Primary Melanoma of the Cervical Spine with Cerebral Metastases: Case Report and Review of the Literature

J Yu, D-D Zhao, S Chen, J-M Zhang and J Xu

Department of Neurosurgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Primary spinal melanoma is a very rare condition: to date < 60 cases have been reported in the literature. A 48-year-old man presented with a 6-month history of upper- and lower-extremity numbness. Spinal magnetic resonance imaging (MRI) revealed a space-occupying lesion at the C2 – C6 level. This was confirmed as a melanoma by immunohistochemistry. Cerebral MRI showed multiple lesions with the same signal characteristics as those seen in the spinal lesion on MRI.

Complete skin, mucosal and retinal examination failed to show any primary lesion, therefore a diagnosis of primary cervical melanoma with brain metastases was made. To our knowledge this is the first report of a primary melanoma of the cervical spine with cerebral metastases at the time of diagnosis. This article presents pertinent reported literature and discusses the aetiology, diagnosis, treatment and prognosis of this unusual condition.

KEY WORDS: PRIMARY SPINAL MELANOMA; CEREBRAL METASTASES; DIAGNOSIS; TREATMENT; PROGNOSIS

Introduction

Primary malignant melanoma of the central nervous system (CNS) accounts for only 1% of all cases of melanoma.1–4 Primary spinal melanoma is an even rarer entity, first reported by Hirschberg in 1906:1,2 fewer than 60 cases have been reported,2,5 among which tumours of the middle and lower thoracic spine are the most common.2,5 Thus, the precise incidence, treatment and prognosis of primary spinal melanoma remains unclear. This paper presents a case of primary melanoma of the cervical spine with brain metastases at the time of diagnosis. In addition, the paper presents pertinent literature on melanoma and discusses the aetiology, diagnosis, treatment and prognosis of this unusual condition.

Case report

The patient's spouse provided verbal consent for this report to be published.

A 48-year-old man was admitted to the Department of Neurosurgery at the Second Affiliated Hospital, Hangzhou, China, on 28 January 2011 having complained of progressive numbness of the upper and lower extremities for the previous 6 months, but with no weakness of the extremities. The patient had also experienced shoulder and neck pain over the 1 month prior to admission.
His physical examination was unremarkable. Neurological examination revealed no abnormalities except for decreased superficial sensation at the C3 – T1 level, bilaterally. Magnetic resonance imaging (MRI) of the cervical spine revealed a space-occupying lesion at the C2 – C6 level, with hyperintense signals relative to the spinal cord on T1-weighted images, and hypointense signals on T2-weighted images (Fig. 1). After intravenous injection of gadolinium diethylenetriamine penta-acetic acid, MRI showed higher signal intensities of the lesion on T1-weighted images, with compression of the corresponding spinal cord. Neurological examination revealed no abnormalities except for decreased superficial sensation at the C3 – T1 level, bilaterally. Magnetic resonance imaging (MRI) of the cervical spine revealed a space-occupying lesion at the C2 – C6 level, with hyperintense signals relative to the spinal cord on T1-weighted images, and hypointense signals on T2-weighted images (Fig. 1). After intravenous injection of gadolinium diethylenetriamine penta-acetic acid, MRI showed higher signal intensities of the lesion on T1-weighted images, with compression of the corresponding spinal cord.

A clinical diagnosis of an intradural–extramedullary tumour was considered; such tumours have a high probability of being melanomas.\textsuperscript{2,3,6,7} Cerebral MRI showed multiple lesions, most of which were located on the surface of the brain within the cisterns or sulci, with hyperintense signals on T1-weighted images and hypointense signals on T2-weighted images (Fig. 2). There was no substantial mass effect or oedematous area around the lesions.

A complete skin, mucosal and retinal examination failed to show any primary lesions, so a diagnosis of primary cervical melanoma with brain metastases was made. Considering that a single lesion of the cervical spine had led to the patient’s symptoms, the team concluded that surgical excision of this mass was the best approach. On 10 February 2011 (13 days after admission), the patient underwent spinal surgery. A laminectomy was performed at the C2 – C6 level through a posterior approach. After incision of the dura, a black mass with intact capsule measuring 5.3 × 1.8 × 1.1 cm was observed ventrally. There were some areas of tight adherence to the pia mater. The neoplasm was only partially removed in order to save neural function because several nerve roots were involved. An intraoperative frozen-section procedure was performed with a Shandon Cryotome\textsuperscript{®} FSE (Thermo Fisher Scientific, Rockford, IL, USA).

FIGURE 1: Magnetic resonance images of the cervical spine in a 48-year-old man with a 6-month history of upper- and lower-extremity numbness, showing a space-occupying lesion at C2 – C6 level. (A) Hyperintense signal relative to the spinal cord on T1-weighted image; (B) hypointense signal on T2-weighted image.
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USA) to prepare 8-µm frozen sections, the findings of which suggested that the neoplasm comprised intradural small cells containing large amounts of pigment.

Tissue samples were sent for standard histopathological examination. Optical microscopy showed spindle and epithelioid cells with dense deposition of melanin granules growing around vessels. After depigmentation, vesicular nuclei and red-staining nucleoli were noted. Immunohistochemistry analysis was performed using standard hospital procedures; the neoplastic cells stained positive for S100 protein and the malignant melanoma monoclonal antibody HMB45 (Fig. 3).

The patient was then referred for radiotherapy and chemotherapy. His condition was, however, already terminal so he received no treatment and died 2 months later. A postmortem examination was not undertaken.

Discussion

Primary spinal melanoma is a very rare entity and, to our knowledge, there are no evidence-based guidelines for its diagnosis, management or prognosis. Some data can, however, be referred to for comparison with the present case. Hirano and Carton summarized 26 cases of malignant spinal cord melanoma before 1960 and, in Table 1, an additional 26 cases of primary melanoma of the spinal cord reported after 1960 are summarized. Thus, various authors have identified a total of 52 published cases of primary spinal cord melanoma – including intramedullary, intradural and extradural lesions – a mean incidence of one case reported every 2 years. Hirano and Carton reported a mean age of 46 years (range 25 – 71 years) for the cases reported prior to 1960 whereas, for the cases reported in Table 1 after 1960, the mean age at presentation was 50 years (range 15 – 80 years). Other findings relating to the 26 cases reported in Table 1 indicate the following: primary spinal cord melanomas were observed more frequently in females than in males (male : female ratio 1 : 1.36); lesions most often occurred during the sixth or seventh decade of life; thoracic
melanomas appear to be the most common type, followed by cervical melanomas. Compared with previously reported cases, the patient described in the current report had a relatively longer lesion, extending from C2 to C6.

Although there is no precise cellular origin for a primary spinal melanoma, it is often believed that a malignant melanoma can occur in any organ in which melanin-producing cells are present, such as the skin, mucosa, iris, retina, chromaffin tissue and the leptomeninges. Melanocytes, which produce melanin, are types of cells that arise from the neural crest during embryogenesis and migrate to the skin, mucous membranes and CNS.

Two theories have been proposed for the origin of CNS melanomas. The mesodermal theory proposes that a primary melanoma

FIGURE 3: (A) Histopathological examination (haematoxylin and eosin staining) showed spindle and epithelioid cells with dense deposition of melanin granules growing around vessels. After depigmentation, vesicular nuclei and red-staining nucleoli were noted (arrow). Immunohistochemistry evaluation showed that neoplastic cells stained positive for: (B) HMB45; and (C) the malignant melanoma monoclonal antibody S100 protein. Original magnification ×100.
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### TABLE 1:
Summary of the 26 cases of primary spinal cord melanoma reported since 1960

<table>
<thead>
<tr>
<th>Publication</th>
<th>Age, years/ Sex</th>
<th>Symptom duration, months</th>
<th>Site</th>
<th>Autopsy</th>
<th>Surgery</th>
<th>Adjuvant therapy</th>
<th>Survival duration, months</th>
<th>Last status</th>
</tr>
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<tr>
<td>Kiel et al., 1961</td>
<td>33/Female</td>
<td>5</td>
<td>C4 – C6</td>
<td>Y</td>
<td>STR</td>
<td>N</td>
<td>25</td>
<td>Dead</td>
</tr>
<tr>
<td>Holaday and Evans, 1968</td>
<td>20/Female</td>
<td>3</td>
<td>S2</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>12</td>
<td>Dead</td>
</tr>
<tr>
<td>Ozden et al., 1984</td>
<td>15/Female</td>
<td>4</td>
<td>C6</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>18</td>
<td>Alive</td>
</tr>
<tr>
<td>Ozden et al., 1984</td>
<td>30/Female</td>
<td>5</td>
<td>T9</td>
<td>N</td>
<td>U</td>
<td>Y</td>
<td>16</td>
<td>Alive</td>
</tr>
<tr>
<td>Larson et al., 1987</td>
<td>73/Male</td>
<td>6</td>
<td>T6 – T8</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>84</td>
<td>Alive</td>
</tr>
<tr>
<td>Larson et al., 1987</td>
<td>63/Male</td>
<td>96</td>
<td>T2 – T9</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>156</td>
<td>Dead</td>
</tr>
<tr>
<td>Larson et al., 1987</td>
<td>67/Female</td>
<td>18</td>
<td>T9 – T11</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>NR</td>
<td>Alive</td>
</tr>
<tr>
<td>Larson et al., 1987</td>
<td>57/Female</td>
<td>3</td>
<td>C1 – C3</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>30</td>
<td>Dead</td>
</tr>
<tr>
<td>Larson et al., 1987</td>
<td>69/Female</td>
<td>24</td>
<td>T9 – T10</td>
<td>N</td>
<td>STR</td>
<td>N</td>
<td>45</td>
<td>Dead</td>
</tr>
<tr>
<td>Yamasaki et al., 1989</td>
<td>31/Male</td>
<td>6</td>
<td>T6</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>23</td>
<td>Alive</td>
</tr>
<tr>
<td>Magni et al., 1996</td>
<td>64/Male</td>
<td>24</td>
<td>T8</td>
<td>N</td>
<td>U</td>
<td>Y</td>
<td>18</td>
<td>Alive</td>
</tr>
<tr>
<td>François et al., 1997</td>
<td>62/Male</td>
<td>18</td>
<td>T8</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>28</td>
<td>Alive</td>
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<tr>
<td>Salpietro et al., 1998</td>
<td>62/Male</td>
<td>1</td>
<td>C3</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>14</td>
<td>Dead</td>
</tr>
<tr>
<td>Salame et al., 1998</td>
<td>76/Female</td>
<td>6</td>
<td>T9 – 10</td>
<td>N</td>
<td>U</td>
<td>Y</td>
<td>15</td>
<td>Alive</td>
</tr>
<tr>
<td>Brat et al., 1999</td>
<td>71/Female</td>
<td>NR</td>
<td>T10</td>
<td>N</td>
<td>TR</td>
<td>N</td>
<td>14</td>
<td>Alive</td>
</tr>
<tr>
<td>Brat et al., 1999</td>
<td>52/Male</td>
<td>NR</td>
<td>C1</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>16</td>
<td>Alive</td>
</tr>
<tr>
<td>Brat et al., 1999</td>
<td>20/Female</td>
<td>NR</td>
<td>C4</td>
<td>N</td>
<td>STR</td>
<td>N</td>
<td>20</td>
<td>Alive</td>
</tr>
<tr>
<td>Brat et al., 1999</td>
<td>57/Female</td>
<td>NR</td>
<td>C4</td>
<td>N</td>
<td>STR</td>
<td>Y</td>
<td>8</td>
<td>Dead</td>
</tr>
<tr>
<td>Bidziński et al., 2000</td>
<td>36/Male</td>
<td>8</td>
<td>C6 – C7</td>
<td>N</td>
<td>TR</td>
<td>Y</td>
<td>48</td>
<td>Alive</td>
</tr>
<tr>
<td>Farrokh et al., 2001</td>
<td>80/Female</td>
<td>NR</td>
<td>T12 – L1</td>
<td>N</td>
<td>STR</td>
<td>N</td>
<td>9</td>
<td>Alive</td>
</tr>
<tr>
<td>Kounin et al., 2005</td>
<td>41/Female</td>
<td>9</td>
<td>C2 – C4</td>
<td>N</td>
<td>TR</td>
<td>N</td>
<td>3</td>
<td>Alive</td>
</tr>
<tr>
<td>Kim et al., 2010</td>
<td>34/Female</td>
<td>12</td>
<td>T4</td>
<td>N</td>
<td>TR</td>
<td>N</td>
<td>36</td>
<td>Alive</td>
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<tr>
<td>Kolasa M et al., 2010</td>
<td>57/Female</td>
<td>2</td>
<td>T10</td>
<td>N</td>
<td>TR^a</td>
<td>Y</td>
<td>12</td>
<td>Alive</td>
</tr>
<tr>
<td>Lee et al., 2010</td>
<td>39/Male</td>
<td>11</td>
<td>C1 – C6</td>
<td>N</td>
<td>TR</td>
<td>Y</td>
<td>14</td>
<td>Alive</td>
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<tr>
<td>Vij et al., 2010</td>
<td>40/Male</td>
<td>9</td>
<td>C1 – C2</td>
<td>NR</td>
<td>U</td>
<td>N</td>
<td>12</td>
<td>Alive</td>
</tr>
<tr>
<td>Fuld et al., 2011</td>
<td>62/Male</td>
<td>NR</td>
<td>C2</td>
<td>N</td>
<td>U</td>
<td>Y</td>
<td>11</td>
<td>Alive</td>
</tr>
</tbody>
</table>

C, cervical; S, sacral; T, thoracic; L, lumbar; STR, subtotal resection; U, unspecified surgery; TR, total resection; Y, yes; N, no; NR, not reported.

^aUnderwent a second surgical procedure due to tumour recurrence 1 year after total resection of the primary neoplasm.
in the CNS may originate from melanoblasts accompanying the pia sheaths of vascular bundles. The alternative theory is that such melanomas may originate from neuro-ectodermal rest cells during embryogenesis. Some researchers have paid much more interest to the second theory than the first, since it suggests a genetic origin for this tumour type and offers the promise that tumours may respond to gene therapy. This concept is, however, only a hypothesis at present and shows no applicable value in clinical medicine.

The clinical symptoms and signs of primary spinal cord melanoma are often nonspecific. Patients usually present with back pain and signs or symptoms of spinal cord compression (such as hemiparesis or sensation impairment). Some patients present with increased intracranial pressure caused by tumour obstruction of the cerebrospinal drainage. With cerebral metastases, patients may report headache or vomiting to a variable extent. In the present case, the ventral tumour compressed the spinothalamic tract, which resulted in numbness and a decrease in superficial sensations.

It has been suggested that MRI is the most effective imaging technique for revealing spinal cord melanoma. According to most authors, the MRI pattern of spinal cord melanoma includes signal hyperintensity on T1-weighted images and signal iso- or hypointensity on T2-weighted images. With injection of an appropriate contrast medium, there should be a moderate enhancement of the lesion. These features are thought to be caused by paramagnetic radicals in melanin or products from haemorrhage and may vary depending on intratumoral bleeding and melanin content. As a result, it is impossible for MRI to distinguish between melanoma and other melanin-containing tumours such as meningeal melanocytoma, pigmented menigioma or schwannoma. The MRI findings in the present case are similar to MRI descriptions for other cases in the available literature.

The immunohistochemical profiles and ultrastructural features of melanin-containing tumours also require consideration. Brat et al. suggested that melanocytic tumours with high-grade histopathological features should be designated as melanomas, with essential features including the following: hypercellularity; nuclear enlargement and atypical, large and multiple nucleoli; increased mitoses (> 2 per 10 high-powered fields); increased MIB-1 labelling index (> 3%); tumour necrosis; invasion of surrounding CNS tissue. In immunohistochemical terms, a melanoma is positive for HMB-45 (which indicates active melanosome formation) and S-100 (which is produced by cells with melanocytic differentiation).

In general, melanomas are malignant and liable to metastasize either locally or at a distance. Conversely, meningeal melanocytoma is a benign melanotic tumour. Ultrastructurally, melanocytomas lack anaplastic features (such as necrosis), significant mitotic activity and pleomorphism. Most importantly, melanocytomas do not metastasize. Tissue from the tumour in the present case was positive for HMB-45 and S-100 protein. Hayward has suggested that the following factors should be considered when trying to differentiate a primary spinal cord melanoma from a metastasis: no malignant melanoma tumour outside the CNS; involvement of the leptomeninges (spinal or cranial); intramedullary spinal lesions; hydrocephalus; tumour in the pituitary or pineal gland; and a single cerebral lesion. It has also been suggested that the diagnosis of primary CNS
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Melanoma should be made after dermatological and ophthalmological consultations have ruled out a metastatic lesion. The following two conditions have been widely accepted as criteria for primary spinal melanoma: (i) location of the tumour in the spine, with melanoma being confirmed histopathologically; (ii) secondary metastases from a cutaneous, mucosal or retinal primary tumour excluded by appropriate evaluation.

At our institute, it is convenient to conduct a thorough physical examination, ophthalmofundoscopy or computed tomography scan to exclude a primary melanoma located outside the CNS. Gastroscopy or enteroscopy are seldom performed if the only justification is to ensure that a primary mucosal melanoma is not present. Consequently, it is impossible to be certain that a CNS melanoma is a primary CNS tumour in any particular case. Autopsy proof of the absence of a melanoma extraneous to the spinal cord has often been difficult to obtain.

Complete postmortem examinations were only performed in nine of the 26 cases listed by Hirano and Carton. In the present case, a postmortem examination was not possible because the next of kin did not provide consent.

The differential diagnosis of a primary CNS melanoma from a metastatic lesion is extremely difficult because melanoma is the third most common cause of brain metastases after lung and breast cancer. The reported incidences of brain metastases in patients with melanoma range from 6% to 43% in clinical series and from 12% to 74% in autopsy series but, for spinal melanoma, the situation is very different.

In a series of 127 patients with spinal cord metastases, only one occurrence of malignant melanoma metastatic to the spinal cord or its coverings (epidurally) was reported: in these cases there were widespread metastases to all organs. In addition, intramedullary spinal cord metastasis has been reported to be an unusual condition in systemic cancers, occurring in as few as 2% of autopsy cases and usually signifying a late-stage event for the patient. Data indicate that intramedullary metastatic disease clinically affects only 0.1 – 0.4% of all cancer patients, which comprises only 1 – 3% of all intramedullary cord neoplasms.

Many reports of spinal metastatic melanomas have been reported, almost all of which are osseous metastases; however, very few cases of solitary intraspinal metastases have been published. Thus, when a spinal cord melanoma with no vertebral involvement is discovered, the clinical findings such as those reported in the present case indicate that a lesion could be a primary tumour if primary lesions in other areas have been ruled out and if the spinal lesion is shown to be attached to the leptomeninges.

We consider that the case reported here represents a primary melanoma of the cervical spine with cerebral metastases, because the following diagnostic procedures were undertaken to exclude other primary tumours. First, a thorough physical examination was performed: chest X-ray, bone scan and retinal examination failed to identify any alternative site of the primary melanoma. Secondly, histopathological and immunohistochemistry analyses ensured that the solitary lesion of the spine was a melanoma that accounted for the main symptoms experienced by the patient. Thirdly, MRI examination indicated that the multiple cerebral lesions observed in this patient shared the same signal characteristics as those observed in the spinal lesion. These findings led to the conclusion that the brain
metastases in this patient arose from cerebrospinal fluid dissemination.

Although data from prospective randomized studies are lacking, it is widely accepted that primary spinal melanomas are more indolent malignancies than the CNS metastases commonly observed in patients with primary cutaneous melanomas: metastatic spinal lesions grow rapidly and usually have a fatal outcome within 6 months.\textsuperscript{17,27}

There is agreement that complete surgical excision is the optimum treatment for primary spinal cord melanoma.\textsuperscript{3,17} The role and efficacy of radiotherapy\textsuperscript{2,7} and chemotherapy\textsuperscript{28} remain controversial. Surgical excision of the lesion is generally incomplete and not curative, therefore adjuvant therapy – especially radiotherapy – is frequently recommended postsurgery even though malignant melanoma does not seem to be particularly radiosensitive.\textsuperscript{2,3,12} It has been suggested that appropriate case-specific therapy – involving surgery, radiotherapy and chemotherapy – should be planned on the basis of a comprehensive diagnosis.\textsuperscript{1}

The lack of information about treatment for primary melanomas of the spinal cord means that data from metastatic melanoma should be considered when considering how to treat a case. For cerebral metastatic melanoma, the combination of surgery and whole-brain radiation therapy may offer the most suitable treatment for a single metastasis, or for patients with absent or limited systemic disease and good neurological condition.\textsuperscript{29} In addition, a combination of fractionated radiation and chemotherapy has reportedly been successful in palliating disseminated melanoma.\textsuperscript{26} The patient presented in the present report received what we considered to be the best and most aggressive treatment available.

Review of the other published case reports has indicated that the survival duration of patients with primary spinal melanoma ranged from 3\textsuperscript{17} to 156\textsuperscript{12} months (13 years) (Table 1). This duration varies considerably depending on several factors including tumour site, extent of resection, response to adjuvant therapy and, in some cases, metastases of the primary spinal melanoma.

In 1961, Kiel et al.\textsuperscript{9} reported a survival rate of 15\% after 2 years following surgical treatment while, in 1987, Larson et al.\textsuperscript{12} found an impressive mean life expectancy of 6 years 7 months when surgery was followed by radiotherapy. In 1998, Salpietro et al.\textsuperscript{2} reported a case of primary cervical melanoma with brain metastases, in which the patient died 15 months after the onset of symptoms but only 1 month after the brain metastases occurred. Such findings imply that metastases within the CNS suggest a poor prognosis.

In conclusion, although there are several reports of cerebral metastases from primary spinal melanoma,\textsuperscript{2,30} to our knowledge the case presented here is the first report of a primary cervical melanoma with cerebral metastases at the time of diagnosis. The outcome was equally poor to that for primary malignant melanoma of the skin followed by brain metastatic melanoma, particularly because total surgical resection could not be achieved.

Conflicts of interest
The authors had no conflict of interest to declare in relation to this article.
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References


Author’s address for correspondence

Associate Professor Jing Xu
Department of Neurosurgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China.

E-mail: jingxu@zju.edu.cn