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Research

Primary Leptomeningeal Melanoma: A Case Report and Review of Literature

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Abstract

Objective

To review the literature about primary melanocytic neoplasms of the central nervous system published on the last ten years and to present a case of primary leptomeningeal melanoma in a child, with its clinical features, neuroimaging scans and histological findings.

Case Report

A 2 years old girl presented with a 3 months history of nausea, vomiting, irritability, loss of weight, consciousness disorder and facial paralysis, with signs of hydrocephalus on the CT scan, so a ventricular peritoneal shunt was placed. Two months later she had persistent vomiting, continuing loss of weight and difficulties for walking and talking. The CT scan had a suspicious suprasellar lesion and a MRI revealed a suprasellar cystic lesion with invasion of the subarachnoid space widely. The characteristics of the CSF analysis and cytology were compatible with an intracranial tumor. A craniotomy with biopsy was performed, and histology and immunohistochemic markers revealed a primary leptomeningeal melanoma. A detailed search excluded extracranial primary melanoma. She was managed for palliation and died within two months.

Conclusion

Although the absence of a history of skin malignancy makes the definite preoperative diagnosis of a primary leptomeningeal melanoma difficult, the correlation of clinical, neuroimaging and histological finding is crucial in helping to determine the diagnosis of this entity, its prognosis and management.

Introduction

In this article we review the literature about primary melanocytic neoplasms of the central nervous system published on the last ten years. We also report a case of primary diffuse malignant leptomeningeal melanoma in a child, which presented both diagnostic and management challenges, and that was diagnosed based on preoperative imaging (MRI), intraoperative pathological features and postoperative histological and immunohistochemical findings.

Review of Literature

Melanocytic tumors of the central nervous system (CNS) are generally metastatic in origin. [1] Primary melanocytic neoplasms of the CNS, first described by Virchow in 1859, are rare lesions arising from melanocytes of the leptomeninges, and their rarity contributes to the high chance of misdiagnosis. According to the WHO 2007 classification they can manifest as diffuse disseminations or as solid masses, including melanosis (diffuse meningeal benign melanocytic proliferation), melanomatosis (diffuse meningeal malignant melanocytic proliferation), melanocytoma (benign mass-forming proliferation) and melanoma (malignant mass-forming proliferation) [1,2,3, 4,5,6,7].

Primary melanocytic lesions involving the CNS are typically concentrated in the perimedullary and high cervical region. These cannot be reliably distinguished from metastatic melanoma on neuroimaging and histopathological characteristics alone; its diagnosis is established only after exclusion of secondary metastatic disease from a cutaneous, mucosal or retinal primary lesion. Primary lesions usually present before 50 years of age, without extracranial disease and may be associated with neurocutaneous syndromes, with better prognosis that metastatic lesions [8].

Incidence

The determination of the incidence has been limited due to misdiagnosis, lack of data and strict diagnostic criteria. Population based incidence of DLM is not known and the incidence for melanocytoma it is 1 per 10 million [2]. Primary intracranial malignant melanomas are exceptionally rare and to date there are

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fewer than 250 cases reported in the literature[9] A Norwegian study of the local cancer registry found an incidence rate of 0.005 new cases per 100,000 population per year for primary leptomeningeal melanoma, and there was only one patient under 20 years of age, demonstrating the rarity of this lesion in children[10].

Embryology

The melanocytes, pigment producing cells, derive from the neural crest during early embryonic development [11, 12], and as the developing cerebral hemispheres expand they take a thin layer of these cells, which migrate to different regions. In the craniospinal axis, they are predominantly located in the leptomeninges at the anterior and lateral surfaces of the spinal cord, the brainstem, and the base of the brain, intimately associated with pia and arachnoid membranes. This distribution of melanocytes closely correlates with the reported distribution of these rare tumors [2, 3,8, 13]

Melanomas are malignant neoplasms of these cells that develop predominantly in the skin, but may occasionally involve the eyes and mucous membranes. Rarely, the melanocytes in the leptomeninges may undergo transformation, giving rise to primary melanocytic lesions of the central nervous system [8].

Diagnosis

Melanosis is an extensive benign melanocytic infiltration of the supra and infra tentorialleptomeninges, mostly of the cerebellum, pons, medulla and temporal lobes. It may present at birth or develop later in life [2], with a diverse clinical presentation that includes stillbirth, intracranial hypertension and hydrocephalus, seizure, ataxia, syringomyelia, cranial nerve palsy, intracranial hemorrhage, sphincter dysfunction and neuropsychiatric symptom [2,4,9], and can also present as chronic meningitis[14]. Clinical deterioration is rapid if malignant transformation occurs. Melanosis has a known association with neurocutaneousmelanosis, neurofibromatosis-1, Sturge-Weber syndrome and Dandy-Walker syndrome; and it has been reported that 15% also developed primary CNS melanoma. [2,4,9].

The malignant form of diffuse involvement is called meningeal melanomatosis, which is more common in adults, and can clinically mimic a wide variety of other conditions, including lymphoma, leukemia, neurosarcoidosis, metastatic carcinoma, acute disseminated encephalomyelitis, subacute meningitis, viral encephalitis, and idiopathic hypertrophic cranial pachymeningitis. Zadro et al reported a case that presented with optic neuritis, cognitive disturbances, and signs of peripheral nervous system involvement [15]

Meningeal melanocytoma and primary CNS melanoma are of similar origin and represent the benign and malignant ends of a spectrum; malignant transformation of melanocytoma to malignant melanoma has been reported. They may be intracranial or spinal because they occur throughout the neuraxis. [2,16]

Meningeal melanocytomas are benign, slowing growing, focal mass lesions. They are usually intraduralextramedullary lesions located in the cervical and thoracic spine, and less frequently, they arise from the leptomeninges in the posterior fossa and supratentorial compartments [2,3,4,16]Ali et al reported about a case of multifocal benign meningeal melanocytoma involving both cerebellopontine angles and the thoracic spinal cord [12]It is assumed that they represent an area of meningeal melanocytosis that has undergone a nodular neoplastic proliferation [16]. The age at diagnosis ranges from 9 to 73 years, with a peak incidence in the fifth decade and a slight female preponderance[2,4,5]. The clinical presentation includes focal neurological signs associated with their location, intracranial hypertension or hemorrhage, neuropsychiatric symptoms, spinal cord compression, myelopathy, radiculopathy, cranial nerve deficits and seizures[2,4].Some case reports had documented a prolonged onset of symptoms, even 10 years prior to diagnosis, may be due to the slow rate of growth of the lesion [3,7,9]. Associated melanotic lesions in the kidneys and adrenal glands and aggressive leptomeningeal spread throughout the neuraxis had been reported[2].

Primary CNS melanomas are lesions with a slight predilection for the posterior fossa and spinal cord, which can produce solid nodular lesions or diffusely infiltrate the leptomeninges [2,8]. They arise in patients from 15 to 71 years of age, with a peak incidence in the fifth decade[2].There is a strong association with neurocutaneousmelanosis, and such cases account for almost all melanomas in the pediatric population [9].

Primary leptomeningeal melanoma is a rare tumor in children and accounts for less than 1% of all pediatric malignancies. Usually, it is an aggressive tumor that originates from pial melanin-bearing cells, which typically reside along the cerebral convexities or at the base of the brain. It has been hypothesized that malignant transformation of the pre-existing precursor cells leads to diffuse infiltration of the meninges by tumor and the onset of neurologic symptoms and signs [10].

Symptoms of primary CNS melanomas typically evolve quicker [3], including intracranial hypertension and hydrocephalus (43.2%) secondary to tumoral obliteration of basal cisterns, lethargy, irritability, headache, poor feeding, nausea, vomiting, focal neurological deficits due to compression of the brain, spinal cord or caudaequina (34.6%), subarachnoid hemorrhage (17.3%) and seizures (11.1%) [2,4,6,9,10]. The absence of a history of skin malignancy ensures that this diagnosis is rarely made preoperatively [13]. A rigorous examination of all other possible anatomic sites of origin should be undertaken, including skin, nail beds, mucosal surfaces, scalp, orbital contents, adrenals, and gastrointestinal tract, to exclude distant primary melanoma [2,16].

Hayward proposed that the absence of melanomas beyond the CNS, the presence of a single intracranial lesion and the involvement of the leptomeninges, among other features, are useful for establishing the diagnosis of primary leptomeningeal malignant melanoma[8,13,17]. Willis also outlined three basic conditions for diagnosing this condition: no skin or eye melanoma, no history of melanoma surgery in the skin or eyes and no extracranial visceral melanoma metastases.Several scholars believe that only a meticulous autopsy can exclude possible extracranial

melanomas[6].

Primary CNS melanomas are rare, and no evidence-based guidelines exist for their diagnosis, work-up, and management. A systematic search of the medical literature identified numerous case reports and small case series of in different locations such as the cerebellopontine angle, pineal gland, perisylvian cortex, medullar oblongata, cervical spinal cord, ventricles, and sellaturcica[8]. But the vast majority of cases reported are in adults [1,2,6,8,13, 16,17,18], with very few in children[10].

Investigations and Neuroimaging

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[2,10].CSF cytology can be non-informative, even in cases with leptomeningeal dissemination[9].Early meningeal biopsy should be considered in patients with meningitis when the CSF profile suggests the possibility of a central nervous system neoplasm[14].

Electroencephalogram may reveal focal or generalized abnormalities[2]. Neuroimaging CT demonstrates melanocytic neoplasms as iso to hyperdense lesions with homogenous contrast enhancement with or without abnormal calcification[2,8,9]. But CT scans generally lack specificity, and may fail to reveal the tumor, because of bone surface and/or interface[6,10].

MRI is the gold standard neuroradiologic diagnostic method. The melanocytic neoplasms of the CNS have unusual paramagnetic properties because of the free radicals in both melanin and blood products[9,17].They are typically hyperintense on T1-weighted images, hypointense on T2-weighted images and enhance homogeneously with gadolinium [2,3,4,6,8,9,13,16]. The lack of characteristic hyperintensity observed on T2 is possibly due to their very cellular or fibrous nature, resulting in diminished water content and the paramagnetismeffects of melanin[19].The appearance may depend on the degree of melanin or previous hemorrhage within the lesion, so for example, intra-tumoral hemorrhage produces heterogeneous signals on T1 and T2 sequences depending upon the duration of the bleed, and amelanotic melanomas or melanomas without hemorrhage are iso-hypointense on T1-weighted images and moderately hyperintense on T2-weighted images[8,17]. Proton MRS findings are non-specific, with elevated choline, reduction of N-acetyl aspartate (NAA) and a lipid resonance peak [17].

Melanosis and melanomatosis appear as diffuse meningeal thickening on both CT and MRI while melanocytomas and primary melanomas appear as solitary nodular lesions[2, 9].In melanomatosis brain MRI findings include T2 hyperintensities in both optic nerves and diffuse involvement of white and gray matter[15].

On MRI imaging the meningeal melanocytoma and primary melanoma cannot be reliably distinguished [17].Melanocytomas are generally dense, extra-axial lesions with dural attachment, which may not show distinct margins. Melanomas have a similar appearance which varies according to the melanin content. In cerebral angiography the melanocytoma is hypovascular with a scant or very thin vascular stain, while primary melanoma shows a vascularized lesion[2].

In leptomeningeal melanoma, the leptomeninges (pia-arachnoid) are more commonly involved than the pachymeninges (dura). So, unlike meningioma, melanoma rarely manifests with a dural tail or hyperostosis of the adjacent bone.MRI is a useful diagnostic tool for narrowing the differential diagnosis and guiding therapeutic decisions[17].

Pathology

During surgery of melanosis the dura appears relatively normal, however on opening the dura, large areas of the leptomeninges appear greenish-black or dark brown with replacement of the subarachnoid space [2,4]. The meningeal layer becomes diffusely thickened and pigmented, most markedly in the brainstem and base of the brain. [9].

Melanocytoma and primary malignant melanoma are solitary mass lesions, which are generally extra-axial. Variable pigment production results in lesions that are grossly black (70%), gray, brown, blue or non-pigmented [2,3]

Meningeal melanocytomas are encapsulated, well circumscribed, soft masses, intradural, attached to the dura, that often compress adjacent neural structures, rarely demonstrate parenchymal invasion, and they may be extremely vascular[2,7,9,12].

Primary leptomeningeal melanomas are well-defined, dark lesions that are often friable, soft, and hemorrhagic [9]They had been classified into two types: one diffusely invades the pia mater and spreads into the subarachnoid space, and the other causes nodular tumors[4,10]. Primary CNS melanoma usually presents as a large solitary, lobulated, extra-axial mass, with frank macroscopic invasion of the underlying parenchyma[3,17]. It is important to distinguish a primary melanoma associated with the meninges from a typical metastatic melanoma in the parenchyma[9].

Histology

A brain or meningeal biopsy remains the only definitive diagnostic procedure[6,10]. The diagnosis can be confirmed through histopathological examination with identification of melanin in tumor cells or associated macrophages[2]. Nevertheless, occasionally melanocytomas or melanomas may be unpigmented and the diagnosis then depends on electron microscopy, immunohistochemistry and cytogenetic analysis, which have become exceedingly important in the accurate recognition of these lesions [1,2,19].

Melanosis is caused by the abnormal proliferation and melanin production of leptomeningeal melanocytes [2]. Consists of increased number of cells distributed diffusely throughout the leptomeningeal layers, which may accumulate within the Virchow-Robin spaces, but do not invade the brain parenchyma. The melanocytes are relatively small, spindle, round, oval or cuboidal

cells with granular brown pigment, with moderate amount of eosinophilic cytoplasm, oval nuclei and large nucleoli [2,9]. Mitosis are typically absent, and the lesion does not form large cellular clusters. The lesions may contain areas of recent and old hemorrhage or reactive changes; however, by definition, no mass is recognized[9].Brain parenchymal invasion indicates malignant change to melanomatosis[2].

Melanocytomas were once thought to represent the "melanotic meningioma" until ultrastructural studies demonstrated that tumor cells were melanocytic in origin, rather than meningothelial[3]. Melanocytomas are solitary, low grade, well-differentiated lesions that do not invade the surrounding brain parenchyma and areas of hemorrhage may be seen. The major architectural pattern takes the form of tight nests, sheets or fascicles of well-differentiated melanocytes, with heavily pigmented cells seen at the periphery. Cells may be spindles or ovals with variable melanin content, oval or bean shaped nuclei and small eosinophilic or prominent nucleoli. Anaplastic features such as mitosis and pleomorphism are generally absent, as well as the hyperchromicity[2,3,4,9,12].

Primary CNS melanoma is histologically similar to melanoma arising in other sites. [2] In both forms, diffuse or nodular, is usually a highly malignant tumor characterized by marked cellular pleomorphism, mitoses, coagulative necrosis, and hemorrhage [2,10]. This highly cellular neoplasm consist of spindled or epithelioid cells arranged in loose nests, sheets or fascicles, with variable cytoplasmic melanin pigment. They may contain large epithelial-like, rounded or spindle-shaped cells with abundant eosinophilic cytoplasm, irregularly contoured hyperchromatic nuclei, intranuclear inclusions, typical or atypical mitotic figures, large eosinophilic nucleoli and heavily pigmented chromatophores. The features are similar to melanocytoma but with higher cell density, cytologicatypia, high mitosis rates (more than 2 per 10 high power fields), MIB-1 labeling index (>3%), necrosis and neural parenchymal invasion [2,3,15,17]. It has been suggested that melanocytic tumors with bland cytologic features, but showing CNS invasion or elevated mitotic activity, be classified as intermediate-grade melanocytic neoplasms. If necessary, cellular pigment can be confirmed histochemically using the Fontana-Masson method [3]; nevertheless, approximately one third of melanomas do not contain detectable amounts of melanin on routine and special histochemical stains [9].

Electron microscopy is a very useful tool in identifying amelanotic melanomas. Most of melanocytomas and melanomas display premelanosomes and melanosomes at various stages of maturity within the cytoplasm, indicating that melanin is produced rather than accumulated. They also demonstrate the lack of cell-to-cell junctions, desmosomes and interdigitating cytoplasmic processes that are characteristic of meningiomas. The absence of basal lamina around individual tumor cells has been confirmed ultrastructurally and is important for distinguishing them from melanotics chwannoma [2,3,5,9].

Immunohistochemically the melanocytomas and melanomas are strongly immunoreactive for markers of melanocytic differentiation, including the S-100 protein, anti-melanoma antibody (HMB-45) and anti-melanosomal antibody MART-1 (Melan-A) [3,7].The S-100 protein is most valuable as an initial screening tool because it can also be positive in various poorly differentiated carcinomas, selected histiocytic proliferations, malignant gliomas, peripheral nerve sheath tumors, and Langerhans' cell proliferations. HMB-45 and melan-A are highly specific for melanocytic cell types, with sensitivity between 60% to 80% [19].Tyrosinase, microphthalmia transcription factor protein (MTFP) and vimentin (VIM) can also be positive [1,5,6,9]. Tyrosinase is a specific marker for melanocytic differentiation, tyrosinase gene transcripts are strictly confined to melanin-producing cells. MTFP plays a role in controlling the activity of melanogenic enzymes, and appears to be sensitive and specific for the identification of melanocytic proliferations [19]. Reactivity for neuron-specific enolase, cytokeratin (CK) and glial fibrillary acidic protein (GFAP) is usually negative. Absence of epithelial membrane antigen (EMA) excludes melanotic meningioma [1,5,6,9].Reticulin stains and immunohistochemical stains for collagen IV and laminin demonstrate basal laminar proteins around blood vessels, but not around individual tumor cells in melanocytoma. [3]

Treatmentand Prognosis

The literature mostly consists of case reports with no high quality evidence regarding the prognostic implications of various treatment options (i.e., surgery, radiation therapy, and chemotherapy)[9].

Melanosis carries a poor prognosis even in the absence of histological malignancy [2,9], with most patients dying before age ten and 50% dying within three years of onset of neurological symptoms. The role of chemotherapy and radiotherapy remains unclear, but neither seems to improve outcome. There is no definitive treatment and palliation consists of tumor debulking and placement of a ventricular shunt with a filter to prevent seeding [2].

The behavior of melanocytoma is difficult to predict; however, because of its potential to transform to malignant melanoma, attempt at complete resection is advised when possible[2]. The majority of low-grade, circumscribed tumors without invasion have a favorable long-term prognosis following complete resection, although this resection sometimes is difficult because of an unfavorable location, a large size, diffuse lesion or tight adhesion[3,11].Despite its benign appearance the tumor may follow an aggressive course, related to the extent of resection or the involvement of CNS parenchyma, with recurrence even after apparently complete excision; therefore follow-up imaging studies are warranted even after total resection [2,3,9,16].In various series, postoperative recurrence rate ranged from 15% to 51% [9], usually presenting from seven months to five years later, with 71% within five years, and shorter with malignant transformation[2].For those who did not achieve a complete resection of tumors, the following adjuvant radiotherapy significantly decreased the chances of recurrence [11,12].Radiation therapy is advised in cases of both complete and incomplete resection [2,11], although some reports

suggest that the decision is primarily based on the extent of tumor resection[9]. Other reports indicate that due to their slow growth the use of postoperative radiation therapy must be individualized and should be reserved for those patients with symptomatic residual or recurrent tumors[16]. Survival rates are better with complete resection with or without radiotherapy. Radiosurgery is a valuable mode of therapy when lesions are not amenable to surgical resection, because stereotactic gamma knife may reduce the size of residual tumor and improve clinical outcome[2, 9]. Complications should be treated as clinically appropriate; for example, hydrocephalus may be treated with a ventricular shunt, but a filter is needed to prevent spread in the event of malignant transformation. [2] The reported postoperative survival time ranges from 1 year to 28 years[9].

Primary CNS melanomas are aggressive tumors that could metastasize to other organs [2], therefore the current treatment does not guarantee an optimistic prognosis[6]. At present, the preferred treatment is surgery, and the role of adjuvant therapy is not clear[17]. Microsurgery, local radiation therapy, whole-brain radiotherapy (WBRT), chemotherapy, immunotherapy and targeted therapies are currently administered or combined for their treatment[6].Most authors agree that whenever possible, complete surgical excision with or without radiotherapy should be the first line management (standard practice) for these patients [2,6], because this had been associated with significantly better outcome [2].

The consideration of surgical resection is dependent upon the location and size of the tumor, the number of lesions, the overall state of systemic disease and symptoms of patients at the time of diagnosis. For single primary intracranial melanomas with a diameter ≥3 cm and significant mass effects (or peritumoral edema) or CSF obstruction, microsurgical excision followed by radiotherapy is recommended. For lesions with diameter < 3 cm or if it is deep in the brain and resection will cause significant neurologic sequelae, the treatment protocol includes local radiotherapy or auxiliary WBRT.Other authors indicate that small (< 3 cm), residual or metastatic lesions are easily treated via radiosurgery (local radiotherapy), such as stereotactic radiosurgery (SRS) and gamma-knife (GK), exceeding 80% of local tumor control. In small case series reports survival following radiosurgery has been quite encouraging, with infrequent neurological complications[6].

Wang et al performed an MRI within 72 h of surgery for all patients to confirm whether there was any remnant tumor[2].Postoperative radiotherapy as well as chemotherapy is recommended in all cases [1,2,16]; but some reports indicate minimal success of chemotherapy [9], because of their inability to penetrate the blood-brain barrier [6].Of the chemotherapy agents studied to date, temozolomide and fotemustine appear to have the most intracranial disease activity; however, no improvement has been observed in the overall survival[6].In some cases immunotherapy-based regimes (such as high dose interleukin-2, autologous tumor-infiltrating lymphocytes or T-cell receptor-transduced lymphocytes, anticytotoxic T-lymphocyte antigen 4 therapy with ipilimumab), had obtained active response, including prolonged overall survival. In addition, recently discovered genetic aberrations in the melanoma genome have led to investigation of "targeted therapy", exploring the efficacy of gene therapy for this condition[6,11].

Although primary nodular melanomas are aggressive and potentially fatal, prognosis depends on tumor site, extent of spread within the CNS, extent of resection, and response to therapy[3]. Localized primary CNS melanomas have favorable long-term outcomes, and there are reports of survival up to 9 and 12 years after presentation. [1] Although long-term survival has been documented, a substantial number of patients experience a malignant course of the disease due to rapid leptomeningeal spread, imparting a worse prognosis [16.] Although aggressive treatment with various modalities, including chemotherapy, radiation therapy and surgery may help prolong survival, most patients die within a year. The average survival rate is 5 to 10 months; however, survival rates of up to 3 years have been reported after surgical resection [9].The prognosis for patients with primary meningeal melanoma appears better than for those with metastatic melanoma, especially if complete resection can be achieved and no distant metastases are present[2,6,9]. The prognosis of patients with metastatic melanoma to the CNS is dismal, with a life expectancy typically less than a year, usually 3 to 6 months [3,8].Recurrence after surgery tends to be localized and distant metastases are rarely seen in primary CNS malignant melanomas[1].Surveillance imaging with MRI or CT is recommended at regular intervals following resection of melanocytic tumors [2,17].

Differential Diagnosis

Primary melanocytic neoplasms of the CNS should be differentiated from metastatic malignant melanoma by a thorough search for a primary lesion[2]. Metastatic tumors present usually after 50 years of age, as multiple small multifocal lesions, intra-axial, located at the junction of the grey and white matter, rarely present with leptomeningeal involvement, with extra-cranial disease almost always present, usually with rapid clinical course and dismal prognosis [1,8,17].

In addition, immunohistochemistry and ultrastructural features are usually helpful in distinguishing these lesions from other pigment-containing CNS tumors including meningioma, melanotic-schwannoma, melanocytic medulloblastoma, melanoticneuroectodermal tumor of infancy, choroid plexus tumor, neurofibroma, pituitary tumor, ependymoma and subependymoma, ganglion cell tumor, astrocytic tumor, neurocytoma, pleomorphic xanthoastrocytoma, and paraganglioma[2, 4].

Case Report

A previously healthy 2 years old girl presented with a 3 months history of nausea, vomiting, irritability, loss of weight, consciousness disorder and facial paralysis (deviation of the labial commissure to the right). She arrived at the emergency service of a local hospital, were a CT scan evidenced hydrocephalus, so a ventricular peritoneal shunt was placed.

Two months later she presented to the emergency department because of persistent vomiting, continuing loss of weight because

food intolerance, with difficulties for walking and talking she did not have previously. At the emergency department a CT scan indicated significant decrease in ventricular size and a suspicion of a suprasellar lesion.

Ophthalmological examination only showed limitation of abduction of the left eye, without any other abnormal findings. She was also assessed by endocrinology without any evidence of hypopituitarism. Tumor markers (alpha-fetoprotein, carcinoembryonic antigen, human chorionic gonadotropin) were normal. Seven days after a MRI revealed a suprasellar cystic lesion with invasion of the subarachnoid space widely.

The same day a lumbar puncture was performed without obtaining liquid outlet, whereby percutaneous tapping of the ventriculoperitoneal shunt access port was done. CSF analysis and cytology reported a high protein content (142mg/dl), normal glucose level, abundant red blood cells, sterile leucocytosis (400 / μL), and 100% cells of tumoral aspect. Histological examination of the cytological extended sample of CSF exhibited groups of cells with a papillary distribution, basophilic nuclei, regular chromatin and abundant pinkish cytoplasm, without pleomorphism or mitosis; compatible with choroidal cells, with no evidence of neoplastic cells.

Two days after, she underwent a pterional craniotomy and frontal cortical biopsy in the operating room. During surgery an extensive infiltration of the subarachnoid space was observed.

Pathology reported multiple fragments of pinkish tissue with some reddish areas, of soft consistence, and some areas of fibrosis. Histological examination showed leptomeninges infiltrated by multiple large cells arranged in loose nests or with a papillary distribution, with eosinophilic cytoplasm, pleomorphic and hypechromatic nuclei, prominent eosinophilic nucleoli. It also contained multiple mitotic figures (12 per 10 high power fields), apoptotic cells and numerous thin-walled blood vessels. It did not have any brain parenchymal invasion or pigment. Immunohistochemic revealed the tumor was positive for the following markers: S-100 protein, anti-melanoma antibody (HMB-45), vimentin, enolase; and focal positive for cytokeratin, Ck 7 and synaptophysin. Reactivity for anti-melanosomal antibody MART-1 (Melan-A), glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), CD 117 and chromogranin were negative.

A detailed search excluded extracranial primary melanoma. The final pathological diagnosis was reported as primary leptomeningeal melanoma. She was managed for palliation and died less than two months after.

Discussion

Primary CNS melanoma is a rare kind of tumor during childhood, and in the past ten years only one case in the pediatric population had been reported.

We report the case of a little girl, who presented with rapid evolving symptoms including hydrocephalus, which is the most common according to literature, lethargy, irritability, poor feeding, loss of weight, nausea, vomiting and focal neurological deficits (facial paralysis, difficulties for walking and talking), as reported by most of the authors. She did not have any past history of skin or eye malignancy.

Because of the initial symptoms, we first suspected a brain tumor, and even though CT scan only revealed a suspicious lesion, the MRI revealed a suprasellar cystic lesion with invasion of the subarachnoid space widely, and the CSF analysis and cytology was compatible with an intracranial tumor. Since biopsy is the only conclusive diagnostic method, she underwent a craniotomy, where an extensive infiltration of the subarachnoid space was observed, in relation to a diffuse form of neoplastic lesion.

During the histological and immunohistochemical analysis a CNS melanoma was suspected. The positivity of S-100 protein and HMB-45 defined the case as melanoma and the negativity of the Melan-A did not invalidate it. The positivity of the enolase, cytokeratin and synaptophysin were interpreted by pathologists as aberrant, and this has been described before in the literature.

Because the radiological studies revealed leptomeningeal involvement (supratentorial, infratentorial and medullary), and a detailed search excluded secondary metastatic disease from cutaneous, mucosal or retinal primary melanoma, the final diagnosis was a diffuse primary leptomeningeal melanoma.

It is important to emphasize that the diagnosis of this entity is difficult when there are no skin lesions, and it is generally a diagnosis of exclusion after ruling out extra-cranial disease. In addition, the differential diagnosis of these lesions with other primary melanocytic neoplasms is often confusing because of their similar radiologic appearance, so diagnostic verification with electron microscopy and immunohistochemical analysis is irreplaceable.

Because the biologic behavior, treatment, and prognosis of the primary melanocytic neoplasms are different, it is important to make the correct pathological diagnosis. In this case the girl presented with extensive infiltrate of the leptomeninges, compatible with a malignant diffuse form of the disease, which had an aggressive and fatal course, with death within two months after the diagnosis.

Conclusions

Although the absence of a history of skin malignancy makes the definite preoperative diagnosis of a primary leptomeningeal melanoma difficult, the correlation of clinical, neuroimaging and histological finding is crucial in helping to determine the diagnosis of this entity, its prognosis and management.

Although current standard treatments with neurosurgery and radiotherapy have improved the overall survival of patients with malignant intracranial melanomas, it still remains an ongoing challenge to neurosurgeons, given the small number of case reports in the literature.

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