive and invasive growth and indistinct borders from surrounding tissues. (B) Coronal section demonstrated that the spinal cord was significantly compressed and displaced to the left side. (C) Transverse sections demonstrated that the tumor grew out of the spinal canal through the intervertebral foramen. (D) Transverse sections demonstrated that the tumor grew out of the spinal canal through the intervertebral foramen significantly.

Primary spinal melanoma should also be differentiated from schwannoma. Schwannoma frequently occurs in association with cranial nerves, spinal nerve roots and the paraspinal sympathetic chain, thereby showing overlap with primary spinal melanoma (18,19). Melanotic schwannoma is a rare type of schwannoma that is composed of melanin-producing cells and has the characteristics of Schwann cells under electron microscopy, intracytoplasmic melanosomes and is reactive for melanoma markers (20). Primary spinal melanoma and melanotic schwannomas are neural crest-derived and are often positive for S100 and other melanocytic markers, such as MelanA and HMB-45 (18,19). Thus, both tumor types have histological overlap and histopathologic discrimination between primary spinal melanoma and melanotic schwannoma in individual patients is often difficult; therefore, immunohistochemistry may not be useful. However, the psammomatous body and the autosomal dominantly inherited Carney complex are associated with melanotic schwannoma and are useful for differentiating between the two tumor types (21,22). Carney complex is a rare multiple neoplasia syndrome characterized by multiple types of skin tumors, cardiac myxomas, pigmented lesions

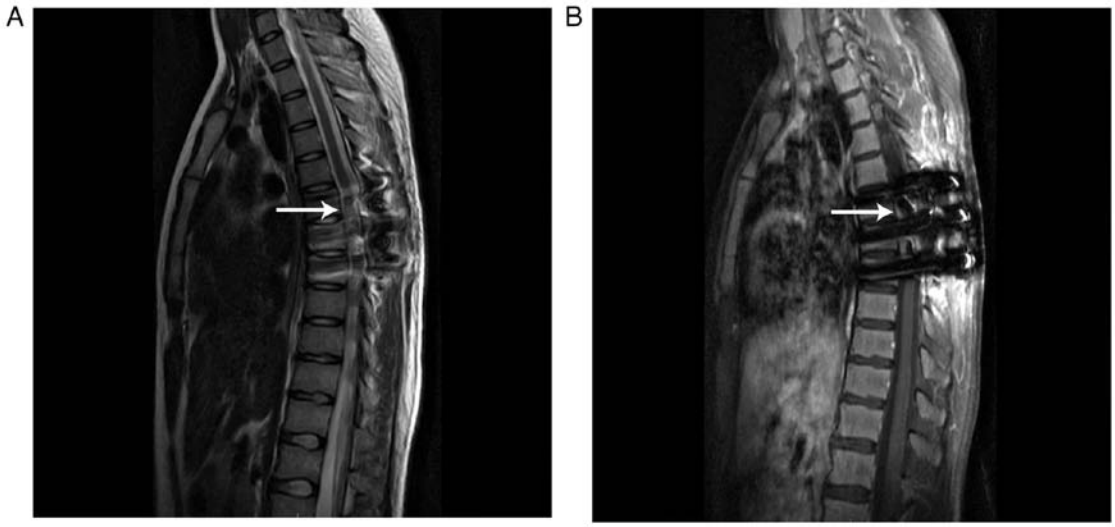

Figure 3. Postoperative MRI of a residual mass in the T6-8 spinal canal (white arrows). (A) T2-weighted image displaying the residual hyperintense mass. (B) T1-weighted image indicating the isointense or hypointense mass.

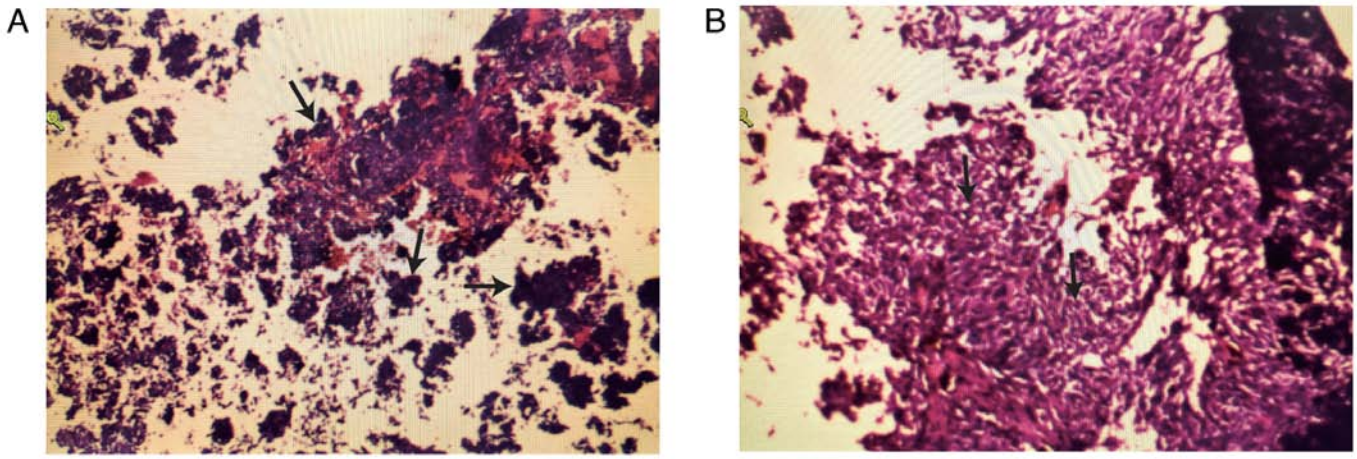

Figure 4. Histopathological examination after hematoxylin and eosin staining of the surgical specimen shows spindle cell features and melanin pigmentation. (A) Melanin pigmentations. (B) Spindle cell features were showed (black arrows). Magnification 400X).

and endocrine tumors, including pigmented nodular adrenocortical disease (23). Melanin schwannomas are highly specific to Carney syndrome, rarely occur in patients who do not have Carney syndrome and usually involve peripheral nerves (21-23). In the present case study, imaging, pathological examination and exclusion of melanotic schwannoma and systemic melanoma were performed prior to patient diagnosis.

CNS melanomas have an unpredictable clinical course and total resection is associated with improved prognosis (5). In a previous review of 67 cases of solitary primary intracranial melanomas with reported therapy, the mean survival after gross total resection was 19.58 months compared with 9.30 months after biopsy and subtotal resection and 3.40 months in patients who did not receive surgery (20,24-26). Therefore, total resection may be associated with longer survival than no or partial resection. However, the efficacy of postoperative radiotherapy or chemotherapy is controversial. Previous studies recommend postoperative radiotherapy in all cases and long-term survival has been reported with combined surgery and radiotherapy (10,24,27). Radiotherapy is also reported to have potential as a primary therapy in disseminated CNS melanomas or as a postoperative prophylactic adjuvant to prevent progression or recurrence (5). Chemotherapy has been used for primary CNS melanomas with variable response rates (5). Puyana *et al* (5) reported that gross total resection plus radiotherapy with or without chemotherapy significantly improved patient survival compared with gross total resection plus chemotherapy. Currently approved chemotherapeutics for malignant melanoma include dacarbazine, temozolomide and fotemustine; however, these drugs have demonstrated low efficacy as single therapeutic agents (26,28,29). Thus, chemotherapy may be paired with gross total resection and radiation, which may increase patient survival.

Biotherapeutic options are a promising, more targeted alternative to chemotherapy. These agents commonly include BRAF and MAPK kinase inhibitors that target the MAPK pathway, such as dabrafenib and vemurafenib (5,26,30). A previous study on the use of immunotherapy, such as programmed death-1 inhibitors and a cytotoxic T lymphocyte

antigen-4 inhibitor, reported improved outcomes in patients with advanced melanoma (31). It has previously been established that melanoma growth and progression depend on angiogenesis (32). Antiangiogenic therapy targeting the VEGF-A pathway has been reported as a possible strategy to prevent melanoma relapse and spread (33). Adjuvant treatment with the anti-VEGF-A antibody bevacizumab after resection of high-risk melanoma improved the disease-free interval but not overall survival in a large multicenter randomized phase 3 trial in patients with melanoma with high a risk of recurrence (34,35).

Radiotherapy or chemotherapy combined with bevacizumab has achieved promising results in the treatment of melanomas, particularly CNS tumors, because in addition to conferring antitumor effects, bevacizumab reduces peritumor edema and thus reduces the need for steroids (36-40). These findings suggest that bevacizumab may be warranted as an adjuvant treatment to minimize the risk of nerve function deficits. In addition, bevacizumab and temozolomide have been included in the Chinese Society of Clinical Oncology (41) and National Comprehensive Cancer Network (NCCN) (30) guidelines for the second- or third-line therapy of advanced melanoma.

In summary, primary malignant melanomas in the spinal canal are rare tumors with a high potential for recurrence and a high mortality rate if residual tumor is present; thus, total resection is essential for patients. However, depending on the tumor location, complete resection may be difficult, highlighting the need for more efficacious systemic treatment regimens and potential integration of newer biological agents. To our knowledge, the present study reported the first case of a primary malignant melanoma originating from the thoracic spinal cord with a residual tumor that responded well to a combination of chemoradiotherapy and bevacizumab. Thus, the present study provided new insight into the diagnosis and treatment of intraspinal tumors in which the spinal cord with a residual tumor responded to a combination of chemoradiotherapy and bevacizumab. Further studies are needed to investigate the mechanisms driving the development and treatment response of this type of tumor.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YZe, YZh and QF identified and selected this case. YZe and YZh drafted the manuscript. RL, JZ, YZe and QF reviewed and edited the manuscript. WJ, JZ and QF were involved in the patient's clinical management. YZh, YZe, RL and QF analyzed and interpreted data. RL and QF confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication of patient data and associated images.

Competing interests

The authors declare that they have no competing interests.

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