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Single Case – General Neurology

Flank Pain as a First Symptom of a Diffuse Midline Glioma

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Midline glioma · Spinal cord tumors · Acute paraparesis · K27M mutation

Abstract
Diffuse midline gliomas are a new entity in the WHO Classification of Tumors of the Central Nervous System, corresponding to grade 4 gliomas. The diagnostic pathognomonic feature is the presence of a H3K27M mutation. Although mainly seen in children, cases in adults have also been reported. The symptoms are highly variable and usually dependent on the location and extent of spinal cord compression.

Introduction

Spinal cord tumors are rare entities. Although they usually become symptomatic through focal neurological deficits resulting from spinal cord compression, unusual symptoms may be the first heralds of disease. This is the case of a patient with flank pain as the first symptom of a spinal cord tumor. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528311).

Case Report

A 31-year-old woman presented to the Emergency Department with a 3-month history of progressive left-sided flank pain. She was discharged a few days ago from the urologic department of another hospital, where nephrolithiasis and other kidney-related problems

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were ruled out as source of the flank pain. There, she underwent extensive examinations, including a head CT due to frequent episodes of headaches. All examinations, including the head CT, were normal; the patient was discharged with the recommendation of a psychiatric consultation.

Due to worsening pain, 2 days after discharge, she presented in our Emergency Department, where an abdominopelvic CT was obtained. Besides a cystic formation in the left ovary, no abnormalities could be detected.

In the ER, additionally to the flank pain, she mentioned frequent headaches as well as an episode of syncope a few weeks ago. She was admitted for further diagnosis and management of the syncopal episode. Due to the recurrent headache episodes, the cranial CT imaging was repeated, again revealing no abnormalities.

During in inpatient stay, the patient continued to complain about flank pain and headaches. A neurological consultation was requested, showing slight signs of meningeal irritation as well as a broad-based gait. The reflexes were brisk with down-going plantar response; no other neurological deficits were detected.

Due to the clinical signs of meningeal irritation, a lumbar puncture was performed. The CSF was xanthochromatic with an elevated cell count of 268 cells/μL. The cells were mainly activated lymphocytes with few polymorphonuclear cells; no tumor cells were detected. Furthermore, the CSF showed significant elevation of protein (4,420 mg/dL) and lactate (24.4 mg/dL); the opening pressure was also elevated. An MRI was obtained on the same day, which showed a tubular, contrast-enhancing lesion in the left cingulate cortex (shown in Fig. 1).

In conjunction with the syncope and the xanthrochromic CSF, a subarachnoid hemorrhage from a cavernoma or an AVM was suspected. A digital subtraction angiography was performed the next day, revealing no source of bleeding.

Due to the significant elevation of protein and opening pressure in the CSF, as well as the broad-based gait of the patient, an MRI of the spine was obtained. This MRI revealed a spinal cord tumor ranging from Th7–Th12 with an additional nodular tumor mass in the conus medullaris, as well as signs of meningeal carcinomatosis (shown in Fig. 2).

After a systemic tumor manifestation was ruled out by additional CT imaging, a biopsy was taken from the nodular parts of the tumor for further classification. H&E staining showed significant cell proliferation with enlarged cell nuclei, staining with KI-67, which is a marker of proliferation, revealed an increased fraction of proliferation (shown in Fig. 3). The immunohistochemical examination confirmed a H3-clustered histone K27M mutation.

In conjunction with the MRI findings, this result was diagnostic for a diffuse midline glioma. The patient was started on steroids upon which the flank improved significantly within few days. Subsequently, a combined therapy with radiation and chemotherapy was initiated.

Currently, about 20 months have passed since the diagnosis; the patient is ambulating independently and continuing to receive radiation therapy.

Discussion

According to the revised 2016 WHO Classification of Tumors of the Central Nervous System, diffuse midline gliomas are a newly added pathological type, in which molecular diagnosis plays a pivotal role in diagnosis. They are considered as a distinct entity, corresponding to grade 4gliomas, notably even in the absence of pathologic features like excessive mitotic activity or central necrosis if a H3K27M mutation is present [1].

On a molecular basis, these tumors show an oncogenic histone K27M mutation in the H3.3 histone A or H3-clustered histone genes that encode for the histone H3 variants. Histones are basic proteins found in eukaryotic cell nuclei that help to condense the DNA into chromatin. The

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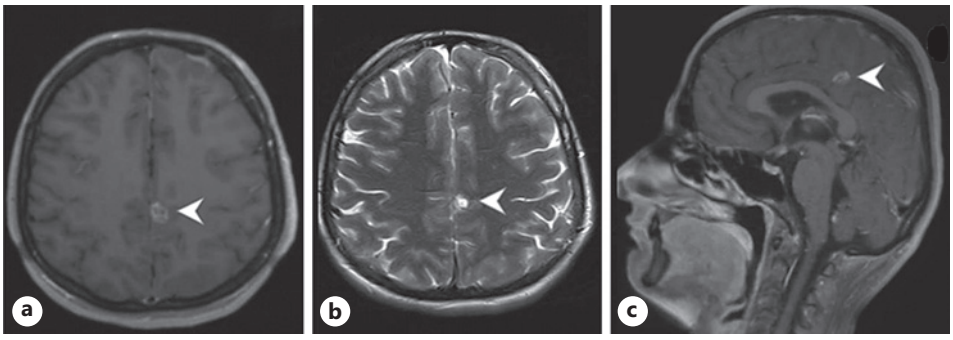

Fig. 1. a Axial contrast-enhanced T1 image, showing a contrast-enhancing lesion in the left cingulate gyrus. **b** T2-weighted axial image. **c** Sagittal contrast-enhanced T1 image.

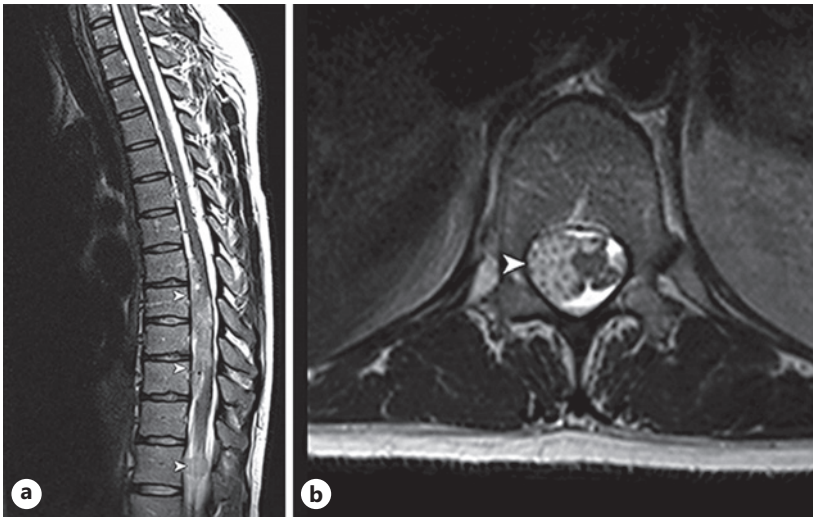

Fig. 2. a Sagittal T2 image of a tumor ranging from Th7 to Th12, significantly compressing the spinal cord ventrally. **b** Axial T2 image of nodular tumor manifestation at conus medullaris and filum terminale.

H3K27M mutation is a mutation that converts lysine to methionine at the 27th position from the N-terminus of the histone tail of core histone H3 and gives rise to decreased methylation of the histone tails, causing blockage of glial differentiation and consequent gliomagenesis [2–4].

Although this tumor is mainly reported in children, adult cases have also been reported in literature. For the definitive diagnosis of the disease, the detection of a H3K27M mutation is mandatory.

These gliomas usually affect midline structures like thalamus, brainstem, or spinal cord. In contrast to this case, many patients show a significantly elevated CSF opening pressure. Retrospectively, the frequent headaches of the patient were probably related to transient increases in ICP. Severely elevated protein CSF levels as well as slightly elevated white cell count are reported in literature, making them difficult to differentiate from infectious meningitis. Treatment usually includes a combination of surgery, radiation-, and chemotherapy.

Spinal cord tumors are notoriously difficult to diagnose since symptoms are usually vague and dependent on their anatomic location. Spinal cord tumors can be intramedullary, intradural, extramedullary, or extradural in location. Symptoms are caused by the disruption of neuronal pathways and can be local or distant. The most frequent local symptom is a continuous pain leading to nocturnal awakening [5].

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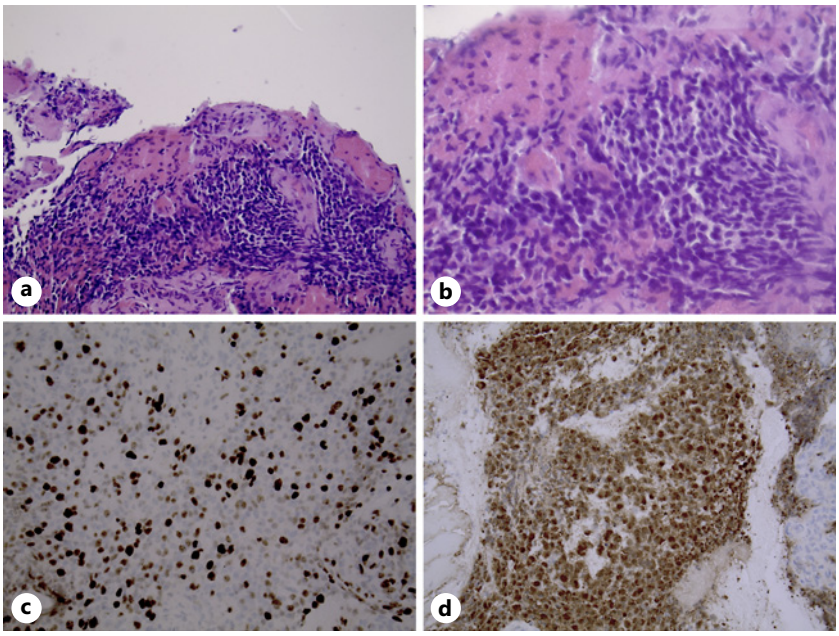

Fig. 3. Histological and immunohistochemical examination of a biopsy specimen of the nodular lesion on the filum terminale. **a** H&E staining showing infiltrating and nodular proliferation of pleomorphic cells with hyperchromatic nuclei and scant cytoplasm. **b** H&E staining, higher magnification. **c** KI-67 staining, a nuclear protein that is associated with cellular proliferation. **d** Specimen with S-100 staining.

Neurological dysfunction distal to the lesion is usually a result of the interruption of ascending and descending pathways. Frequent neurological abnormalities include sensory deficits and muscular weakness, usually leading to progressive difficulties in ambulation.

Despite intensive treatment, these tumors are usually associated with a poor prognosis. Currently, the median survival is around 19.7 months despite maximal multimodal therapy [6].

Novel immunotherapies, that could potentially alter this outcome, are intensively investigated. The multicenter INTERCEPT-H3 trial analyzes the effect of the subcutaneous injection of a long peptide vaccine containing a K27M-mutated histone-3 sequence with the aim of eliciting an antitumor immune response. The estimated study completion date is March 2025 [7].

Statement of Ethics

This study was conducted in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Burc Bassa: case description and initial draft of the manuscript; Achim Battmann: preparing and commenting immunohistological images; Eva Maria Craemer: case description and literature research; and Uta Meyding-Lamadé: supervision and final editing.

Data Availability Statement

All data generated or analyzed in this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author, Dr. Burc Bassa.

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