Diffuse leptomeningeal melanocytosis

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Primary melanocytic tumors 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 [1].

Diffuse leptomeningeal melanocytosis is a rare tumor of meninges arising from leptomeningeal melanocytes, characterized by diffuse infiltration of the leptomeninges (pia mater and arachnoidea) anywhere in the central nervous system.

Leptomeningeal melanocytes, are derived from neural crest and include diffuse melanocytosis, melanocytomas, and malignant melanomas. Meningeal melanocytomas are extremely rare benign lesions.

Pathology

The aim of a study was to analyze melanocytic proliferation in 2 rare and severe cases of isolated Diffuse leptomeningeal melanocytosis (DLM) and neurocutaneous melanocytosis (NCM) of prenatal onset by neuropathologic and molecular analysis. Uguen et al. performed neuropathologic examination, comparative genomic hybridization arrays, fluorescence in situ hybridization, BRAF and NRAS pyrosequencing in the 2 cases, and next-generation sequencing in the case of isolated DLM. The neuropathologic examination showed diffuse meningeal melanocytic proliferation involving the whole central nervous system with multiple areas of intraneural invasion, associated with large nevi in 1 case. They did not find any chromosomal imbalances. A NRAS(Q61K) mutation was found in the cutaneous and meningeal lesions from the NCM. No mutation was found within a panel of oncogenes including BRAF, NRAS, HRAS, KIT, GNAQ, and GNA11 concerning the isolated DLM. They reported 2 exceptional cases of hydrocephalus of prenatal onset related to DLM and NCM. The molecular mechanisms underlying the case of DLM remain unsolved despite the panel of analysis applied [2].

Clinical features

May include stillbirth, intracranial hypertension and hydrocephalus, seizure, ataxia, syringomyelia, cranial nerve palsy, intracranial hemorrhage, sphincter dysfunction and neuropsychiatric symptoms. Transformation into malignant melanoma of the central nervous system was reported. It may be associated with congenital nevi, as a part of neurocutaneous melanosis.

Diagnosis

Brain MRI showing diffuse thickening of the leptomeninges with T1 shortening is useful in diagnosing Neurocutaneous melanocytosis. Heterocellular melanin may be of great value for early diagnosis of NCM in challenging cases [3].

Over a 5-year period (1989-1994) Byrd et al. evaluated with MR imaging the central nervous system of five children with a confirmed histologic diagnosis of neurocutaneous melanosis. The children ranged in age from 7 to 10 years and consisted of two girls and three boys. They all had multiple pigmented skin lesions (cutaneous nevi) and presented with seizures, signs of raised intracranial pressure, cranial nerve palsies and/or myelopathy. The MR studies were performed with T1-weighted, T2-weighted and T1-weighted post-gadolinium images of the brain in addition to T1-weighted post-gadolinium images of the entire spine. The MR findings in all the children consisted of marked, diffuse enhancement of thickened leptomeninges surrounding the brain and spinal cord which was only demonstrated on the post-gadolinium T1-weighted images and mild to moderate hydrocephalus. We present our MR findings and compare these findings with other imaging findings in the literature. The findings represent part of a spectrum of imaging abnormalities seen in patients with neurocutaneous melanosis [4].

Differential diagnosis

Pigmented lesions of the central nervous system (CNS) are a diverse group of entities that run the gamut from benign to malignant. These lesions may be well circumscribed or diffuse, and their imaging appearances are influenced by the degree of melanin content as well as the presence or absence of hemorrhage. Pigmented lesions include primary melanocytic lesions of the CNS and metastatic melanoma, as well as other CNS neoplasms that may undergo melanization, including schwannoma, medulloblastoma, and some gliomas. Primary melanocytic lesions of the CNS arise from melanocytes located within the leptomeninges, and this group includes diffuse melanocytosis and meningeal melanomatosis (seen in neurocutaneous melanosis), melanocytoma, and malignant melanoma. Primary melanin-containing lesions of the CNS must be differentiated from metastatic melanoma because these lesions require different patient workup and therapy. Absence of a known primary malignant melanoma helps in the differential diagnosis, but an occult primary lesion outside the CNS must be sought and excluded. Pigmented lesions of the CNS are uncommon, and knowledge of their imaging characteristics and pathologic features is essential for their identification [5].

Melanocytoma and meningeal melanocytosis, are similar but different lesions.

Meningeal melanomatosis is an extra-axial well-encapsulated malignant tumour with diffuse meningeal growth and dark coloration (due to high melanin contents), while meningeal melanocytoma is the focalized benign variant. Melanocytic tumors may be secondary to melanoma or be histologically benign, however, their diffuse nature makes them impossible to cure. Melanocytosis is a diffuse tumour that can form solitary extra-axial tumours, which invades the parenchyma and presents signs of malignancy with increased mitosis and Ki67, observed in 1 to 6% of

immunopathological exams. Melanoma of the leptomeninges, presents signs of malignancy with anaplastic cells, which cluster in fascicles of melanin in the cytoplasm, with more than 3 atypical mitoses per field and Ki67 presenting in more than 6% of the immunopathological fields analysed [6].

Treatment

The usual treatment of intradural extramedullary melanocytomas involves surgical removal through a posterior approach using a laminectomy or laminotomy.

Outcome

Diffuse leptomeningeal melanocytosis (DLM) is a rare nevomelanocytic proliferation arising in the meninges. Despite their lack of morphological features of malignancy, these clonal nevomelanocytic cells are capable of extensive invasion and of malignant behavior. When associated with congenital melanocytic nevi, the disorder is named neurocutaneous melanocytosis (NCM). When symptomatic, DLM is usually revealed during childhood, but some cases remain clinically silent [7].

Leptomeningeal melanocytosis: a fatal course of a benign tumor [8].

Case reports

A 30-year-old female harboring a C6-T1 ventrally located intradural extramedullary lesion compressing the cord anteriorly. The lesion was totally resected via an anterior approach with oblique corpectomy even if the usual treatment involves surgical removal through a posterior approach using a laminectomy or laminotomy.

There is no evidence of recurrence at 4-year follow-up records of the patient [9].

A 38 years old male with primary diffuse leptomeningeal melanomatosis with presence of a NRASQ61K mutation without features of neurocutaneous melanosis [10].

Two cases of primary leptomeningeal melanomatosis presenting as subacute meningitis. Both cases have pleocytosis and high protein on cerebrospinal fluid analysis, and demonstrated atypical cells on cytology. On magnetic resonance imaging, there is diffuse leptomeningal thickening and avid enhancement of intracranial and intraspinal leptomeninges. One of them demonstrates T1 shortening due to magnetic effects of melanin, the other case is amelanotic and shows Hypointensity on precontrast T1-weighted images. Both cases can be diagnosed with biopsy. In conclusion, these cases highlight the importance of the correct interpretation of cytological and magnetic resonance imaging findings in patients with atypical findings [11].

Padilla-Vázquez et al. presented the case of a patient with long-term meningeal melanomatosis, with progressive neurologic deficit and characteristic radiologic features, and another case of meningeal melanocytoma.

Benign melanocytic neoplasms of the central nervous system must be treated aggressively in the early phases with strict follow-up to avoid progression to advanced phases that do not respond to any treatment method. Unfortunately, the prognosis for malignant melanocytic lesions is very poor irrespective of the method of treatment given [12].

Uguen et al. reported 2 exceptional cases of hydrocephalus of prenatal onset related to DLM and NCM. The molecular mechanisms underlying our case of DLM remain unsolved despite the panel of analysis applied [13].

A 30-year-old woman with a giant congenital melanocytic nevus covering nearly the entire right thoracodorsal region and multiple disseminated melanocytic nevi presented with neurological symptoms. Cerebral magnetic resonance imaging revealed a large expansive lesion in the left frontal region. Postsurgically pathological diagnosis revealed characteristics of melanoma. Immunohistochemical examination showed S100(+), HMB45(+), MelanA(+), and MiTF(+). She received radiotherapy with temozolomide followed by two more chemotherapy cycles with temozolomide. She followed a rapidly progressive course, reflecting widespread leptomeningeal infiltration, and she died of multiorgan failure seven months after diagnosis of cerebral melanoma. Discussion. This patient was diagnosed as having a neurocutaneous melanosis with malignant widespread leptomeningeal infiltration. Diffuse spinal involvement is unusual and is described in only another patient [14].

An autopsy case of leptomeningeal melanomatosis associated with neurocutaneous melanosis (NCM) involving a 44-year-old male is reported. The autopsy showed that the leptomeningeal surface of the brain and the spinal cord were covered with a diffuse black lesion. A histological examination detected diffusely distributed, proliferating, melanin-containing cells and demonstrated that the lesion consisted of three different components; i.e. regions of melanomatosis, melanocytosis, and melanocyte hyperplasia. In the leptomeningeal melanomatosis component, tumor cells with pleomorphic nuclei and prominent nucleoli had infiltrated into the cerebral parenchyma via Virchow-Robin spaces. The Ki-67 labeling index and the nuclear accumulation of p53 and p16 protein were immunohistochemically examined in each component. The Ki-67 labeling indices of the melanomatosis, melanocytosis, and melanocyte hyperplasia components were 8.7%, 0.8%, and 0%, respectively. Immunostaining of nuclear p16 produced a negative result in the melanomatosis component, but positive results in the melanocytosis and melanocyte hyperplasia components, whereas nuclear p53 expression was not detected in any of the components. This case suggests that p16(INK4) /CDKN2 may play a significant role in progression of leptomeningeal melanocytic neoplasms. We also reviewed previously reported cases of leptomeningeal neoplasms associated with NCM and discussed the relationship between the biological behavior and proliferative activity of such lesions [15].

A 43-year-old woman presented with a 1-week history of neck pain and dizziness. Computed tomography of brain showed communicating hydrocephalus and subarachnoid hyperintensity suspicious of previous subarachnoid haemorrhage. Investigations revealed no underlying vascular lesion and leptomeningeal biopsy showed diffuse melanocytosis [16].

Dechaphunkul A, Kayasut K, Oearsakul T, Koonlaboon K, Sunpaweravong P. Common presentation in an uncommon disease: case report of a patient with primary diffuse leptomeningeal melanocytosis. J Clin Oncol. 2011 Nov 20;29(33):e816-8. doi: 10.1200/JCO.2011.37.3175. Epub 2011 Oct 24. PMID: 22025160.

A rare and atypical case of a 31-year-old adult male with no evident congenital melanocytic lesions who presented with neurologic symptoms and was found to have leptomeningeal melanocytosis. The brain biopsy demonstrated a conspicuous but benign-appearing melanocytic infiltrate that was discordant with the severity of the patient's symptoms. Ultimately, the patient was suspected to represent a case of former fruste neurocutaneous melanosis. Herein the relevant clinical and histopathologic features are discussed along with a brief review of the literature [17].

A 75-year-old man, undergoing treatment for metastatic prostate cancer with a novel cancer cell vaccine, presented with a 4 week history of poor balance, gait disturbance and cognitive decline. Blood tests including HIV and onconeuronal and voltage gated potassium channel antibodies were normal. Computed tomography and two magnetic resonance images of the brain showed possible non-specific meningeal or vascular enhancement. Two cerebrospinal fluid analyses, including cytology, were negative, other than six lymphocytes in the former. Despite intravenous aciclovir and dexamethasone the patient deteriorated over 16 days, with worsening confusion and involuntary movements, and died. Postmortem examination showed that the leptomeninges overlying the brain and spinal cord were diffusely infiltrated by a melanocytosis with a focal area of melanomatosis. Moreover, there were two sites of metastases of a highly malignant clone present in the pulmonary parenchyma [18].

A rapidly fatal case in an 18-year-old man presenting with symptoms and imaging features suggestive for subarachnoid hemorrhage or meningitis. The laboratory findings and imaging examination were still confusing and the diagnosis remained unclear during the patient's life. Autopsy was the cornerstone in disclosing the lesion, confirming its usefulness in the assessment of such unusual cases. The complete profile of the tumor was obtained only by histology and immunohistochemistry. Clinicians and pathologists must be aware of diagnosis difficulties in this rare disease which can represent a serious challenge in clinical practice [19].

1-year-old boy with congenital melanocytic nevi had met normal developmental milestones until the age of 11 months, when he began regressing in ambulation and language function. Intractable

vomiting had developed 1 week later. Magnetic resonance (MR) imaging of the brain revealed DWC with hydrocephalus, and spinal MR images demonstrated a proliferative process within the meninges, consistent with NM. The patient underwent right frontal VP shunt placement resulting in immediate symptom relief, but 3 weeks later became irritable, increasingly lethargic, unable to pull to stand, and unable to tolerate solid food without choking. Due to these symptoms and intractable vomiting, the patient presented to the authors' institution. Brain MR imaging revealed a new-onset diffuse cystic process with anterior and posterior brainstem compression, marked kinking of the cervicomedullary junction, melanocyte pigmentation of the left temporal lobe, diffuse leptomeningeal enhancement, and no evidence of hydrocephalus. Consistent with these imaging findings, the degree of brainstem involvement upon gross visualization predictably deterred resection attempts beyond those necessary for biopsy. Pathological examination revealed diffuse melanocytosis, and the family decided not to pursue aggressive measures postoperatively. This report indicates the potential for rapid intracranial manifestation of diffuse melanocytosis in NM patients. Although the prognosis is poor, early neurosurgical involvement in these patients may provide tissue diagnosis and the potential for decompression if the process is caught early in its course [20].

A 26-year-old man had had a large patch of pigmented nevus over his back and left arm since birth. He had begun to have seizures as well as symptoms and signs of increased intracranial pressure about six months before admission. Serial computed tomography of brain showed hydrocephalus, diffuse leptomeningeal enhancement and multiple well-enhanced, rapid-growing nodules on the surface of the cerebellum and left parietal lobe. Magnetic resonance imaging (MRI) revealed T1 shortening of leptomeninges on precontrast T1 weighted imaging. Skin biopsy was done twice and showed intradermal nevus. Biopsy on one of the intracranial nodules revealed malignant melanoma arising in the melanocytosis. He died one year after the onset of neurologic symptoms. For early diagnosis of neurocutaneous melanocytosis, we suggest 1) MRI, and 2) leptomeningeal biopsy in patients with suspected leptomeningeal malignant melanoma [21].

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