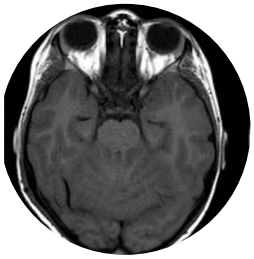

Primary leptomeningea presentation of tumors with diffusion restriction. Report of two cases

Presentación leptomeníngea primaria de tumores con restricción en difusión. Presentación de dos casos

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Summary

Primary leptomeningeal tumors in pediatrics are uncommon entities. They mostly consist of diffuse glioneuronal tumors, although a few cases of embryonal tumors have also been reported. The complexity in diagnosing this presentation is due to atypical clinical manifestations and difficulties in the differential diagnosis. Diffusion-weighted imaging (DWI) is an imaging modality that is extremely sensitive in detecting water movement in the extracellular space. In neuro-oncology, its utility lies in differentiating between tumors with low cellular density and those with high cellular density, particularly those composed of "small, round, and blue" cells. In this study, we present two cases of disseminated primary leptomeningeal tumors of embryonal origin without a primary brain mass, showing restriction on DWI (hypercellularity). The cases, studied at Garrahan Hospital in the last 3 years, along with a literature review, indicate that the most common imaging finding is diffuse intracranial and intra-spinal leptomeningeal nodular thickening and enhancement. However, no reports were found on the utility of DWI in diagnosing these entities. The article analyzes neuroimaging approaches and diagnostic confirmation to provide opportunities for effective treatment of these diseases in clinical practice.

Resumen

Los tumores leptomeníngeos primarios en pediatría son entidades poco comunes. En su mayoría, se trata de tumores glioneuronales difusos, aunque también se han descrito algunos casos de tumores embrionarios. La complejidad del diagnóstico de esta presentación se debe a las manifestaciones clínicas atípicas y a las dificultades en el diagnóstico diferencial. La secuencia de imagen ponderada por difusión (DWI) es una modalidad de imagen altamente sensible que detecta el movimiento del agua en el espacio extracelular. En neurooncología, su utilidad radica en diferenciar entre tumores de baja densidad celular de aquellos con alta celularidad, particularmente de los que se encuentran compuestos por células "pequeñas, redondas y azules". En este estudio se describen dos casos de tumores leptomeníngeos primarios diseminados de origen embrionario, sin una masa cerebral primaria, con restricción en la secuencia de DWI (hipercelularidad). Los casos, estudiados en el Hospital Garrahan en los tres últimos años, y la revisión de la literatura indican que el hallazgo imagenológico más frecuente es el engrosamiento y realce nodular leptomeníngeo intracraneal e intraespinal difuso. Sin embargo, no se encontraron informes sobre la utilidad de la secuencia de DWI para el diagnóstico de estas entidades. En el artículo se analizan los enfoques de neuroimagen y la confirmación diagnóstica con el fin de proporcionar oportunidades para un tratamiento efectivo de estas enfermedades en la práctica clínica.

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Introduction

The fifth edition of the Central Nervous System (CNS) Tumor Classification (1). Central Nervous System (CNS) embryonal tumors (ET) of the World Health Organization (WHO), presents new entities as histologic features are not always specific to a particular entity, and integration of microscopic and molecular findings is required. If, in addition, these lesions present as diffuse

primary leptomeningeal involvement without a primary intra-axial lesion, their diagnosis becomes even more difficult.

Primary leptomeningeal tumors in pediatrics are rare entities (2). They are mostly primary diffuse glioneuronal tumors; although some cases of high-grade embryonal tumors have also been documented (3-5).

CNS ETs are rare, occur predominantly in children and adolescents and are characterized by early onset and an aggressive clinical course. They can arise in the cerebral hemispheres, brainstem and spinal cord. Leptomeningeal dissemination is a common complication, but primary leptomeningeal ET in the absence of a solid parenchymal tumor is extremely rare.

On histopathologic examination they show a common histologic feature: small, round, blue, dense cells. These tumors show an overlap in histologic and radiologic appearance, reflecting their high cellularity. Therefore, they should be considered ET when they present hyperdensity in computed axial tomography (CT), low signal intensity in T2 images and restriction in DWI (6).

In this article we report the clinical features and the imaging and histopathologic findings of two patients with primary leptomeningeal involvement of high-grade tumors without intraparenchymal mass, composed of "small, round and blue" cells and DWI sequence restriction.

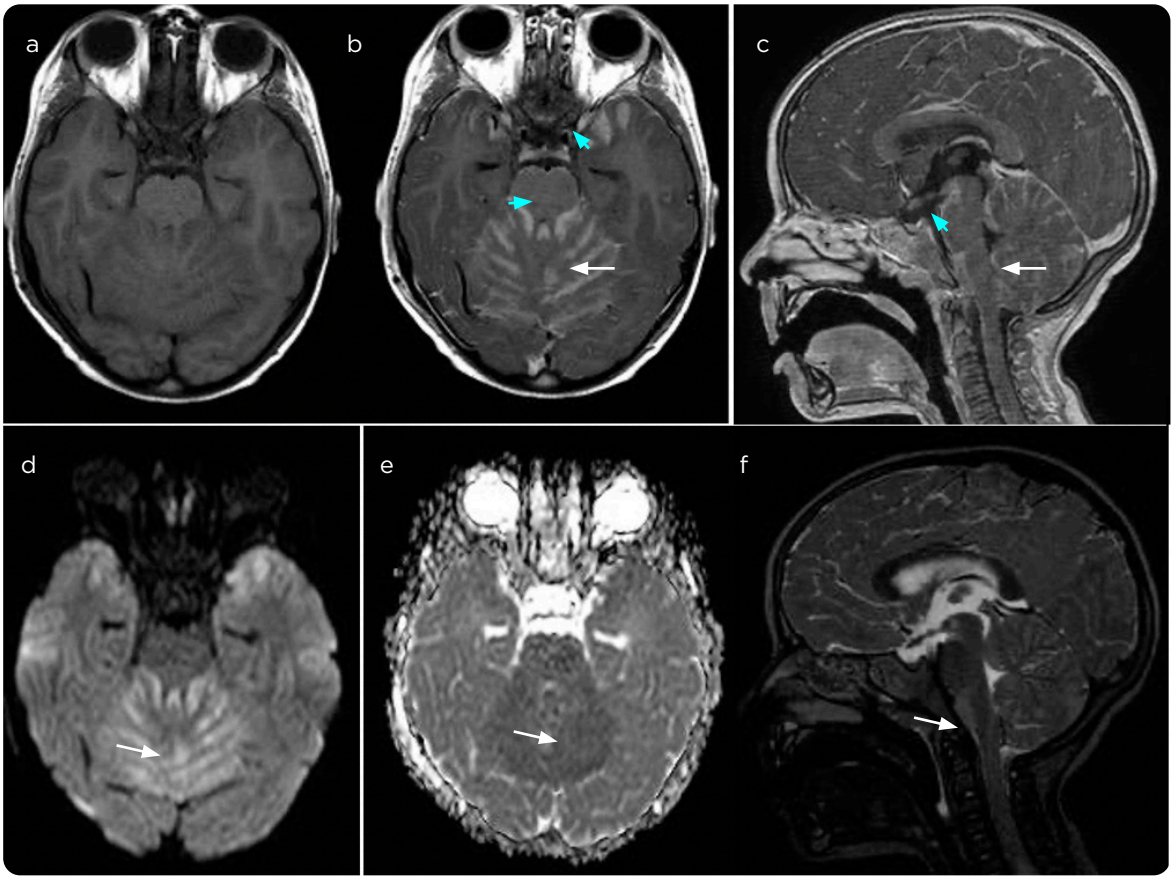
Case presentation

Patient 1

We conducted a retrospective descriptive study that included 377 oncologic patients who were i A 4-year-old boy consulted for persistent headache for two weeks, accompanied by nocturnal vomiting with little response to analgesics and weight loss. Subsequently, he developed ataxic gait.

A CT scan identified obstructive hydrocephalus and signs of persistent intracranial hypertension, despite a ventriculoperitoneal shunt, so it was decided to perform a surgical decompression of the posterior fossa and take a biopsy. Subsequently, a magnetic resonance imaging (MRI) with gadolinium was performed in a 1.5T equipment. The results showed a diffuse leptomeningeal involvement with slightly hyperintense lesions in T2 sequences, DWI (Diffusion Weighted Image) restriction and irregular enhancement after administration of intravenous contrast medium (Figure 1).

Histopathological examination showed a neoplastic proliferation with embryonal appearance, composed of cells with round hyperchromatic nuclei, pleomorphism and scant cytoplasm. They were densely clustered and distributed in beaches, with increased reticulinic network



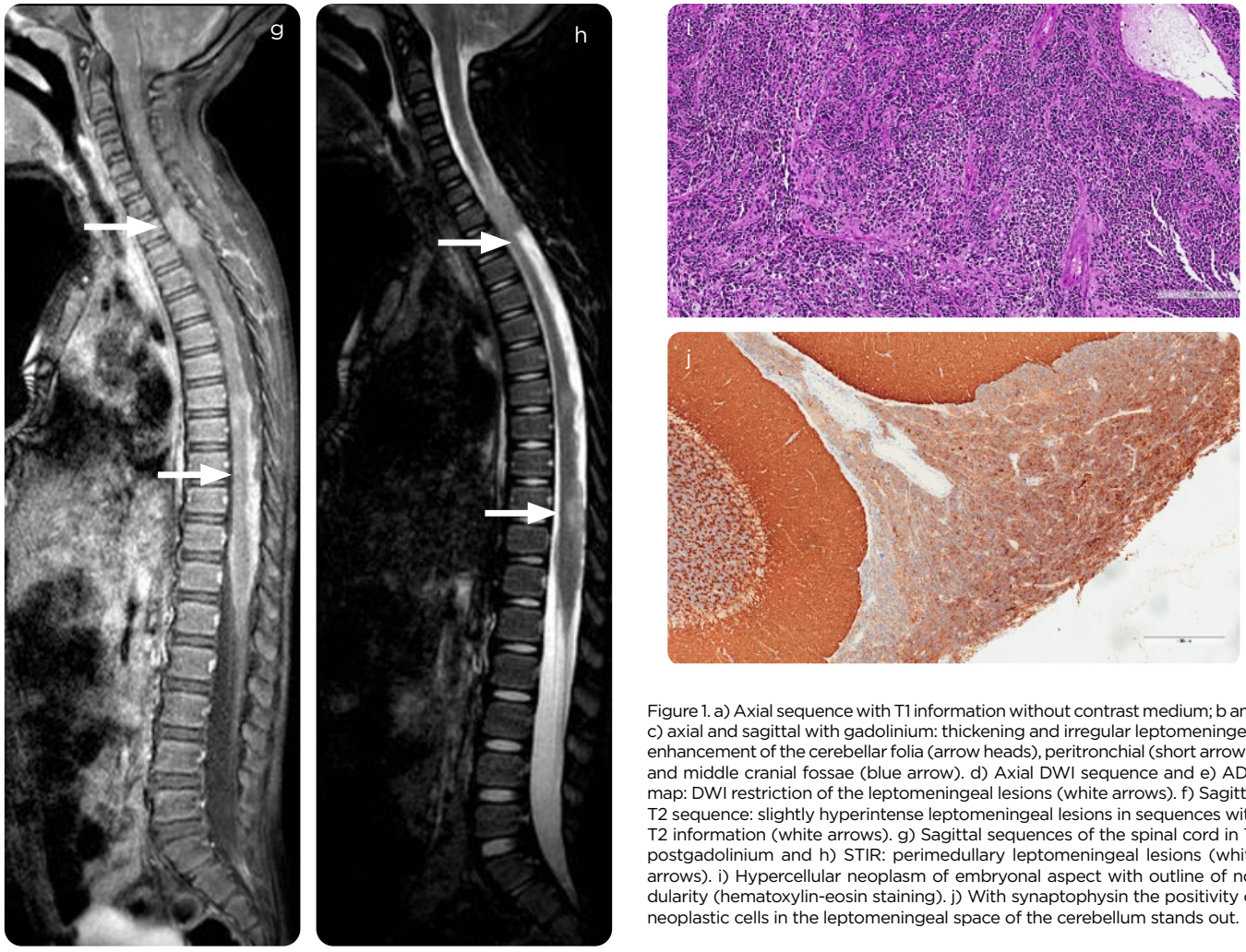


Figure 1. a) Axial sequence with T1 information without contrast medium; b and c) axial and sagittal with gadolinium: thickening and irregular leptomeningeal enhancement of the cerebellar folia (arrow heads), peritronchial (short arrows) and middle cranial fossae (blue arrow). d) Axial DWI sequence and e) ADC map: DWI restriction of the leptomeningeal lesions (white arrows). f) Sagittal T2 sequence: slightly hyperintense leptomeningeal lesions in sequences with T2 information (white arrows). g) Sagittal sequences of the spinal cord in T1 postgadolinium and h) STIR: perimedullary leptomeningeal lesions (white arrows). i) Hypercellular neoplasm of embryonal aspect with outline of nodularity (hematoxylin-eosin staining). j) With synaptophysin the positivity of neoplastic cells in the leptomeningeal space of the cerebellum stands out.

delineating nodules. Most of the neoplasm was located in the leptomeningeal space between the cerebellar folia. Immunohistochemistry showed positivity for synaptophysin, NEU-N, GFAP, P53 and BCOR, and negativity for B-catenin. The Ki67 proliferation index was 70%. Positive amplification of N-MYC was also identified.

The final diagnosis was grade 4 nodular desmoplastic medulloblastoma, according to the WHO classification.

The patient presented rapid neurological deterioration, so he underwent a cycle of systemic chemotherapy with carboplatinoetoposide. Subsequently, he underwent radiotherapy including cranium and rachis: 36 Gy with boost in complete spine followed by 6 cycles of chemotherapy with cisplatin-cyclophosphamide-vincristine. There was partial response to oncologic treatment with improvement of neurological status. Currently, the patient continues with stable tumor disease 12 months after the initial diagnosis.

Patient 2

A 2-year-old girl consulted for a clinical picture of three weeks of evolution characterized by pain and functional impotence in the lower limbs. MRI findings were similar to those observed in patient 1, including diffuse supra- and infratentorial leptomeningeal nodular thickening with hyperintense lesions in T2 sequences, DWI restriction and diffuse postgadolinium enhancement. In the spinal canal he had extensive intradural extramedullary lesions with lumbosacral predominance (Figure 2). Due to the development of spinal shock, the patient underwent spinal decompressive surgery with biopsy.

Histopathologic examination revealed a densely cellular neoplastic proliferation with embryonal appearance, composed of atypical cells of small size, scant cytoplasm and round, hyperchromatic nuclei. On immunohistochemistry, the cells were negative for vimentin, CD45, CD99, desmin and NB84, whereas they showed positivity for synaptophysin and GFAP. B-catenin was negative, INI-1 preserved and P53 negative. The rearrangement for EWRS1 by FISH technique was negative, which allowed ruling out Ewing sarcoma. The final diagnosis was embryonal tumor NOS (not specified).

The patient received treatment strategy for ET (embryonal tumor) in infants with induction chemotherapy (cisplatin-cyclophosphamide-etoposide-vincristine-methotrexate) for three cycles without clinical or imaging response. Subsequently, she continued with metronomic chemotherapy (temozolamide and etoposide) for six cycles until disease progression. The girl died 11 months after the initial diagnosis.

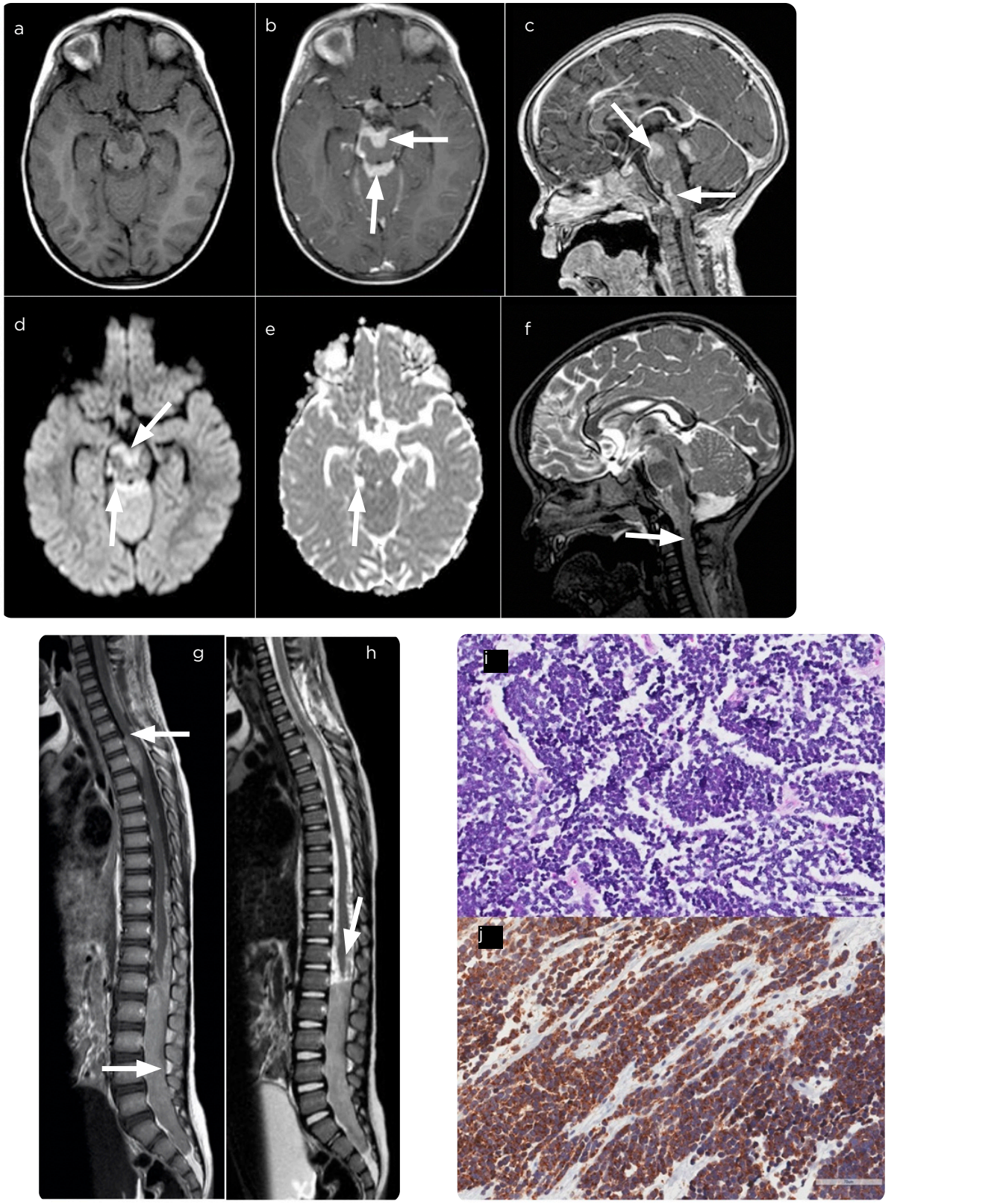


Figure 2. a) Axial sequence with T1 information without contrast medium, b) axial T1 and c) sagittal sequence with intravenous contrast medium showing thickening and nodular leptomeningeal enhancement with peritronchal predominance (white arrows). d) Axial DWI sequence and e) ADC map: DWI restriction of leptomeningeal lesions (white arrows). f) Sagittal T2 sequence: slightly hyperintense leptomeningeal lesions in sequences with T2 information (white arrows). g) Sagittal sequences of the spinal cord in sequences with postgadolinium T1 and h) T2 information showing extensive leptomeningeal and intradural lesions with greater lumbosacral involvement (white arrows). i) Microscopy (hematoxylin-eosin staining): The cells are small and monomorphous, undifferentiated, with rounded nucleus and scanty cytoplasm. j) Diffuse positivity for synaptophysin.

Discussion

Leptomeningeal CNS involvement in patients with ET is usually due to dissemination of a primary intraparenchymal lesion. The primary disseminated leptomeningeal form of ET is extremely rare and is associated with an unfavorable prognosis.

According to the literature, five cases of medulloblastomas with primary leptomeningeal involvement have been described in pediatric patients (7-11). Reviewing works prior to the 2016 WHO classification, we find the description of 19 similar cases, but with a diagnosis of primitive neuroectodermal tumor (PNET) (12). The patients presented signs of endocranial hypertension, thickening and leptomeningeal enhancement, as in the case described here. In addition, four cases of primary diffuse leptomeningeal atypical teratoid/rhabdoid atypical leptomeningeal tumor, which is another high-grade ET with a poor prognosis, have been reported (13-16).

CNS TEs are a spectrum of highly aggressive neoplasms with a common histology composed of small, round blue cells and presumably of common neuroectodermal origin, with morphologic, immunohistochemical and molecular peculiarities that allow them to be differentiated.

The histologic and radiologic appearance of these tumors shows remarkable overlap, reflecting their high cellularity. Therefore, it is crucial to consider this category when analyzing CNS and spinal tumors with high attenuation on CT, low signal intensity on T2-weighted images and restriction on DWI sequences (6).

Quantitative assessment by DWI has largely focused on estimating cellularity by analyzing the diffusivity of water in the extracellular compartment. Therefore, the apparent diffusion coefficient (ADC) can be considered a tumor biomarker: as tumor grade increases, a decrease in average ADC values is observed (17). High-grade tumors, such as ET, are histopathologically characterized by high cellularity, reduced extracellular space, and cells with a high nucleus-to-cytoplasm ratio, which decreases diffusion. For ET such as medulloblastoma, cut-off values $<0.9 \times 10^{-3}$ mm²/s have been suggested with high specificity (18).

Diffuse leptomeningeal enhancement has a broad differential diagnosis. Meningitis is the most common cause, with diverse etiologies. Among all causes, bacterial and viral meningitis are the most frequent and are characterized by a smooth and linear enhancement in the cisternal sulci, instead of being nodular (19). In endemic regions, tuberculous meningitis is a frequent cause and confluent leptomeningeal enhancement of the basal cisterns without restriction is seen in DWI, along with hydrocephalus and, eventually, vasculitis. The vesicular stage of neurocysticercosis may present with multiple cysts with characteristic internal "dots" of the scolex deep within the cerebral sulci, with an intense inflammatory reaction in the adjacent parenchyma.

Diffuse leptomeningeal glioneuronal leptomeningeal tumor (DLGNT), is a mixed neuronal and glial neoplasm incorporated into the 2016 WHO classification of brain tumors. Diffuse abnormal nodular leptomeningeal nodular growth without evidence of a primary intraparenchymal focus is the most common imaging feature, particularly around the basal cisterns, and extending over the surface of the brain and spinal cord (20); although, unlike the cases described, it does not show restriction in DWI. Another finding, which is believed to be quite specific to this entity, are the numerous small subpial cysts (possibly corresponding to dilatation of the Virchow-Robin spaces) (21,22), expansion of the basal cisterns and of the cavum of Meckel (20). These findings may be present with or without an isolated spinal cord mass.

Neoplastic meningeal seeding often presents with thickened, nodular enhancement, which shows considerable variability in imaging findings. CNS TEs, ependymoma, germinoma, pineoblastoma, and high-grade glioma are common causes of carcinomatous meningitis, although a primary intraparenchymal lesion is recognized in most cases (19).

Secondary involvement of the meninges by oncohematologic diseases may show a pattern similar to that described, with diffuse leptomeningeal nodular enhancement and diffusion restriction (23); although, in general, in the context of a systemic disease.

No descriptions of the diffusion-weighted sequence behavior of primary hypercellular leptomeningeal tumors have been found in the literature. In the two described cases of tumors composed of "round, small, blue cells" corresponding to CNS embryonal tumors, restriction in the diffusion sequence was observed. This finding could be useful in the diagnosis of these entities.

Conclusion

Primary leptomeningeal tumors are a group of rare neoplasms that represent a diagnostic challenge due to the nonspecific clinical symptoms, and the variety of radiological presentations that encompass a wide spectrum of differential diagnoses. Diffusion sequencing allows the identification of a subgroup of high-grade tumors composed of "round, small, blue cells" that carry a more severe prognosis.

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