Clinical Case Reports

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Spinal cord diffuse midline glioma with H3K27M mutation: case report in a pediatric patient

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Introduction/Background: Pediatric diffuse midline gliomas are predominantly localized within the brainstem, pons, or are bi-thalamic, while in adolescents and adults, they predominantly arise unilaterally in the thalamus or spinal cord. Epidemiological data remain scarce for this recently described entity. They represent 10-15% of all pediatric brain tumors and 75% of all pediatric brainstem tumors.

Case presentation: Herein we report a case of Diffuse Midline Glioma in a 10-year-old male pediatric patient, with an unusual location in the spinal cord, presenting with atypical clinical features. Histopathological and immunohistochemical analysis confirmed the diagnosis and the presence of K27M (lysine to methionine at codon 27) mutations in the histone 3 gene.

Conclusions: Early and differential diagnosis of atypical spinal cord tumors is crucial to avoid dismal consequences for the patient and provide them with a better quality of life. Highlighting rare cases with fatal outcomes is essential for emphasizing the importance of understanding this pathological entity within the medical community.

Keywords: Pediatric, diffuse glioma, H3K27M mutation

INTRODUCTION

Pediatric diffuse midline gliomas are predominantly localized within the brainstem, pons, or are bi-thalamic, while in adolescents and adults, they predominantly arise unilaterally within the thalamus or spinal cord [1]. Occurrence in other midline locations, such as the pineal region, hypothalamus, and cerebellum, is exceptional [2].

Most patients with diffuse midline gliomas present the classic clinical triad: cranial nerve palsy, signs of long tract involvement such as pyramidal tract impairment, and ataxia [3]. Common initial symptoms when thalamic involvement occurs include intracranial hypertension and motor or sensory deficits [4].

Epidemiological data remain scarce for this recently described entity. The incidence is estimated at 0.54 cases per 1 million person-years overall and 2.32 cases per 1 million person-years in individuals aged ≤ 20 years, without predilection for gender. They represent 10-15% of all pediatric brain tumors and 75% of all pediatric tumors of the brainstem [5].

Due to few cases reported in medical literature, the poor outcome and the necessity to shed light on the diagnosis, the objective of this study is to describe a case of diffuse midline glioma with atypical spinal cord localization in a pediatric patient, at a philanthropic university hospital in Curitiba, State of Paraná.

CASE REPORT

A 10-year-old male patient was referred to Mackenzie Evangelical University Hospital due to a condition of pain in the cervico-thoracic spine transition area followed by lower limb paresthesia, which began seven days ago, with a diagnostic suspicion of Guillain-Barré syndrome. The mother reported two similar episodes of cervical pain, the first occurring 2 months and the second approximately two weeks ago, without apparent sensory symptoms, both resolving spontaneously.

Laboratory analysis conducted at the originating institution revealed pertinent findings, including a positive COVID-PCR result, which was performed under the suspicion

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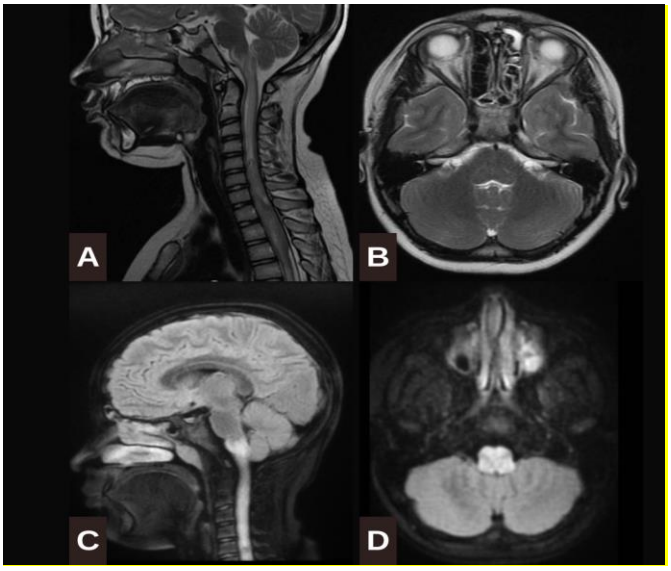

Figure 1- MRI findings of a pediatric patient with suspected neoplastic lesion in the spinal cord. (a) Axial and (b) sagittal sections demonstrate diffuse intramedullary signal alterations extending from the medulla oblongata to T4, with a tumefactive appearance and disruption of the hematospinal barrier at the C5 to T4 segment. (c) Axial and (d) sagittal sections depict normal signal intensity on T2-weighted sequences.

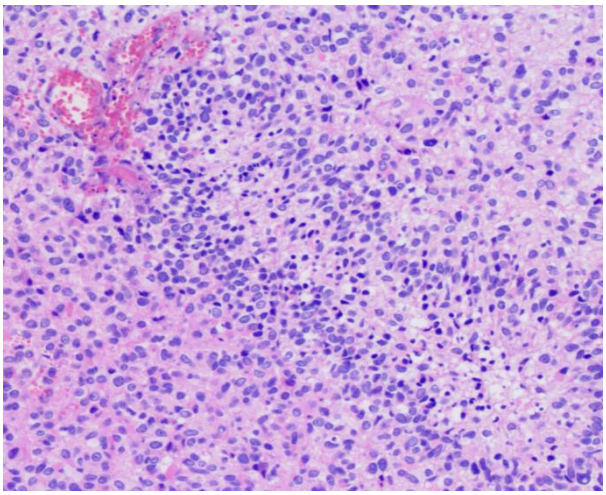

Figure 2- Presence of astrocytic spectrum composed of relatively uniform neoplastic cells, with oligodendrocyte-like morphologyn. (Optical Microscopy, Hematoxylin-eosin, 100x). Source: The authors, 2023

of Guillain-Barré syndrome associated with COVID infection. Additionally, the patient exhibited elevated levels of serum lactate dehydrogenase (689 U/L - reference range: 60 – 170 U/L), an increased erythrocyte sedimentation rate (VHS) of 20mm/h (reference range up to 10 mm/hour), and elevated C-reactive protein levels at 2.1 mg/dL (reference range: 0.3 to 1 mg/dL). Lactate levels were also slightly elevated at 16 mg/dL (reference range: 5.7 to 22.0 mg/dL).

Furthermore, cerebrospinal fluid (CSF) analysis revealed a clear yellowish appearance with slight turbidity, along with heightened protein levels. The CSF exhibited a mild leukocytosis, primarily consisting of lymphomononuclear cells, and the presence of erythrocytes was noted (2300 cells/mm3). No microorganisms were detected upon culture of this sample and no research study was initially conducted to detect neoplastic cells in the CSF.

During the physical examination, the patient had a temperature of 36 degrees Celsius and was alert, demonstrating appropriate reactivity. Assessment of the cranial nerves revealed normal findings across all evaluated aspects. However, decreased sensation was noted in the lateral aspect of the left lower limb. Muscle strength was assessed as grade 4+ in the lower limbs and grade 3+ in the upper limbs. Notably, hyperreflexia was observed in the lower limbs, accompanied by sustained clonus. The abdominal cutaneous reflex was absent, while the plantar cutaneous reflex elicited a positive Babinski sign bilaterally.

An urgent magnetic resonance imaging (MRI) was performed, revealing diffuse intramedullary signal alterations of a tumefactive appearance extending from the medulla oblongata to T4, with disruption of the hematospinal barrier at the C5 to T4 segment, suggesting a neoplastic lesion (possible astrocytoma or ependymoma) (Figure 1). This finding justified surgical intervention involving intraoperative frozen section examination.

For the surgery, the patient underwent general anesthesia and was positioned in ventral decubitus on articulating cushions with the head positioned on a Mayfield support. The cervical region was aseptically prepared with chlorhexidine, sterile drapes and adhesive were applied, cutaneous infiltration with lidocaine with vasoconstrictor was performed, and an incision was made in the midline extending from the spinous process of C4 to C7. Layer-by-layer opening and hemostasis were achieved, followed by the placement of retractors to expose the paravertebral musculature. The laminae of C4 to C7 were exposed, and laminectomy of the C6 and C7 vertebrae was performed. Midline dural opening and repair stitches with 4.0 prolene were placed to expose the spinal cord. Owing to the exigent nature of the surgical procedure, intraoperative neurophysiological monitoring (IONM) was not available.

A purplish lesion intermingled with blood vessels of paramedian origin was identified, and a biopsy of the lesion was performed and sent to the pathology laboratory for

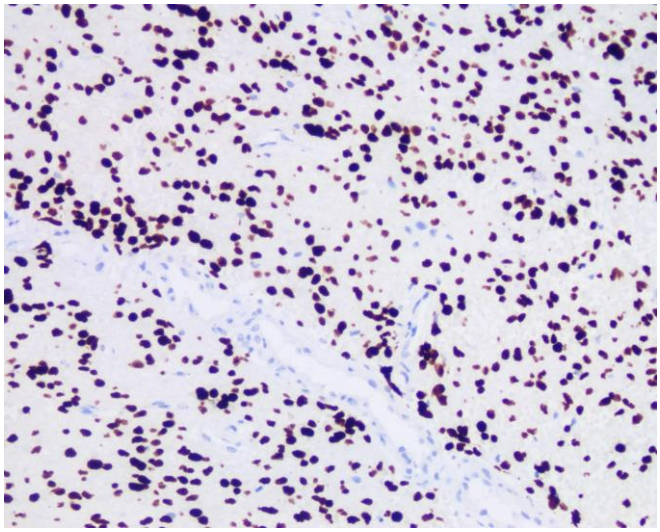

Figure 3- Note the nuclear positivity for Histona H3K27M (Optical Microscopy, Immunohistochemistry, 200x). Source: The authors, 2023.

intraoperative examination. The intraoperative examination revealed a suspicion of a low-grade glioma, prompting continuation of the surgery with aims of attaining a full exeresis of the neoplasm. With an incision in the midline up to the spinous process of T4 the laminae from C4 to T7 was exposed. Due to signs of spinal cord edema, decompression of the canal was performed with laminectomy from C5 to T4, assisted by surgical microscope for microsurgery of the neoplastic lesion.

During the immediate postoperative period, extensive anticoagulation was required to treat a pulmonary embolism episode, showing good recovery. The surgical specimen was sent to pathology for further examination.

Microscopically, tumor cells exhibited astrocytic morphology, being relatively small and monomorphic, occasionally displaying large and pleomorphic cells. The growth pattern was infiltrative, with neoplastic cells diffusely growing among native neurons. At times, a pattern resembling oligodendroglial cells with a clear perinuclear halo could be observed (FIGURE 2). There were foci with an increased number of mitoses and evidence of microvascular proliferation, while no tumor necrosis was identified. Additional immunohistochemical examination showed positivity for GFAP and Histone H3K27M (FIGURE 3) in neoplastic cells. ATRX expression was preserved, TP53 exhibited a wild-type pattern, and IDH1 R132H was negative. The proliferative index was high, with 70% positivity of cells with Ki67. The immunohistochemical profile, in addition with morphological findings, was consistent with H3K27M-mutated Diffuse Midline Glioma, WHO grade 4, in spinal cord location.

The patient presented with paralysis of both lower limbs post-operation. The thoracic and cervical spine magnetic resonance imaging performed five days after the surgical procedure showed a heterogeneous solid-cystic lesion with areas of barrier disruption extending from the levels between C3-C4 to D4, with a mild mass effect occupying a significant portion of the transverse axis of the vertebral canal, reducing the amplitude of adjacent cerebrospinal fluid spaces (FIGURE 4).

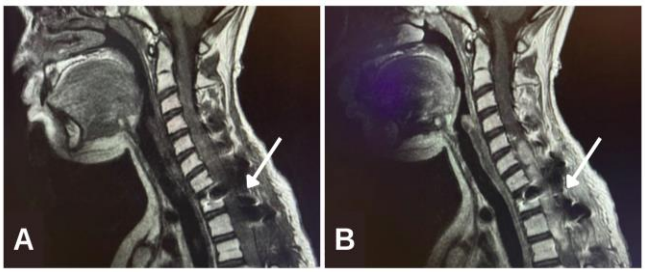

Figure 4- Post-surgical magnetic resonance imaging of the cervical and dorsal spine demonstrated massive solid expansile lesion with contrast enhancement involving the spinal cord in the segment between C5-C6 and D3, compatible with residual lesion resulting from the underlying disease (diffuse glioma). The arrow in the image points to the lesion. A- No contrast; B - With contrast. Source: The authors, 2023.

DISCUSSION

There is no known specific genetic susceptibility to these neoplasms; however, exceptionally, they may occur in the context of a cancer predisposition syndrome, such as Li-Fraumeni syndrome or mismatch repair deficiency. Regarding pathogenesis, they correspond to high-grade infiltrative gliomas, predominantly showing astrocytic differentiation, harboring K27M (lysine to methionine at codon 27) mutations in the histone 3 gene 3 [6].

Diffuse midline glioma H3 K27M-mutant typically occurs in the pons among pediatric patients, while occurrences in the spinal cord are highly uncommon, with only a few cases have been documented in the current literature. The cervical region stands out as the area most frequently affected within the spinal cord. Its clinical presentations lack specificity and diversify based on the specific location within the spinal cord and the tumor's progression. Localized pain stands as the most prevalent symptom that might precede the onset of neurological impairments. When approaching patients with similar clinical presentations, it is essential to consider other diagnostic hypotheses, such as Guillain-Barre syndrome [7].

Macroscopically, there is diffuse infiltration of the parenchyma by neoplastic cells and associated edema causing enlargement and distortion of anatomical structures, as well as softening and discoloration of tissues with areas of hemorrhage or necrosis [8].

On magnetic resonance (MRI) imaging, these tumors classically have their epicenter in the pons and generally involve > 50% of its surface, often asymmetrically, with frequent involvement of the basilar artery [9]. In cases

located in the spinal cord, poses a challenge due to the absence of specific MRI characteristics, with the tumor's margins poorly defined, and there might be mild peritumoral edema present, which are characteristic radiological views in high-grade gliomas. In this manner, due to the location, clinical features, and radiological characteristics, we should contemplate other central nervous system tumors in the differential diagnosis such as astrocytoma and ependymoma. [7].

In terms of histopathology, these gliomas infiltrate diffusely into the central nervous system (CNS) parenchyma, usually without specific perivascular or perineuronal tropism. Most cells are small and monomorphic, but they can be polymorphic, exhibiting astrocytic, piloid, oligodendroglial, giant cell, undifferentiated, or epithelioid cytology, and are considered Grade 4 by WHO regardless of the presence of microvascular proliferation or necrosis [10]. Even though mitotic figures are frequent and microvascular proliferation and/or necrosis may be observed, these features are not necessary for diagnosis and are not independent predictors of survival [11] .

For definitive diagnosis, immunophenotypic studies are necessary. Typically, by immunohistochemistry, they express OLIG2, MAP2, and S100, while the immunoreactivity for GFAP varies. The combination of antibodies H3 p.K28M (K27M) and H3 p.K28me3 (K27me3) is highly effective as a diagnostic aid [12].

Regardless of location, the prognosis for pediatric diffuse midline gliomas is poor, with a 2-year survival rate of < 10% [13]. Surgical options are limited due to the tumor's location. Age (< 3 or > 10 years), longer symptom latency (> 24 weeks), and systemic therapy at the time of diagnosis are predictors of longer survival, and there are no specific guidelines available for this tumor [14]. Due to infiltration into the spinal cord parenchyma, complete surgical resection may be unfeasible. Adjuvant chemoradiotherapy may be useful in prolonging progression-free survival. Furthermore, specific markers can be useful in an individualized approach, such as anti-EGFR antibody, which has lower toxicity. Other medications, such as monoclonal antibodies, tyrosine kinase inhibitors, and angiogenesis inhibitors have also been described as possible therapies for diffuse midline gliomas [15].

CONCLUSION

Considering that delayed diagnosis of Diffuse Midline Glioma can have dismal consequences on the patient's prognosis and quality of life, early and differential diagnosis in cases with atypical spinal cord localization in pediatric patients should be considered. It is important to bring rare cases with fatal outcomes to the attention of the medical community to emphasize the significance of understanding this pathological entity in this context.

ACKNOWLEDGMENTS

DISCLOSURES

Ethical approval

The Institutional Review Board (IRB) of “Faculdade Evangélica Mackenzie” in Curitiba, Paraná approved the study, report number 6.439.563, CAAE (submission for ethical review) number 73196423.5.0000.0103, in compliance with Resolution 466/20129 of the National Health Council.

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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CONTRIBUTIONS

-**Vitor Bonk Rizzo**: Conceptualization, Formal Analysis, Validation, Writing – original draft, Writing – review & editing
-**Michelle Arrata Ramos**: Data curation, Formal Analysis, Writing – review & editing
-**André Leonardo Bacellar Mota**: Formal Analysis, Writing – original draft, Writing – review & editing
-Samya Hamad Mehanna: Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing
-Julia Costa Linhares: Formal Analysis, Writing – review & editing
-Marcela Santos Cavalcanti: Validation, VisualizationFormal Analysis, Writing – review & editing

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