Review

Primary melanocytic neoplasms of the central nervous system

Simon V. Liubinas [a,*], Nicholas Maartens [a,b], Katharine J. Drummond [a,b]

[a] Department of Neurosurgery, The Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia
[b] Department of Surgery (RMH/WH), The University of Melbourne, Parkville, Victoria, Australia

ARTICLE INFO

ABSTRACT

Primary melanocytic neoplasms of the central nervous system (CNS) are rare lesions arising from melanocytes of the leptomeninges. They include diffuse leptomeningeal melanocytosis or melanomatosis, melanocytoma and primary malignant melanoma. We have reviewed the English literature regarding these lesions, which consists of case reports and a small number of larger case series. The presenting features, radiological, surgical and histological findings are reviewed, as are current management options and prognosis. We also present illustrative case reports of diffuse leptomeningeal melanocytosis and primary melanoma of the CNS.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Primary melanocytic neoplasms of the central nervous system (CNS) are rare lesions arising from melanocytes of the leptomeninges. These lesions include diffuse and focal as well as benign and malignant types. First described by Virchow in 1859, they continue to present a diagnostic and management challenge to the modern neurosurgeon.[1] They include diffuse leptomeningeal melanocytosis (DLM) or melanomatosis, melanocytoma and primary malignant melanoma.[2] We have reviewed the English literature regarding these lesions, which consists of case reports and a small number of larger case series. A Medline search was performed and the bibliographies of retrieved reports were also searched for additional reports. We review the presenting features, radiological, surgical and histological findings, and discuss current management options and prognosis. Illustrative cases of DLM and primary melanoma of the CNS are presented.

2. Incidence

Determination of the incidence of primary melanocytic neoplasms of the CNS has been limited by a paucity of data and lack of strict diagnostic criteria.[3] Some authors have excluded DLM from their data, and in some cases it is not certain whether lesions reported as primary CNS melanomas are in retrospect, actually secondary melanomas.[4] The incidence of primary CNS melanoma is estimated to be 0.005 cases per 100 000 population and for melanocytoma it is 1 per 10 million. Population based incidence of DLM is not known.[2,4]

3. Embryology

The neural crest consists of a population of multipotent cells that arise on day 22 of embryogenesis at the lateral margins of the neural tube and differentiate into a number of cell types including the leptomeninges, glial cells, adrenal medullary cells and melanocytes.[5] As the developing cerebral hemispheres expand they take with them a thin layer of neural crest cells, which form the leptomeninges.[6,7] When induced in vitro to proliferate in the presence of high concentrations of endothelin-3, both differentiated glial cells and melanocytes revert to an immature bipotent common ancestral cell. Although the cell of origin is still unclear, this provides evidence for the plasticity of neural crest cell fate in vivo and their likely role in the pathology of primary melanocytic neoplasms of the CNS.[8]

4. Clinical presentation

4.1. Diffuse leptomeningeal melanocytosis

DLM is characterised by extensive melanocytic infiltration of the supra- and infra-tentorial leptomeninges, particularly the cerebellum, pons, medulla and temporal lobes.[2] At least 67 cases have been reported in the literature since 1970 (Table 1). Ten (15%) of these patients also developed primary CNS melanoma. DLM may present at birth or develop later in life. Clinical features may include stillbirth, intracranial hypertension and hydrocephalus,

* Corresponding author. Tel.: +61 3 93428959; fax: +61 3 93428231.
E-mail address: simon.liubinas@gmail.com (S.V. Liubinas).

Table 1
Location of disease, sex and age at diagnosis (years) in 67 patients reported in the English literature with diffuse leptomeningeal melanocytosis.

Location	Cerebral 53	Spinal 5	Both 9		
Sex	Male 32	Female 18	Not noted 17		
Age at diagnosis	<10 41	10–30 15	30–50 3	>50 2	Not noted 6

seizure, ataxia, syringomyelia, cranial nerve palsy, intracranial haemorrhage, sphincter dysfunction and neuropsychiatric symptoms. Clinical deterioration is rapid if malignant transformation occurs.[9–15]

DLM has a known association with neurocutaneous melanosis (NCM), neurofibromatosis-1, Sturge-Weber syndrome and Dandy-Walker syndrome.[16–23] NCM is a rare, non-hereditary phakomatosis characterised by multiple or large congenital cutaneous naevi in conjunction with melanocytic tumours of the CNS. It generally presents in infancy.[2,14,18,24]

4.2. Meningeal melanocytoma and primary CNS melanoma

Meningeal melanocytomas and primary CNS melanomas occur throughout the neuraxis and thus, may be intracranial or spinal.[2–4,25,26] They are of similar origin and represent the benign and malignant ends of a spectrum, respectively.[27] Malignant transformation of melanocytoma to malignant melanoma has been reported.[28–31]

Meningeal melanocytomas are mass lesions and present with focal neurological signs associated with their location, intracranial hypertension or haemorrhage, neuropsychiatric symptoms, spinal cord compression, or seizures.[3,25,32–37] They most commonly occur in the cervical and thoracic spine as intradural, extramedullary lesions. The age at diagnosis ranges from 9 to 73 years, with a peak

incidence in the fifth decade and a slight female preponderance.[25,28,38] Associated melanotic lesions in the kidneys and adrenal glands and aggressive leptomeningeal spread throughout the neuraxis have been reported[38–40] (Table 2).

Primary CNS melanomas arise in patients ranging from 15 to 71 years of age, with a peak incidence in the fifth decade.[2,4] Symptoms at presentation include intracranial hypertension and hydrocephalus (43.2%), focal neurological deficits due to compression of the brain, spinal cord or cauda equina (34.6%), subarachnoid haemorrhage (17.3%) and seizures (11.1%)[4,28,35,41] (Table 3). There is a slight predilection for the posterior fossa and spinal cord. Primary malignant melanomas of the CNS may be found in isolation or in the context of neurocutaneous melanosis.[27,41] Dermatological and ophthalmological examination must be performed to exclude a distant primary source.

5. Investigations

Lumbar puncture may show increased opening pressure, and CSF analysis may demonstrate a high protein content, red blood cells, malignant cells, melanin containing cells or melanin granules, xanthochromia, normal or low glucose or a sterile leucocytosis.[12,14,17,35,42–44] Electroencephalogram (EEG) may demonstrate focal or generalised abnormalities.[4,9,14,27]

6. Neuroimaging

CT demonstrates melanocytic neoplasms as iso- to hyperdense lesions with homogenous contrast enhancement with or without abnormal calcification.[3,4,9,11,17,32–35]

The paramagnetic properties of melanin give melanocytic neoplasms of the CNS their characteristic appearance on MRI.[2,9,45] They are typically hyperintense on T1-weighted images, hypointense on T2-weighted images, hyperintense on fluid-attenuated inversion recovery (FLAIR) images and enhance homogeneously with gadolinium[17,33,34,46–49] (see *Illustrative case 2*).

Table 2
Location of disease, sex and age at diagnosis (years) in 112 patients reported in the English literature with cerebral and spinal melanocytoma

Cerebral	Supratentorial	Infratentorial	Supra- and infratentorial	Cerebellopontine	Meckel's cave	Intraventricular	Spinal and cerebral	Multiple lesions	Others	N/N
	76	13	1	11	1	7	2	0	21	16
Spinal	Cervical 15	Thoracic 28	Lumbosacral 10	Cauda equina 2	N/N 4					
Age	<10 18	10–30 23	30–50 19	>50 39	N/N 95					
Sex	Male 45	Female 59	N/N 105							

N/N = Not noted.

Table 3
Location of disease, sex and age at diagnosis (years) in 209 patients reported in the English literature with cerebral and spinal primary melanoma

Cerebral	Supratentorial	Infratentorial	Supra- and infratentorial	Cerebellopontine	Meckel's cave	Intraventricular	Spinal and cerebral	Multiple lesions	Others	N/N
	14	12	0	8	8	1	1	2	13	0
Spinal	Cervical 19	Thoracic 25	Lumbosacral 5	Cauda equina 3	N/N 0					
Age	<10 3	10–30 18	30–50 37	>50 44	N/N 10					
Sex	Male 46	Female 57	N/N 9							

N/N = Not noted.

DLM appears as diffuse meningeal thickening on both CT and MRI while melanocytomas and primary melanomas appear as solitary nodular lesions.[2,4,32,34] Melanocytomas are generally dense, extra-axial lesions with dural attachment, which may not show distinct margins. Melanomas have a similar appearance which varies somewhat with the melanin content.[32–34]

Cerebral angiography of primary intracranial melanoma shows a vascularized lesion while meningeal melanocytoma is hypovascular with a scant or very thin vascular stain.[4,32–34,50,51]
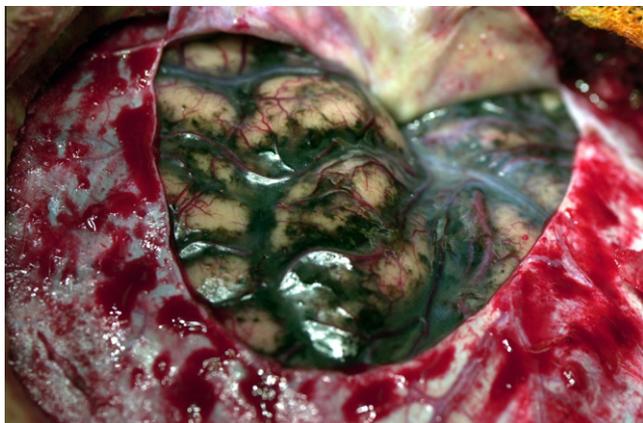
7. Surgical appearance

In DLM the dura appears relatively normal, however on opening the dura, large expanses of the leptomeninges appear greenish-black or dark brown with replacement of the subarachnoid space[2,11,17] (see *Illustrative case 1*).

Primary malignant melanoma and melanocytoma are solitary mass lesions, which are generally extra-axial. Approximately 70% of these lesions are black, however dark-brown, red-brown, blue and non-pigmented lesions have been reported[2–4] (see *Illustrative case 2*). Meningeal melanocytomas are encapsulated, intradural with dural attachments, soft in consistency and rarely demonstrate parenchymal invasion.[3,25,32,35] They may be extremely vascular.[51]

7.1. Illustrative case 1: diffuse leptomeningeal melanocytosis/melanomatosis

A 43-year-old man, with an unremarkable past history, presented with progressive headache, drowsiness and confusion. A CT of the brain was normal but MRI demonstrated diffuse leptomeningeal enhancement; most pronounced in the right Sylvian fissure. A lumbar puncture demonstrated a raised opening pressure of 32 cm CSF with a raised protein level and a few atypical cells but no malignant cells. A leptomeningeal brain biopsy revealed diffuse dark pigmentation of the subarachnoid space (Fig. 1).

Histopathology revealed dense sheets of pleiomorphic, predominantly spindle shaped pigmented cells suggestive of a melanocytic neoplasm. Frequent mitoses were visible and the Ki-67 index was high. Immunohistochemical stains were positive for S-100 protein, vimentin and tyrosinase. Subsequent dermatological and ophthalmological examination was normal. Despite intravenous dexamethasone and serial lumbar punctures, his level of consciousness declined and a ventriculoperitoneal shunt was inserted. Urgent radiotherapy was considered to be futile. Active treatment was withdrawn and he died a few days later.

8. Histopathology

The identification of melanin in tumour cells or associated macrophages is central to the diagnosis. Occasionally melanocytomas or melanomas may be unpigmented and diagnosis then depends on electron microscopy or immunohistochemistry.

DLM is caused by the abnormal proliferation and melanin production of leptomeningeal melanocytes.[2] The melanocytes are relatively small and contain a moderate amount of cytoplasm. They diffusely involve the leptomeninges and may accumulate within the Virchow-Robin spaces, but do not invade the brain parenchyma. They have short processes and may be spindled, round, oval or cuboidal and are cytologically devoid of neoplastic features. Brain parenchymal invasion indicates malignant change to melanomatosis.[2,17,47]

Melanocytomas are solitary low grade lesions that do not invade the surrounding brain parenchyma. Abnormal mitoses and atypical cytology are generally absent. Cells may be spindles or ovals with variable melanin content, oval or bean shaped nuclei and small eosinophilic or prominent nucleoli.[2,3,28,32,33,52] Melanocytoma cells

Fig. 2. Patient 2: MRI demonstrating primal spinal melanoma at the level of T11. The lesion is (a) hyperintense on sagittal T1-weighted, and (b) isointense on sagittal T2-weighted images. (c) Homogeneous contrast enhancement is seen on axial T1-weighted images with gadolinium. It has both intra- and extra-medullary components.

Fig. 1. Patient 1: Intraoperative image demonstrating surgical appearance of diffuse leptomeningeal melanocytosis.

may be in a whorled, storiform, vasocentric or sheet-like arrangement and macrophages may be present at the periphery, which also contain melanin. Areas of haemorrhage may be seen.[2,3,25,32] Electron microscopy may show a variable amount of melanin, melanosomes at various stages of maturity and premelanosomes in the cytoplasm, prominent nucleoli and marginated heterochromatin. The basal lamina is not well developed and cell-to-cell junctions, desmosomes and interdigitating cytoplasmic processes are generally lacking.[2,3,25,28,32,33,53] In this way, meningeal melanocytoma may be distinguished from melanotic meningioma as interdigitating processes and desmosomes are characteristic of meningiomas but generally absent in melanocytomas.[33,53]

Primary CNS melanoma is histologically similar to melanoma arising in other sites.[2] This highly cellular neoplasm may be arranged in a syncytial pattern or as irregular clusters or sheets of variably pigmented cells infiltrating the leptomeninges. Tissue invasion (including diffuse leptomeningeal melanomatosis), haemorrhage or coagulative necrosis may be seen.[2–4,52] They may contain large epithelial-like, rounded or spindle-shaped cells with abundant eosinophilic cytoplasm, irregularly contoured nuclei, intranuclear inclusions, typical or atypical mitotic figures, prominent eosinophilic nucleoli and heavily pigmented chromatophores. The features are similar to melanocytoma but with higher cell density and more anaplastic, pleiomorphic cells[2,4,52,54] (see *Illustrative case 2*).

Anti-melanoma antibody (HMB-45) and tyrosinase are usually strongly positive in primary melanocytic lesions of the CNS.[2–4,28,32,52,55–57] Unlike melanin containing meningiomas, melanocytic lesions are typically negative for epithelial membrane antigen (EMA).[3,28,33,58,59]

Primary melanocytic lesions of the CNS also react positively with the anti-melanosomal antibody MART-1 (Melan-A) and microphthalmia transcription factor. Reactivity with vimentin, and S-100 protein is variable although often reported as positive or strongly positive.[2,3,25,27,28,32,33,35,52,58] Reactivity for neuron-specific enolase, cytokeratin and glial fibrillary acidic protein (GFAP) is usually negative in meningeal melanocytomas.[28,32] Overall, the immunohistochemical patterns reported in the literature do not display a consistent pattern.[2–4,27,32,33,35]

Abnormalities on the short arm of chromosome 6 (isochromosome 6p) have been reported in primary meningeal melanomas, cutaneous and uveal melanomas, suggesting a common molecular mechanism in the tumourigenicity of melanocytes.[60]

8.1. Illustrative case 2: primary melanoma of the CNS

A 72-year-old female with an unremarkable past history presented with six months of progressively decreasing mobility and gait disturbance, back pain, right leg weakness and left leg paraesthesia. Spinal MRI demonstrated a 15 mm × 11 mm × 16 mm bilobed mass at the level of T11 with both extra- and intramedullary components causing oedema and expansion of the spinal cord. The lesion was hyperintense on T1-weighted and isointense on T2-weighted images. Avid homogeneous enhancement was seen on contrast enhanced T1-weighted images (Fig. 2).

High dose intravenous dexamethasone was commenced and a T10 to T12 laminectomy was performed urgently. The lesion was black with evidence of haemorrhage and appeared to originate from a nerve root but was embedded in the anterior spinal cord (Fig. 3). The lesion was debulked to minimise neurological deficit in an elderly patient, particularly as frozen section histopathological diagnosis suggested benign melanocytoma or other pigmented lesion such as a schwannoma.

Formal histopathology, however, demonstrated a moderately cellular melanocytic tumour composed of spindle and epithelioid cells forming intersecting short fascicles and occasional nests.

Fig. 3. Patient 2: Intraoperative image demonstrating surgical appearance of primary melanoma of the spinal cord. Back tumour tissue is seen under the elevated nerve roots.

The tumour cells had enlarged pleomorphic nuclei, prominent nucleoli and moderate amounts of ill-defined eosinophilic cytoplasm. Clumps of melanin were visible. No necrosis or mitoses were seen but the Ki-67 index was 5–6%. The tumour cells stained strongly for tyrosinase and melan-A and the diagnosis was revised to malignant melanoma. A repeat laminectomy and complete excision of the lesion was performed 2 weeks later in view of the malignant histopathology and as neurological function had not improved. Histopathological examination of the specimen showed tumour invasion into spinal cord parenchyma and occasional mitoses (Fig. 4). CT brain, chest, abdomen and pelvis found no evidence of metastatic disease. Comprehensive dermatological and ophthalmological examination found no other lesions.

She underwent radiation therapy of 44 Gray in 22 fractions. There has been no recurrence on MRI at 2 years 4 months and she is able to walk short distances unaided and live independently.

9. Treatment and prognosis

9.1. Diffuse leptomeningeal melanocytosis

DLM carries a poor prognosis even in the absence of histological malignancy. A series of 39 patients with symptomatic NCM reported most patients dying before age ten and 50% dying within three years of onset of neurological symptoms.[14] The role of chemotherapy and radiotherapy remains unclear, but neither seem to improve outcome.[14,18] There is no definitive treatment and palliation consists of tumour debulking and placement of a ventricular shunt.[2,12,14,17,47] A filter should be placed on the shunt to prevent seeding.[27,61,62]

9.2. Meningeal melanocytoma and primary CNS melanoma

As meningeal melanocytoma may transform to malignant melanoma, attempt at complete resection is advised when possible.[27,28,32,33,63] Despite its benign appearance the tumour may follow an aggressive course with recurrence possible even after apparently complete excision. The time to recurrence for cerebral melanocytoma ranges from seven months to five years, with 71% recurrence within five years, and is shorter with malignant transformation.[25,28,32,58] Therefore adjuvant radiation therapy is advised in cases of both complete and incomplete resection.[25,33,39,40] In a series of 89 intracerebral and spinal melanocytomas, 5-year sur-
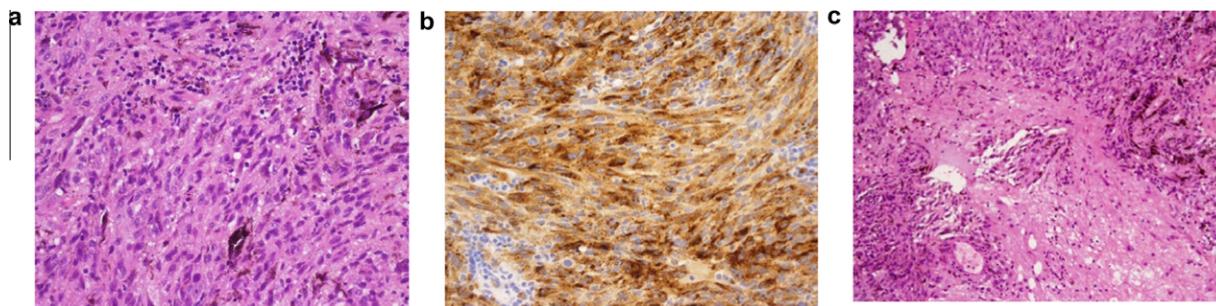
Fig. 4. Patient 2: (a) Haematoxylin and eosin staining demonstrating atypical melanocytes; (b) immunohistochemical staining with tyrosinase, a melanocyte marker; (c) haematoxylin and eosin staining demonstrating invasion of spinal cord parenchyma.

vival rates were reported as follows: complete resection 100%, complete resection plus radiotherapy 100%, incomplete resection plus radiotherapy 100%, incomplete resection only 46%.[28]

Stereotactic gamma knife radiosurgery may reduce the size of residual tumour by as much as one-fourth and improve clinical outcome.[58] Complications should be treated as clinically appropriate. Hydrocephalus may be treated with a ventricular shunt, but a filter is needed to prevent spread in the event of malignant transformation.[27]

Reports of primary treatment with radiotherapy of doses between 30–54 Gray indicate that, although variable, tumour control of up to 42 months can be achieved where surgery is not feasible.[58,63] Concomitant intrathecal methotrexate has been reported in recurrent spinal melanocytoma, with uncertain effect.[39] One case of post-resection treatment with intrathecal recombinant interleukin-2 has been reported with promising results.[64]

Primary CNS melanoma is an aggressive tumour and may metastasise to other organs.[2] Patients in whom total resection is possible have a significantly better outcome than those in whom only partial resection is performed, and post-operative radiotherapy is recommended is all cases.[4,52] The prognosis of primary meningeal melanoma appears better than that of secondary cerebral malignant melanoma, especially if complete resection can be achieved and no distant metastases are present.[2,4,52]

Surveillance imaging with MRI or CT is recommended at regular intervals following complete or incomplete resection of melanocytic tumours.[28]

9.3. Illustrative case 3: primary melanoma of the CNS

A 59 year old female with an unremarkable past history presented with six months of left leg weakness and paraesthesia. MRI spine showed a homogenously enhancing intradural, intramedullary lesion with an associated syrinx at the level of T11, which was isointense to hyperintense on T1-weighted images and isointense on T2-weighted images.

Intravenous dexamethasone was commenced prior an urgent T10 to T12 laminectomy. A heavily pigmented lesion was completely resected from the left side of the spinal cord and a partially excised on the right to preserve spinal cord function.

Histopathology demonstrated a hypercellular tumour arranged in diffuse sheets on a vascular stroma composed of plump spindle and epithelioid cells with moderately pleomorphic nuclei. Many of the cells contained enlarged nucleoli, a moderate amount of cytoplasm and brown-black cytoplasmic pigment. Tyrosinase and Melan-A staining was strongly positive and the Ki-67 index was approximately 3%. Imaging of the remainder of the body and dermatological and ophthalmological examination revealed no lesions. Therefore a diagnosis of primary spinal cord melanoma was made.

She underwent radiation therapy of 36 Gray in 12 fractions to the spinal cord and residual tumour. At 35 months she underwent a second gross macroscopic resection for recurrence. Histopathology again demonstrated primary melanoma. At 36 months a repeat MRI shows no recurrent disease and she can mobilise short distances with a frame.

10. Differential diagnosis

Primary melanocytic neoplasms of the CNS should be differentiated from metastatic malignant melanoma by a thorough search for a primary lesion. In addition, a number of other CNS lesions can be pigmented and produce melanin including schwannoma, medulloblastoma, neurofibroma, meningioma, astrocytoma and pituitary tumours. Immunohistochemistry and ultrastructural features are usually helpful in distinguishing these lesions.[2,4,25,52,65–69]

11. Conclusion

Diffuse leptomeningeal melanocytosis, meningeal melanocytoma and primary CNS melanoma are rare tumours which present a diagnostic and management challenge for the modern neurosurgeon and neuro-oncologist. Our understanding of these tumours relies on a relatively small number of reported cases, thus management is not standardised, with surgery and radiotherapy being the mainstays of treatment. In common with metastatic malignant melanoma to the CNS, they carry a generally grave prognosis. Advances in treatment of non-CNS melanoma may hold promise for these lesions.

References

1. Virchow R. Pigment und diffuse Melanose der Arachnoides. *Virchows Arch* 1859;**16**:180–2.
2. Brat DJ, Perry A. WHO classification of tumours affecting the central nervous system. 1993.
3. Litofsky NS, Zee C-S, Breeze RE, et al. Meningeal melanocytoma: diagnostic criteria for a rare lesion. *Neurosurgery* 1992;**31**:945–8.
4. Rodriguez y Baena R, Gaetani P, Danova M, et al. Primary solitary intracranial melanoma: case report and review of the literature. *Surg Neurol* 1992;**38**:26–37.
5. Larsen WJ. *Human Embryology*. 2nd ed. Churchill Livingstone; 1997.
6. Erickson CA, Duong TD, Tosney KW. *Dev Biol* 1992;**151**:251–72.
7. Jiang X, Iseki S, Maxson RE, et al. Tissue origins and interactions in the mammalian skull vault. *Dev Biol* 2002;**241**:106–16.
8. Dupin E, Le Douarin NM. Development of melanocyte precursors from the vertebrate neural crest. *Oncogene* 2003;**22**:3016–23.
9. Demirci A, Kawamura Y, Sze G, et al. MR of parenchymal neurocutaneous melanosis. *AJNR Am J Neuroradiol* 1995;**16**:603–6.
10. Vanzieleghem BD, Lemmerling MM, Van Coster RN. Neurocutaenous melanosis presenting with intracranial amelanotic melanoma. *AJNR Am J Neuroradiol* 1999;**20**:457–60.
11. Leaney BJ, Rowe PW, Klug GL. Neurocutaneous melanosis with hydrocephalus and syringomelia. *J Neurosurg* 1985;**62**:148–52.

12. Chang C-S, Hsieh PF, Chia L-G, et al. Leptomeningeal malignant melanoma arising in neurocutaneous melanocytosis: a case report. *Chin Med J (Taipei)* 1997;**60**:316–20.
13. Thomas CS, Toone BK, Rose PE. Neurocutaneous melanosis and psychosis. *Am J Psychiatry* 1988;**145**:649–50.
14. Kadonaga JN, Frieden IJ. Neurocutaneous melanosis: definition and review of the literature. *J Am Acad Dermatol* 1991;**1991**:747–55.
15. Peters R, Jansen G, Engelbrecht V. Neurocutaneous melanosis with hydrocephalus, intraspinal arachnoid collections and syringomyelia: case report and literature review. *Pediatr Radiol* 2000;**30**:284–8.
16. Berker M, Oruckaptan H, Oge H, et al. Neurocutaneous melanosis associated with Dandy-Walker malformation. Case report and review of the literature. *Pediatr Neurosurg* 2000;**33**:270–3.
17. Alwatban J, Tampieri D, Salazar A, et al. MRI of leptomeningeal melanocytosis in a patient with neurofibromatosis. *J Comput Assist Tomogr* 1997;**21**:38–40.
18. Di Rocco F, Sabatino G, Koutzoglou M, et al. Neurocutaneous melanosis. *Childs Nerv Syst* 2004;**20**:23–8.
19. Mena-Cedillos C, Valencia-Herrera A, Arroyo-Pineda A, et al. Neurocutaneous melanosis in association with the Dandy-Walker complex, complicated by melanoma: report of a case and literature review. *Pediatr Dermatol* 2002;**19**:237–42.
20. Kalayci M, Cağavi F, Bayar U, et al. Neurocutaneous melanosis associated with Dandy-Walker malformation. *Acta Neurochir* 2006;**148**:1103–6.
21. Schreml S, Gruendobler B, Schreml J, et al. Neurocutaneous melanosis in association with Dandy-Walker malformation: case report and literature review. *Clin Exp Dermatol* 2008;**33**:611–4.
22. Kadonaga J, Barkovich A, Edwards M, et al. Neurocutaneous melanosis in association with the Dandy-Walker complex. *Pediatr Dermatol* 1992;**9**:37–43.
23. Caceres A, Trejos H. Neurocutaneous melanosis with associated Dandy-Walker complex. *Childs Nerv Syst* 2006;**22**:67–72.
24. Reyes-Mugica M, Chou P, Byrd S, et al. Nevomelanocytic proliferations in the central nervous system of children. *Cancer* 1993;**72**:2277–85.
25. Prabhu SS, Lynch PG, Keogh AJ, et al. Intracranial meningeal melanocytoma: a report of two cases and a review of the literature. *Surg Neurol* 1993;**40**:516–21.
26. Ferraresi V, Ciccarese M, Zeuli M, et al. Central nervous system as exclusive site of disease in patients with melanoma: treatment and clinical outcome in two cases. *Melanoma Res* 2005;**15**:467–9.
27. Faillace W, Okawara SH, McDonald JV. Neurocutaneous melanosis with extensive intracerebral and spinal cord involvement. *J Neurosurg* 1984;**61**:782–5.
28. Rades D, Schild SE, Tatagiba M, et al. Therapy of meningeal melanocytomas. *Cancer* 2004;**100**:2442–7.
29. Roser F, Nakamura M, Brandis A, et al. Transition from meningeal melanocytoma to primary cerebral melanoma. *J Neurosurg* 2004;**101**:528–31.
30. Uozumi Y, Kawano T, Kawaguchi T, et al. Malignant transformation of meningeal melanocytoma: case report. *Brain Tumor Pathol* 2003;**20**:21–5.
31. Wang F, Li X, Chen L, et al. Malignant transformation of spinal meningeal melanocytoma. *J Neurosurg Spine* 2007;**6**:451–4.
32. Maiuri F, Iaconetta G, Benvenuti D, et al. Intracranial meningeal melanocytoma: case report. *Surg Neurol* 1995;**44**:556–61.
33. Uematsu Y, Yukawa S, Yokote H, et al. Meningeal melanocytoma: magnetic resonance imaging characteristics and pathological features. *J Neurosurg* 1992;**76**:705–9.
34. Naul LG, Hise JH, Bauserman SC, et al. CT and MR of meningeal melanocytoma. *AJNR Am J Neuroradiol* 1991;**12**:315–6.
35. Painter TJ, Chaljub G, Sethia R, et al. Intracranial and intraspinal meningeal melanocytosis. *AJNR Am J Neuroradiol* 2000;**21**:1349–52.
36. Hino K, Nagane M, Fujioka Y, et al. Meningeal melanocytoma associated with ipsilateral nevus of ota presenting as intracerebral hemorrhage: case report. *Neurosurgery* 2005;**56**:1376–7.
37. Leonardi MA, Lumenta CB, Stolzle A, et al. Unusual clinical presentation of a meningeal melanocytoma with seizures: case report and review of the literature. *Acta Neurochir* 1998;**140**:621–8.
38. Oruckaptan HH, Soylemezoglu F, Kutluk T, et al. Benign melanocytic tumor in infancy: discussion on a rare case and review of the literature. *Pediatr Neurosurg* 2000;**32**:240–7.
39. Bydon A, Gutierrez JA, Mahmood A. Meningeal melanocytoma: an aggressive course for a benign tumor. *J Neurooncol* 2003;**64**:259–63.
40. Rades D, Heidenreich F, Tatagiba M, et al. Therapeutic options for meningeal melanocytoma. *J Neurosurg* 2001;**95**:225–31.
41. Arunkumar MJ, Ranjan A, Jacob M, et al. Neurocutaneous melanosis: a case of primary intracranial melanoma with metastasis. *Clin Oncol* 2001;**13**:52–4.
42. Kounin G, Romansky K, Traykov L, et al. Primary spinal melanoma with bilateral papilledema. *Clin Neurol Neurosurg* 2005;**107**:525–7.
43. Madonick MJ, Savitsky N. Subarachnoid hemorrhage in melanoma of the brain. *Arch Neurol Psychiatry* 1951;**65**:628–36.
44. Aichner F, Schuler G. Primary leptomeningeal melanoma: diagnosis by ultrastructural cytology of cerebrospinal fluid and cranial computed tomography. *Cancer* 1982;**50**:1751–6.
45. Fukui MB, Meltzer CC, Kanal E, et al. MR imaging of the meninges. Part II. Neoplastic disease. *Radiology* 1996;**201**:605–12.
46. Lanzieri CF, Bangert BA, Tarr RW, et al. Neuroradiology case of the day: Leptomeningeal melanocytosis. *Am J Roentgenol* 1997;**169**:294, 299.
47. Poe LB, Roitberg D, Galyon DD. Neurocutaneous melanosis presenting as an intradural mass of the cervical canal: magnetic resonance features as a clue to diagnosis. *Neurosurgery* 1994;**35**:741–3.
48. Offiah CJ, Laitt RD. Intracranial meningeal melanocytoma: a cause of high signal on T1- and low signal on T2-weighted MRI. *Clin Radiol* 2006;**61**:294–8.
49. Hayashi M, Maeda M, Maji T, et al. Diffuse leptomeningeal hyperintensity on fluid-attenuated inversion recovery MR images in neurocutaneous melanosis. *AJNR Am J Neuroradiol* 2004;**25**:138–41.
50. Clarke DB, Leblanc R, Bertrand G, et al. Meningeal melanocytoma. Report of a case and a historical comparison. *J Neurosurg* 1988;**88**:116–21.
51. O'Brien DF, Crooks D, Mallucci C, et al. Meningeal melanocytoma. *Childs Nerv Syst* 2006;**22**:556–61.
52. Brat DJ, Giannini C, Scheithauer BW, et al. Primary melanocytic neoplasms of the central nervous system. *Am J Surg Pathol* 1999;**23**:745–54.
53. Limas C, Tio FO. Meningeal melanocytoma ("melanotic meningioma"). Its melanocytic origin as revealed by electron microscopy. *Cancer* 1972;**30**:1286–94.
54. Kumar V, Abbas AK, Fausto N, editors. *Pathologic Basis of Disease*, 7th ed.. Elsevier Saunders; 2005.
55. Ordonez NA, Sneige N, Hickey R, et al. Use of monoclonal antibody HMB-45 in the cytologic diagnosis of melanoma. *Acta Cytol* 1998;**32**:684–9.
56. Sheffield MV, Yee H, Dorvault CC, et al. Comparison of five antibodies as markers in the diagnosis of melanoma in cytologic preparations. *Am J Clin Pathol* 2002;**118**:930–6.
57. Kwon BS. Pigmentation genes: the tyrosinase gene family and the pmel 17 gene family. *J Invest Dermatol* 1993;**100**(Suppl. 2):134S–40S.
58. Kurita H, Segawa H, Shin M, et al. Radiosurgery of meningeal melanocytoma. *J Neurooncol* 2000;**46**:57–61.
59. Schnitt SJ, Vogel H. Meningiomas. Diagnostic value of immunoperoxidase staining for epithelial membrane antigen. *Am J Surg Pathol* 1986;**10**:640–9.
60. Baudrier-Reginier A, Bodenant C, Proust F, et al. An isochromosome 6p in a primary meningeal malignant melanoma. *Cancer Genet Cytogenet* 2000;**119**:80–2.
61. Gattuso P, Carson H, Attal H, et al. Peritoneal implantation of meningeal melanosis via ventriculoperitoneal shunt: a case report and review of the literature. *Diagn Cytopathol* 1995;**13**:257–9.
62. Cajaiba M, Benjamin D, Halaban R, et al. Metastatic peritoneal neurocutaneous melanocytosis. *Am J Surg Pathol* 2008;**32**:155–61.
63. Classen J, Hehr T, Werner P, et al. Suprasellar melanocytoma: a case of primary radiotherapy and review of the literature. *J Neurooncol* 2002;**58**:39–46.
64. Fathallah-Shaykh H, Zimmerman C, Morgan H, et al. Response of primary leptomeningeal melanoma to intrathecal recombinant interleukin-2. *Cancer* 1996;**77**:1544–50.
65. Er U, Kazanci A, Eyripmark T, et al. Melanotic schwannoma. *J Clin Neurosci* 2007;**14**:676–8.
66. Kanatas AN, Bullock MD, Pal D, et al. Intradural extramedullary primary malignant melanoma radiographically mimicking a neurofibroma. *Br J Neurosurg* 2007;**21**:39–40.
67. Portugal JR, Alencar A, Brito Lira LC, et al. Melanotic meningioma complicated by disseminated intravascular coagulation. *Surg Neurol* 1984;**21**:275–81.
68. Turnbull IM, Tom MI. Pigmented meningioma. *J Neurosurg* 1963;**20**:76–80.
69. Keegan HR, Mullan S. Pigmented meningiomas: an unusual variant. Report of a case with review of the literature. *J Neurosurg* 1962;**19**:696–8.