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Primary intramedullary melanoma

Case report and histogenetic features

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Primary intramedullary melanoma is a very rare tumor, most frequently occurring in the middle or lower thoracic spinal cord. The authors present a new case of primary cervical cord melanoma that developed in a 62-year-old man whose tumor was surgically treated and subsequently received radiation therapy. Clinical and histogenetic features of this neoplasm, results of chemo-, radio-, and immunotherapy are reported. Both "disembryogenetic" and "mesodermal" hypotheses on the origin of primary spinal melanoma are discussed.

Key Words * melanoma * spinal cord tumor * intramedullary lesion

Primary malignant melanoma in the central nervous system (CNS) accounts for approximately 1% of all melanoma cases. Primary spinal melanoma is a rare tumor first reported by Hirschberg[20] in 1906. Since then, only 35 cases have been reported,[26] with the tumor most frequently occurring in the middle and lower thoracic spinal cord.[17,19,22,23,30,46] A review of the 37 cases (including our case) of primary spinal melanomas is reported in Table 1.

TABLE 1
PRIMARY MELANOMAS OF THE SPINAL CORD (37 CASES) PREVIOUSLY REPORTED IN THE LITERATURE

Case No.	Authors & Year	Age (yrs), Sex	Duration of Symptoms (mos)	Site of Tumor	Laminectomy	Diagnosis	Metastasis
1	Hirschberg, 1906	67, F	3	thoracic	no	autopsy	
2	Boit, 1907	51, M	11	thoracic	no	autopsy	liver, spleen
3	Esser, 1907	32, M	15 d	thoracic	yes	during life, autopsy	
4	Kawashima, 1910	26, F	7	thoracic	no	autopsy	diffuse leptomeningeal dissemination
5	Lindbom, 1912	45, F	2	cervical	no	autopsy	
6	Koelichen, 1916	25, M	18	cervical	yes	autopsy	
7	Ringerz, 1926	61, F	6	thoracic	yes	autopsy	brain not examined
8	Schmid, 1926	71, M	14	thoracic	no	autopsy	small pigmented foci over cerebral dura mater
9	Bau-Prussak & Mackiewicz, 1929	29, M	21 d	thoracolumbar	yes	during life	
10	Bell, 1930	48, F	3	cervicothoracic	yes	during life	
11	De Blasi, 1930	71, F	6	thoracic	yes	autopsy	brain not examined
12	Van Bogaert & Verbrugge, 1933	38, M	6	thoracic	yes	during life, autopsy	brain not examined
13	Schnitker & Ayer, 1938	49, F	?	thoracic	yes	autopsy	lung, liver, uterus, diffuse leptomeningeal dissemination
14	Da Costa & Love, 1939	55, F	24	thoracic	yes	during life	
15	Garcin, 1941	52, M	21 d	lumbosacral	yes	during life	
16	Mackay & Hurteau, 1942	32, F	10	cervical	no	autopsy	lesion extending to lower medulla & cervical cord
17	Castaner, et al., 1950	52, F	12	lumbar	yes	during life	
18	Forbes & Maloney, 1950	57, M	?	thoracic	yes	autopsy	diffuse leptomeningeal dissemination
19	Kissel, et al., 1950	25, F	2	cervical	yes	during life	
20	King & Propst, 1951	47, M	2	lumbar	yes	during life, autopsy	nodules at base of brain & ventricles ependyma; diffuse leptomeningeal dissemination
21	De Assis & De Luccia, 1951	26, M	7	lumbar	yes	during life	
22	King, et al., 1952	53, M	12	lumbar	yes	during life, autopsy	pigmented foci over dura mater & brain base
23	Perino, 1953	40, M	?	thoracic	yes	during life	
24	Roca de Vináls, 1954	50, F	6	thoracolumbar	yes	during life	
25	Gibson, et al., 1957	51, F	?	thoracic	no	autopsy	diffuse leptomeningeal dissemination
26	Hirano & Carton, 1960	42, M	1	thoracic	yes	during life, autopsy	
27	Kiel, et al., 1961	33, F	5	cervical	yes	during life, autopsy	cerebral leptomeningeal pigmentation
28	Özden, et al., 1984	15, F	4	cervical	yes	during life	
29		30, F	5	thoracic	yes	during life	
30	Larson, et al., 1987	73, M	6	thoracic	yes	during life	
31		63, M	96	thoracic	yes	during life	
32		67, F	18	thoracic	yes	during life	
33		57, F	3	cervical	yes	during life	
34		69, F	24	thoracic	yes	during life	
35	Yamasaki, et al., 1989	31, M	6	thoracic	yes	during life	
36	Magni, et al., 1996	64, M	24	thoracic	yes	during life	
37	Present case	62, M	1	cervical	yes	during life	nodules diffused to all brain tissue; three large lesions in the cerebellum, rt frontal hemisphere & lt pons-midbrain; diffuse leptomeningeal dissemination

* ? = unknown; d = days.

To diagnose a primary intramedullary melanoma, Hayward's classification criteria[17] should be fulfilled: 1) no malignant melanoma, either primary or metastatic, should be present elsewhere outside the CNS; 2) nerve roots and the dura should not be involved by the tumor; and 3) the lesion should be pathologically confirmed. Primary spinal melanoma must be differentiated from primary melanotic tumor of the leptomeninges, usually known as meningeal melanocytoma, which is a benign lesion with a prolonged clinical course, that carries a better prognosis. We present here a new case of primary intramedullary cervical melanoma.

CASE REPORT

History and Examination. This 62-year-old man was admitted to the Department of Neurosurgery in October 1996 complaining of mild neck pain, gradual onset of weakness in the left arm and leg, and "pins and needles" sensation in the left hand. The pain

had progressively worsened 1 month before admission. Results from neurological examination demonstrated spastic paresis with hyperreflexia of the left arm and sensory disturbances in the neck and proximally in both arms. The results of laboratory tests indicated no abnormalities. Magnetic resonance (MR) imaging of the cervical spine revealed an intramedullary lesion at the C-3 level, with a hyperintense signal relative to the spinal cord both on T₁- and T₂-weighted images. Intravenous injection of gadolinium diethylene triamine pentaacetic acid clearly showed an enhanced higher signal intensity lesion on T₁-weighted images (Fig. 1).

Fig. 1. Spin-echo T₁-weighted MR image, sagittal section, showing a high signal intensity mass at the C-3 level, with hypointense signal above and below the lesion.

The patient underwent angiography of the spine, which revealed a pathological circle with feeding vessels from the anterior spinal artery, visible through the left radicular artery positioned between C4-5 (Fig. 2).

Fig. 2. Angiogram of the spine showing a pathological blush with feeding vessels of the anterior spinal artery visible through the left radicular artery at C4-5.

Operation. On October 17, the patient underwent spinal surgery; a laminectomy at C-3 was accomplished via a posterior approach. At operation, the dura appeared to be intact. Once exposed, the spinal cord appeared normal on the surface, although it was swollen and enlarged pial arteries were visualized. No nerve root involvement or extramedullary extension was observed.

After performing a midline cordotomy, a soft, vascularized bluish-black mass lesion within the spinal cord on the left side at the C-3 level was revealed. The intramedullary tumor was partially removed because of vascularization, adherence in the anterior region, and poorly defined margins of the lesion itself. Intraoperative histological examination of a frozen section demonstrated a malignant melanoma. The permanent specimens of the lesion demonstrated spindle cell proliferation with extensive deposition of melanin granules (Fig. 3 upper). Nuclear aplasia and mitoses were observed (Fig 3 lower). The tumor was subjected to immunocytochemical examination with monoclonal antibody anti-HBM-45, a useful marker for melanocytic differentiation in a neoplasm, which is indicative of active melanosome production and is localized in Stages 1 and 2 melanosomes.[5,41] Tumor cells stained positive for HBM-45.

Fig. 3. Photomicrographs of the patient's malignant melanoma. H & E. Upper: Clusters of malignant spindle cells with deposition of melanin granules; nuclear anaplasia and mitoses are observed. Original magnification X 90. Lower: A markedly cellular lesion made of epithelioid and spindle cells with dense deposition of melanin granules. Original magnification X 180.

Postoperative Course. The patient's postoperative clinical examination revealed mild neurological improvement. The patient underwent dermatological and ophthalmological examination, which did not show other evidence of a primary origin of melanoma. He was discharged on October 31, 1996 and underwent postoperative radiotherapy of the entire cervical spine with two opposed, evenly weighted, laterolateral fields. Radiation therapy was performed with cobalt-60 to a dose of 44 Gy administered in 22 fractions of 2 Gy per fraction 5 days per week, with both fields treated daily over a period of 36 days. The superior and inferior borders of the fields included at least two vertebral bodies in either direction from the target volume determined by MR image. The field width encompassed the whole vertebra. The dose was calculated at midplane. The patient tolerated the treatment well and had good improvement of sensitive and motor symptoms. The toxicity of treatment was negligible (dermatitis II degree responsive to local steroid-antibiotic therapy). Follow-up examination at 14 months showed good improvement of the left hemiparesis.

Follow-Up Examination. In February 1998, the patient started complaining of headache, vomiting and weight loss. Magnetic resonance images of the brain were obtained, and we observed metastasis through CSF dissemination in the right left frontal hemisphere, cerebellum, left pons, and midbrain. Death occurred 1 month later, 15 months after onset of symptoms.

DISCUSSION

We describe a patient with a rare primary malignant melanoma of the cervical spinal cord. Primary spinal melanoma most

frequently occurs in the middle and lower thoracic cord.[17,19,22,23,46] An extensive review of 27 cases of malignant melanoma involving the CNS was reported in 1976 by Hayward,[17] and four of these lesions were located in the spinal cord. One lesion was situated in the cervical cord, two were dorsal, and one involved the conus medullaris. In records from the Mayo Clinic of patients with primary melanoma of the spinal cord reviewed by Larson, et al.,[23] only one patient presented with a cervical cord lesion; in the other patients, the melanoma was found in the thoracic cord at the T-6 level or more distally. Magni, et al.,[26] in their recent review of the literature reported the tumor more often located in the middle or lower thoracic cord.

In our case, according to Hayward's[17] classification criteria, melanoma was not detected outside the CNS; the nerve root and the dura were not involved by the tumor, and the lesion was confirmed pathologically. As Hayward points out, a malignant melanoma could occur in any organ in which melanin-containing cells are present. These cells are a normal constituent of many sites in addition to the skin; for example, the iris, ciliary body, choroid, and retina of the eye, and chromaffin tissue. An accurate physical examination to search for a primary cutaneous, mucosal, or ocular melanoma is recommended and is usually sufficient to exclude evidence of systemic disease. In our patient, an angiogram of the spine revealed a pathological circle, in contrast to the recent case of thoracic melanoma reported by Yamasaki, et al.,[46] in which no feeding vessels or pathological blush were observed. The appearance of the lesion on MR imaging was found to be compatible with the reports in the literature: preoperative MR images revealed a pattern similar to that of intracerebral melanoma, which is thought to be caused by the paramagnetic products of subacute and chronic hemorrhage, as well as the paramagnetic stable free radicals known to exist within melanin.[25,46] The eccentric intramedullary location of the tumor in the cervical cord explained the asymmetric myelopathy observed at neurological examination.

Primary intramedullary melanoma exhibits either slow progression or rapid decline, and this lesion is different from either meningeal melanocytoma or the more common type of melanoma of the skin with metastases to the CNS. Meningeal melanocytoma (or primary melanotic tumor of the leptomeninges) is a rare benign melanotic tumor deriving from the melanocytes of the leptomeninges and occurring anywhere in the cranial and spinal meninges. Complete surgical removal is the treatment of choice, and radiotherapy is usually unnecessary. In spite of the tumor's benign biological behavior, the prognosis remains uncertain, because of possible local recurrences. Magnetic resonance imaging reveals variable appearance because of differing degrees of melanization and does not reliably distinguish meningeal melanocytomas from other pigmented tumors such as primary malignant melanoma. Meningeal melanocytoma usually shows increased signal intensity on T₁-weighted images, iso- or low intensity on T₂-weighted images, and mild but homogeneous enhancement after administration of contrast material.[9,43] Surgical, ultrastructural, and immunohistochemical criteria are more relevant when distinguishing meningeal melanocytoma from primary malignant melanoma. At surgery, the well-defined margins of the lesion and the absence of nerve roots and dura involvement by the tumor are suggestive of meningeal melanocytoma. Ultrastructurally, melanocytomas lack anaplastic features such as necrosis, significant mitotic activity, and pleomorphism. Neither recent nor old hemorrhage is present, in contrast with primary melanomas. Magnetic resonance imaging cannot reliably distinguish between the presence of melanin and hemosiderin, both of which produce decreased T₂ relaxation images. Immunohistochemically, meningeal melanocytomas cells are immunoreactive for S-100 protein and vimentin but not for epithelial membrane antigen. The low proliferative activity in bromodeoxyuridine labeling, associated with the absence of anaplastic features, gives a better prognosis to patients affected by melanocytoma: complete surgical resection of the lesion can be curative.[43]

Melanoma of the skin with metastases to the CNS progresses rapidly and is often fatal within 6 months.[1,5,19,23,35,46] Primary spinal melanoma is a more indolent malignancy than melanoma which metastasizes to the CNS.[17,19,23,39,42] The surgical excision of the lesion alone is not usually curative:[2,17,37] radiotherapy and chemotherapy are often performed after surgery, although malignant melanoma does not seem to be responsive to those treatments.[7,15,18,21,23,24,26,29,34,42] Active specific immunotherapy has also been used, often with encouraging results,[27,28] and the best results have been obtained in patients with minimal residual disease after resection of the tumor. Prolonged survival of several years has been achieved, with little toxicity attributable to the treatment.[27,28]

It is of interest to discuss the histogenesis of primary intramedullary melanomas. Melanocytic cells arise in the neural crest by the 6th week and migrate to their destination, reaching the skin by the 10th week and the meninges by the 20th week of embryological development.[10,11,33,44] An interesting pathogenetic hypothesis of primary intramedullary melanoma suggests that, during embryogenesis, few neuroectodermal rest cells migrate to and reside within the neural tube and its coverings.[23,31,41] These cells are, therefore, not "committed" and are unable to establish correct connections with other cells and to interact with chemical markers, which may mediate outward migration and cellular maturation.[3,8,9,12,13,32] The development of neoplasm could be dependent on the stamina of these cells. Cellular migration-related anomalies occur early or late. Early migration disorders are usually genetically determined.[6,40] However, they may be secondary to environmental causes.[4,16,45,47] Primary intramedullary melanoma, consequently, could be dependent on defective genomic expression. The "mesodermal" theory of primary spinal melanoma origin, on the other hand, suggests that melanoma may occur in any organ in

which melanoblasts can normally be found;[17,23,31] this includes the pia mater, which not only covers the brain but also sheathes the blood vessels passing into it and the spinal cord. These pial pigmented cells, although present everywhere, are most numerous around the spinal cord and on the ventral aspect of the brain.[14,17,36,38] The former hypothesis is most interesting, because it suggests a genetic origin of this tumor, thus raising the new possibility of genic treatment of this lesion in the future.

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