

Accepted Manuscript

Title: Primary scattered multifocal melanocytomas in spinal canal mimicking neurofibromatosis

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PII: S1529-9430(16)00452-6

DOI: <http://dx.doi.org/doi: 10.1016/j.spinee.2016.03.007>

Reference: SPINEE 56950



To appear in: *The Spine Journal*

Received date: 3-10-2015

Revised date: 4-2-2016

Accepted date: 4-3-2016

Please cite this article as: Chenlong Yang, Jingyi Fang, Guang Li, Jun Yang, Yulun Xu, Primary scattered multifocal melanocytomas in spinal canal mimicking neurofibromatosis, *The Spine Journal* (2016), <http://dx.doi.org/doi: 10.1016/j.spinee.2016.03.007>.

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Primary Scattered Multifocal Melanocytomas in Spinal Canal Mimicking

Neurofibromatosis

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3 **STUDY FUNDING:** No targeted funding reported.

4 **DISCLOSURE:** The authors report no disclosures relevant to the manuscript.

5

6 **Abstract**

7 **Background context:** Meningeal melanocytoma is an extremely rare pigmented tumor
8 derived from leptomeningeal melanocytes. By and large it is considered to be a
9 well-differentiated and slow-growing benign lesion. Generally, meningeal melanocytomas
10 are solitary lesions, and the occurrence of the primary multifocal form in the central
11 nervous system is exceedingly rare; it has been previously reported in only six cases.

12 **Purpose:** The present report illustrates a 41-year-old woman with primary multifocal
13 meningeal melanocytoma in the spinal canal. Contrary to earlier reports, the tumors
14 presented with a scattered appearance mimicking neurofibromatosis.

15 **Study design:** A case report and review of literature.

16 **Methods:** On admission, the cerebral MR images of the patient were normal, whereas
17 the spinal MR images showed scattered multifocal nodules mimicking neurofibromatosis.
18 Surgical resection of the responsible lesions was scheduled. In addition to this case
19 presentation, relevant previous reports were reviewed, and the challenging diagnosis,
20 management, and prognosis of meningeal melanocytoma are discussed.

21 **Results:** Gross total resection of the two largest lesions was achieved, and
22 histopathological examinations confirmed the diagnosis. Despite the benign

1 histopathological findings, the patient had an aggressive clinical course. On follow-up at
2 18 months after surgery, she succumbed to the disease.

3 **Conclusions:** Clinicians should be alert to a potential aggressive clinical course of
4 meningeal melanocytoma, despite its benign histopathological nature. Of particular note
5 is multifocality and diffuse leptomeningeal hyperpigmentation, which may suggest a poor
6 prognosis. A combined treatment including surgical resection and adjuvant radiotherapy
7 should be considered, and long-term close follow-up is necessary.

8

9 **Key words:** Meningeal melanocytoma; Melanocytoma; Spinal tumor; Multifocality;
10 Neurofibromatosis

11

1 **Introduction**

2 Meningeal melanocytoma is an extremely rare pigmented tumor of the central
3 nervous system (CNS) derived from leptomeningeal melanocytes, with the majority
4 located in the posterior fossa and spinal canal [1-3]. Meningeal melanocytoma is
5 generally considered as a well-differentiated and slow-growing benign tumor,
6 corresponding histologically to World Health Organization (WHO) grade I [3].
7 However, malignant progression with infiltrative growth or leptomeningeal spread
8 secondary to malignant transformation has also been reported in previous studies
9 [4-7].

10 Generally, meningeal melanocytomas are solitary lesions, and the occurrence of
11 the primary multifocal form in the CNS is exceedingly rare; only six previous cases
12 have been reported [8-13]. Ali et al. proposed that primary multifocal meningeal
13 melanocytoma should be considered as a distinct pathological entity, and multifocality
14 may portend an aggressive clinical course and a poor prognosis [8]. Herein, we report
15 another case with primary multifocal meningeal melanocytoma in the spinal canal.
16 Contrary to earlier reports, the tumors presented with a scattered appearance
17 mimicking neurofibromatosis. The relevant literature has been reviewed, and the
18 challenging diagnosis, management, and prognosis are discussed.

19 **Case report**

20 A 41-year-old woman presented with a 7-month history of pain in the left lumbosacral
21 region and radiating pain to the left lower extremity. Over the month prior to admission,

1 the patient indicated that the pain had increased impairing her gait, and it was
2 exacerbated by coughing or sneezing. She also complained of a new onset of
3 numbness in the anterior surface of the left thigh in the final 10 days prior to admission.
4 Physical examination revealed a loss of sensation in the distribution of the L2 and L3
5 dermatomes. No motor deficit, sphincter dysfunction, or cutaneous abnormality was
6 noted. Vision and hearing were both normal. There was no remarkable finding in the
7 patient's past medical history, and she denied a family history of central nervous
8 system tumors. She had no history of hypertension, diabetes mellitus, cigarette
9 smoking, polyarthritis, stroke, or cardiac disease. The baseline laboratory data were
10 normal. Cerebral magnetic resonance imaging (MRI) was requested and revealed no
11 abnormality. Spinal MRI demonstrated scattered multifocal nodules in the
12 thoracolumbar segments (Figure 1). The T1-weighted images showed homogeneous
13 hyperintensity, and the T2-weighted images showed homogeneous hypointensity.
14 After the administration of gadolinium-diethylene triamine pentaacetic acid
15 (Gd-DTPA), the tumors were homogeneously enhanced; nevertheless, the contrast
16 enhancement of the nodules was evidently not revealed by visual assessment
17 because of strong T1 hyperintensity on unenhanced images. Additionally, diffuse
18 leptomeningeal enhancement was noted. The largest mass at the T12-L1 vertebral
19 level was extradural, and the other masses appeared to be intradural-extramedullary.
20 A suspected diagnosis of neurofibromatosis was made.

21 A surgical strategy including laminotomy at the T11-L1 vertebral level and
22 tumorectomy of the two largest masses via a posterior midline approach was adopted.

1 An epidural tumor was encountered at the T12-L1 level, and the other tumor was
2 found subdurally at the T11-T12 level after dural incision. The tumors as well as the
3 local duramater were black-pigmented. The tumor had a tight dural attachment and its
4 vascularity was derived from dural vessels. The two largest responsible masses were
5 grossly removed as total excisions. The pathological and immunohistochemical
6 examinations confirmed a diagnosis of multifocal melanocytoma (Figure 2).
7 Microscopically, the diffusely distributed black melanin-pigmented deposits obscured
8 the observation of cell morphology and microstructure, necessitating a bleaching
9 procedure. The tumor was highly cellular and composed of monomorphic spindle or
10 epithelioid cells arranged in a fascicled or nested growth pattern, with variable
11 amounts of melanin pigment in the cytoplasm. Tumor cells had prominent
12 oval-shaped nucleoli without pleomorphism. Mitotic activity and necrosis were absent.
13 Immunohistochemical examinations supported the diagnosis, with positive staining for
14 antimelanoma monoclonal antibody (HMB-45), vimentin, and S-100 protein, but
15 negative staining for glial fibrillary acidic protein (GFAP), epithelial membrane antigen
16 (EMA), and synaptophysin (SYN). The proportion of Ki-67 positive cells was
17 approximately 4%.

18 Given the WHO classification as grade I and the reported indolent biological
19 activity of meningeal melanocytomas, no adjuvant radiotherapy or chemotherapy was
20 recommended. Immediately after surgery, the patient's radicular pain significantly
21 improved. The numbness and anesthesia in the anterior surface of the left thigh were
22 relieved by 1 month after the operation. Unfortunately, at follow-up 18 months after

1 surgery, the patient presented with cough and dysphagia, and lapsed into a coma
2 within 1 week. Brain MRI at the local institution revealed multiple nodules with
3 hyperintensity on T1-weighted images and hypointensity on T2-weighted images in
4 the posterior fossa, which was presumed to represent intracranial metastasis. Given
5 the disease progression and the poor Karnofsky score (20%), no further intervention
6 was considered and the patient succumbed to the disease 2 weeks later.

7 Discussion

8 Meningeal melanocytoma is an extremely rare tumor arising from leptomeningeal
9 melanocytes, and it consist of approximately 0.06–0.1% of all CNS tumors [14]. This
10 entity can be found in any spinal region including intramedullary, intradural
11 extramedullary, and extradural compartments. Meningeal melanocytoma is the
12 histologically benign variant of a continuous melanocytic tumor spectrum in which
13 primary malignant melanoma represents its malignant counterpart, their
14 aggressiveness being entirely different. As distinct from malignant melanomas,
15 meningeal melanocytomas are generally considered as a benign tumor with a
16 nonaggressive clinical progression and non-proliferative histological characteristics.
17 Meningeal melanocytoma corresponds to grade I in WHO 2007 classification of CNS
18 tumors [15]. Given the malignant progression has been described in a few isolated
19 case reports, it is crucial for the clinicians to be aware of the potential aggressive
20 behavior of meningeal melanocytomas.

1 The preoperative diagnosis of spinal meningeal melanocytoma is challenging, as
2 it can be easily mistaken for more common spinal neoplasms such as meningioma
3 and schwannoma, and MRI can provide suggestive information pointing to
4 melanocytic tumors. The paramagnetic properties of free radicals in melanin shorten
5 the T1 and T2 relaxation times, leading to a characteristic MRI appearance with
6 hyperintensity on T1-weighted imaging and hypointensity on T2-weighted imaging
7 [16-18]. Moreover, these typical signal characteristics are strongly related to the
8 concentration of the melanin pigment [16]. On gross inspection, the tumor can appear
9 encapsulated and remarkably black-pigmented. The dura mater attachment is usually
10 tight, and the local dura mater can also be pigmented. However, these typical
11 radiological patterns and gross findings cannot permit distinction between meningeal
12 melanocytoma and other melanotic tumors.

13 The differential diagnosis of spinal meningeal melanocytoma includes malignant
14 melanoma, intermediate-grade melanocytoma, melanotic meningioma, melanotic
15 schwannoma, cavernous malformation, and hypervascular metastatic tumors [19-22].
16 Additionally, in the current patient, the multifocal tumors presented with a scattered
17 appearance mimicking neurofibromatosis, which has not been identified in previous
18 studies; and preoperatively a suspected diagnosis of neurofibromatosis should be
19 considered. A definitive diagnosis of melanocytoma still depends on postoperative
20 pathological and immunohistochemical analyses, and a benign pathological
21 appearance in favor of the low-grade WHO classification. Following a
22 melanin-bleaching procedure if necessary, the tumor was found to be highly cellular

1 and composed of monomorphic spindle or epithelioid cells arranged in a fascicled or
2 nested growth pattern; there were no anaplastic features such as mitotic activity and
3 necrosis. Immunohistochemical examinations can facilitate the diagnosis, showing
4 positive staining for HMB-45, vimentin, and S-100 protein, whereas staining for GFAP,
5 EMA, and SYN is negative. The absence of nuclear atypia, mitotic figures, necrosis,
6 and microvascular invasion and a low proliferation index (Ki-67, <5%) help distinguish
7 melanocytoma from malignant melanoma [12].

8 In fact, in 1989, Cordoba et al. noted the potentially aggressive behavior of
9 meningeal melanocytomas, and suggested that they should be considered as a
10 borderline malignant tumors [23]. In the subsequent period, malignant progression
11 with infiltrative growth or leptomeningeal spread secondary to malignant
12 transformation has been reported in a few case reports, despite the well-differentiated
13 and benign histopathological features of melanocytomas [5-7, 24, 25].

14 Primary malignant melanomas are usually solitary lesions, the multifocal form
15 being exceedingly rare. As Ali et al. considered, notwithstanding the possible
16 leptomeningeal seeding that can also explain the multifocality, multiple tumors are
17 usually found after malignant transformation; the subsequent histopathology
18 confirmed a transformed "malignant melanoma". They believed that multifocal
19 meningeal melanocytoma is a distinct pathological entity, which portends an
20 aggressive clinical course and a poor prognosis, even when malignant pathological
21 features are absent. These authors also reported a patient with multifocal meningeal

1 melanocytomas involving both cerebellopontine angles and the thoracic spinal cord,
2 and neurofibromatosis was suspected, which is similar to the preoperative diagnosis
3 of the current case [8]. Further, we reviewed the relevant literature, and were able to
4 retrieve only six case reports involving primary multifocal meningeal melanocytomas.
5 The clinical profiles are summarized in Table 1. Foit et al. identified distinct
6 pathological types from different tissue samples, and they proposed that primary
7 multifocal meningeal melanocytomas may be non-uniform in pathology [9]. Among the
8 five cases reported with detailed therapeutic and follow-up data, two were treated with
9 gross-total tumor resection alone, and the other three were treated with a combined
10 strategy including surgical resection and radiotherapy. Only one patient died during
11 the follow-up period [8], and no progression or recurrence of the tumors were noted in
12 the other cases. Indeed, this seemingly favorable prognosis may be associated with
13 the relatively short follow-up period (range from several weeks to 1.5 years) and the
14 absence of a long-term outcome.

15 For many years, gross total resection has been considered the ideal treatment for
16 solitary melanocytoma, and incomplete removal has a risk of recurrence, infiltrative
17 growth, metastasis, or transitioning into a malignant melanoma [3, 4, 24, 26, 27]. The
18 role of adjuvant radiotherapy has yet to be determined because of the rarity of
19 melanocytoma; however, some case reports have shown that adjuvant high-dose
20 radiotherapy (>45 Gy) or stereotactic radiosurgery may help to control tumor growth
21 and to improve prognosis [11, 28]. Rades et al. suggested the use of radiotherapy to

1 prevent recurrence, even after complete resection [28, 29]. The role of radiotherapy in
2 the management of meningeal melanocytoma still requires further study.

3 Another concern is the accompanying diffuse leptomeningeal hyperpigmentation.
4 This condition may manifest as linear enhancement after the administration of
5 Gd-DTPA contrast agent; nevertheless, it is unusual in cases with solitary meningeal
6 melanocytoma. Bydon et al. and Kim et al. both described a solitary intraspinal
7 melanocytoma with leptomeningeal spread, which showed an aggressive clinical
8 course resulting in fatal outcomes [24, 25]. Diffuse leptomeningeal hyperpigmentation
9 has also been reported in two patients with primary multifocal melanocytomas, and
10 one of them died a few weeks after surgery [8, 9]. Herein, we speculate that the
11 multifocality of meningeal melanocytoma, as well as diffuse leptomeningeal
12 hyperpigmentation, may portend an aggressive behavior and a poor prognosis.

13 Given all of these considerations, one-fold surgical resection may be inadequate
14 for the treatment of scattered multifocal meningeal melanocytomas and those with
15 diffuse leptomeningeal hyperpigmentation; this is because complete removal of all the
16 tumors along with the pigmented meningeal melanocytoma is not feasible. Adjuvant
17 radiotherapy may be able to address this treatment inadequacy. Owing to the extreme
18 rarity of these tumors, the available data do not provide a solid basis to define the
19 optimum therapeutic strategy. Hence, the treatments and clinical outcomes of patients
20 with meningeal melanocytomas need to be carefully documented in long-term
21 follow-up studies.

1 **Conclusion**

2 Clinicians should be alert to a potential aggressive clinical course of meningeal
3 melanocytoma, despite its benign histopathological nature. Of particular note are
4 multifocality and diffuse leptomeningeal hyperpigmentation, which may suggest a
5 poor prognosis. A combined treatment including surgical resection and adjuvant
6 radiotherapy should be considered, and long-term close follow-up is necessary.

7 **Acknowledgments**

8 We thank the patient and all her relatives who trusted us, and all of the physicians and
9 staff who helped in this study.

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1 **Figure Legends**

2 **Figure 1.** Spinal magnetic resonance imaging (MRI). Spinal MRI showing scattered
3 multifocal nodules (arrows) in the thoracolumbar segments; the largest mass at the
4 T12-L1 level is extradural, and the other masses appear to be
5 intradural-extramedullary. The masses are hyperintense on T1-weighted images (A
6 and D) and remarkably hypointense on T2-weighted images (B and E). After
7 Gd-DTPA administration, the tumors were homogeneously enhanced (C and F).
8 Nevertheless, the contrast enhancement is not clearly evident using visual
9 assessment because of strong T1 hyperintensity on the unenhanced images. The two
10 largest masses (asterisks) were completely resected.

11 **Figure 2.** Histopathological analysis of the melanocytomas. The diffusely distributed
12 black melanin-pigmented deposits obscured the observation of cell morphology and
13 microstructure (A, original magnification $\times 400$). A bleaching procedure was performed
14 (B, $\times 400$). Immunohistochemical staining (C-F, $\times 200$). The tumors are positive for
15 HMB45 (C) and S-100 protein (D), and negative for EMA (E). The positive rate of
16 Ki-67 is approximate 4% (F).

17

1

2 **Table 1** Literature review of primary multifocal melanocytoma profiles previously reported.

Case report	Gender	Age (yrs)	Symptoms	Lesion location	Pathology	Treatment	Outcome	Follow-up period
Showkeen HN et al. 2002	Male	38	Neck pain radiating to the bilateral upper extremities; tingling and numbness of the upper extremities	1) An intradural and extramedullary lesion at the C3–C4 level; 2) Two intradural and extramedullary satellite lesions at the C4 and C5 levels	Melanocytoma	Surgical resection (Extent N.A.)	N.A.	N.A.
Ali Y et al. 2009	Male	31	Headache; vomiting; hearing impairment	1) Bilateral cerebellopontine angle lesions; 2) An intradural and extramedullary lesion at the T5–T6 level; 3) Diffuse leptomeningeal hyperpigmentation	Melanocytoma	Gross-total resection	Died	A few weeks

Franken SP et al. 2009	Male	26	Headache; nausea; vomiting	1) Two separate lesions in the subarachnoid space in the posterior fossa; 2) Two lesions in the spinal canal at the L3–L4 level	Melanocytoma	Gross-total resection of the intracranial tumors;	No progression or recurrence	1.5 years
Reddy R et al. 2011	Female	43	Neck pain	1) An intradural and extramedullary lesion at the C1–C2 level; 2) An adjoining satellite nodule about a centimeter from the lower pole of the tumor	Melanocytoma	Gross-total resection	No progression or recurrence	6 months
Merciadri P et al. 2011	Male	68	Back pain; lower extremity weakness	1) An intradural and extramedullary lesion at the T12–L1 level; 2) Three infratentorial lesions at the level of the left cerebellopontine angle, the left caudal vermis and the right	Melanocytoma	Gross-total resection of the spinal tumor; Stereotactic external beam irradiation to each intracranial	No progression or recurrence	12 months

		cerebellar tonsil		lesion				
Foit NA et al. 2013	Male	43	left neck and shoulder pain; paraesthesia of the left hand; left-sided cephalgia radiating to the jaw	1) An intradural and extramedullary lesion at the C2–C3 level with extradural extension; 2) An intradural and extramedullary lesion at the T1–T2 level 3) Diffuse leptomeningeal hyperpigmentation	C2–C3: Melanocytoma; T1–T2: intermediate-grade Melanocytoma	Both partially resection; Stereotactic external beam irradiation to both tumor locations	No progression or recurrence	18 months

1 yrs years, N.A. not available

2