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Case Report

An extremely rare case of primary alveolar rhabdomyosarcoma in the central nervous system

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ABSTRACT

Background: Alveolar rhabdomyosarcoma (ARMS) shows a predilection for the peripheral extremities and is very rarely identified as a primary in the brain. Here, we report a case of ARMS with multiple lesions exclusively within the central nervous system (CNS).

Case Description: A 20-year-old man presented to our hospital with a gradually increasing headache and disturbance of consciousness. Neuroimaging showed hydrocephalus and multiple tumor lesions, including in the brainstem and cerebellum, with uniform gadolinium enhancement on T1-weighted magnetic resonance imaging, as well as spinal cord seeding. Cerebrospinal fluid (CSF) analysis showed a slightly elevated cell count (6/μL; normal, <5/μL) and highly elevated protein (153 mg/dL). In addition, atypical cells were cytologically identified in the CSF. No other laboratory findings were abnormal. Emergency ventricular drainage was performed to control cerebral pressure, followed by a biopsy to confirm the diagnosis. Histological examination revealed a fascicular arrangement of oval cells with eosinophilic cytoplasm and tumor cells with pleomorphic nuclei and prominent nucleoli. Immunohistochemical studies showed negative results for glial fibrillary acidic protein and positive results for desmin and myogenin. In addition, molecular analysis revealed that this tumor had the H3F3A p.Lys28Met mutation and no paired box (PAX)3-forkhead box O1 (FOXO1) or PAX7-FOXO1 fusion genes. ARMS was, therefore, diagnosed. Chemotherapy and radiotherapy were subsequently initiated, but tumor growth could not be controlled, and the patient died 6 months after surgery.

Conclusion: This report describes an extremely rare case of ARMS arising exclusively within the CNS.

Keywords: Alveolar rhabdomyosarcoma, Central nervous system, H3F3A p.Lys28Met mutation, Myogenin, Spinal dissemination

INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive neoplasm characterized by rapid growth and metastatic invasion.[1,4,5] This rare disease represents around 1.7% of nonepithelial malignancies.[5,16] While the majority of cases of this tumor occur as pediatric cases, a few instances of primary brain RMS in adults have been reported. Alveolar RMS (ARMS) is the second most common subtype after fetal RMS and is histologically characterized by undifferentiated small round cells surrounded by vascular fibrous connective tissue in a foci-like structure or showing full proliferation. As soft-tissue tumors mainly represent proliferation of small round cells, differentiation is often difficult due to the morphological similarities. We report herein our experience with a case of primary brain ARMS

presenting with multiple central nervous system (CNS) lesions, in which diagnosis and treatment were difficult. We also present the pathological and molecular features of this entity.

CASE DESCRIPTION

A 20-year-old man with no relevant medical history presented to our department with a 1-week history of progressive headache and nausea. Intracranial computed tomography revealed marked ventricular enlargement [Figure 1a], leading to urgent ventricular drainage. Magnetic resonance imaging (MRI) demonstrated multiple lesions at various sites in the CNS, including the spinal cord, appearing hypointense on T1-weighted imaging (WI) and hyperintense on T2-WI and fluid-attenuated inversion recovery imaging, with strong enhancement on T1-WI using gadolinium contrast [Figures 1b and c, 2a]. Markedly high ^{18}F-fluorodeoxyglucose (FDG) uptake was seen on positron emission tomography within the enhanced region (tumor-to-contralateral normal brain tissue ratio: 2.91), with no obvious ^{18}F-FDG accumulations in tissues outside the CNS [Figure 2b and c]. Cerebrospinal fluid (CSF) analysis showed a slightly elevated cell count (6/μL) and highly elevated protein (153 mg/dL). In addition, atypical cells were cytologically identified in CSF. On initial consideration, the history and results of laboratory examinations and radiological studies seemed most consistent with malignant lymphoma or multifocal glioma. To confirm a histological diagnosis and plan effective treatment for the primary disease, we, therefore, performed a surgical biopsy of the right cerebellar lesion under image-guided navigation. Histological examination revealed a fascicular arrangement of oval cells with eosinophilic cytoplasm and tumor cells with pleomorphic nuclei and prominent nucleoli. Immunohistochemical studies showed negative results for glial fibrillary acidic protein (GFAP) and positive results for both desmin and myogenin. ARMS was, therefore, diagnosed. Seven days after surgery, the patient started chemotherapy with vincristine, actinomycin D, and cyclophosphamide (VAC regimen). He received a total of three cycles, but serial MRI during treatment showed no shrinkage of any tumors, so radiotherapy was administered (whole brain and spine: 36.8 Gy in 20 fractions). The ventricular-peritoneal shunt was also added for the hydrocephalus. However, due to a lack of treatment efficacy, vincristine, doxorubicin and cyclophosphamide (VDC regimen), and ifosfamide and etoposide (IE regimen) were added. No therapeutic effects were observed, and lesions continued to grow, and the patient died 6 months after surgery. The ethics committee of our institution approved the clinical study of this case, and informed consent was obtained from the patient.

Pathological findings

Postoperative histopathology obtained using hematoxylin and eosin (HE) staining demonstrated a highly cellular area

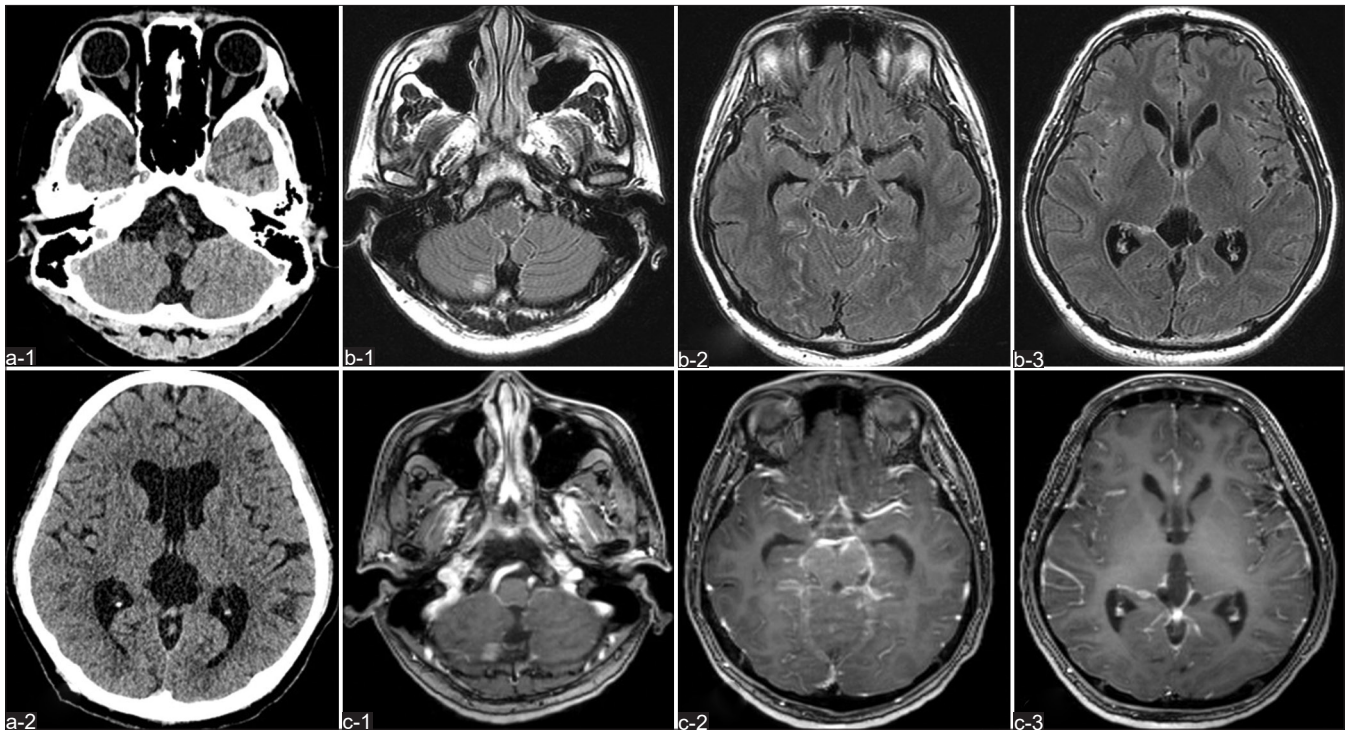

Figure 1: (a-1, a-2) Computed tomography (CT) without contrast enhancement shows no abnormal masses, but marked ventricular enlargement. Preoperative (b-1, b-2, b-3) axial fluid-attenuated inversion recovery and (c-1, c-2, c-3) gadolinium (Gd)-enhanced T1-weighted imaging (WI) on MRI reveal multiple intracranial areas of abnormal intensity.

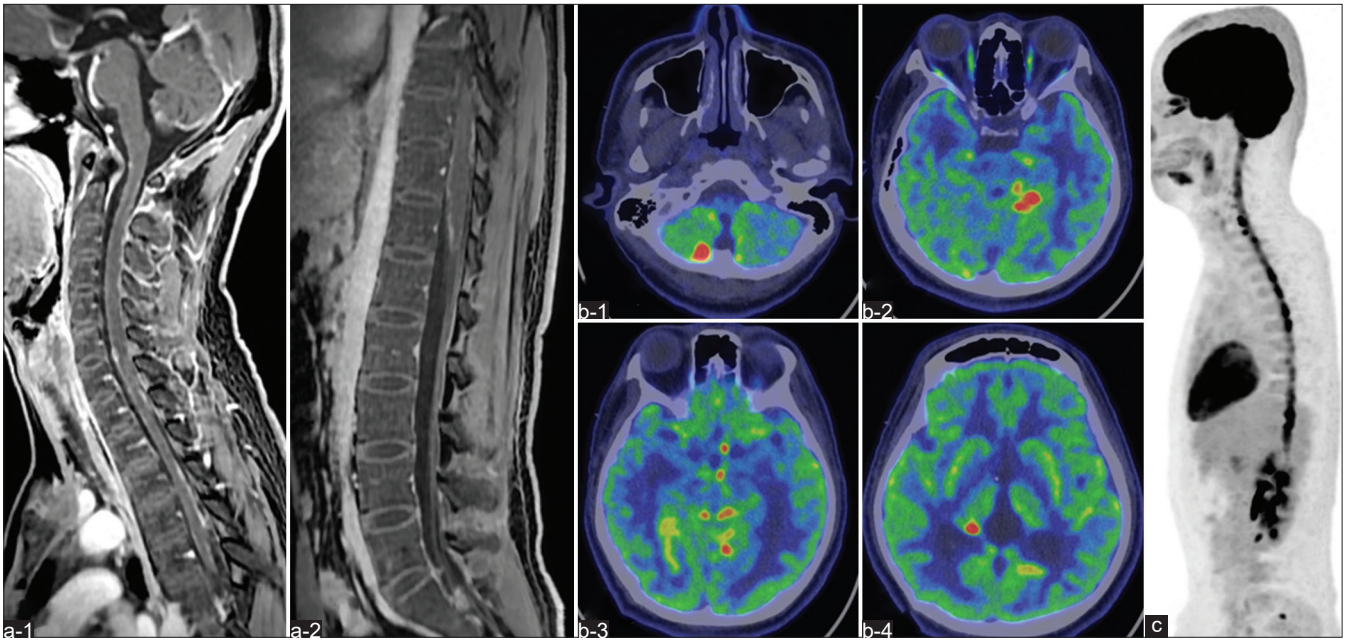

Figure 2: (a-1, a-2) Magnetic resonance imaging (MRI) demonstrates a longitudinally extending intradural lesion within the spinal cord with Gd enhancement on T1-WI. On 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), abnormally high uptakes are evident in the (b-1, b-2, b-3, b-4) cranial and (c) spinal region, representing the same sites identified on MRI.

comprising oval and round cells with eosinophilic cytoplasm [Figure 3a-d]. Mitotic figures were elevated, and scattered necrotic foci were evident. Entrapped islands of neuropil were noted focally. Rare neoplastic cells with pleomorphic nuclei, evident nucleoli, and eosinophilic cytoplasm were present. Immunohistochemistry revealed that tumor cells were negative for the glial marker GFAP. Negative results were obtained for smooth muscle antigen, but myogenin and desmin were positive. Moreover, an immunohistochemical study showed negativity for S-100 and integrase interactor 1, excluding the diagnoses of malignant peripheral sheath tumor and atypical teratoid/rhabdoid tumor [Figure 4a-f]. HE staining and immunohistochemical studies revealed morphological characteristics consistent with ARMS. Molecular analyses revealed that this tumor had the H3F3A p.Lys28Met mutation with no formation of the paired box (PAX)3-forkhead box O1 (FOXO1) or PAX7-FOXO1 fusion genes.

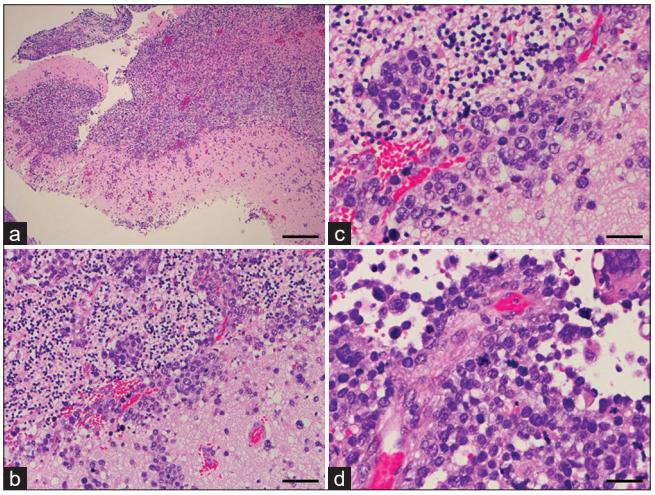

Figure 3: Histopathology of the biopsy specimen. Hematoxylin and eosin staining show a fascicular arrangement of oval cells with eosinophilic cytoplasm and tumor cells with pleomorphic nuclei and prominent nucleoli. Mitotic figures are elevated, and scattered necrotic foci are apparent. (a) Magnification, ×40; scale bar, 500 μm. (b) Magnification, ×200; scale bar, 100 μm. (c and d) Magnification, ×400; scale bar, 250 μm.

DISCUSSION

RMS is a common tumor of the head and neck in children and rarely in adults. Among adults, RMS is more common in males (male: female ratio 1.6:1) with a peak age at onset of 44–58 years.[5,6,9] As an aggressive and highly malignant tumor, the prognosis is poor. In fact, over the past 30 years, the incidence of RMS has increased by approximately 1.16% each year, but the 5-year survival rate has remained basically unchanged.[15,17] Survival correlates with the site of the primary, amenability of the lesion to resection, and age. Primary involvement of the head and neck is associated with a worse prognosis due to early invasion of major structures.[8,14] While the 5-year overall survival rate for localized pleomorphic RMS is 53.4%, an initial diagnosis of diffuse or multiple disease carries the worst prognosis, with a dismal 5-year overall survival rate of only 4.3%.[7] As a life-threatening disease, prompt

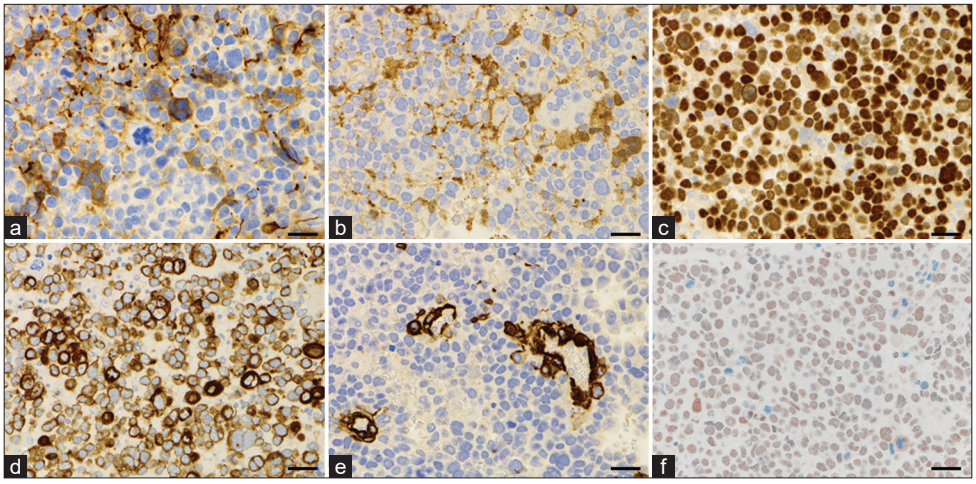

Figure 4: Photomicrographs revealing the tumor histopathology. (a)Immunohistochemically, tumor cells are negative for the glial marker glial fibrillary acidic protein (GFAP). Negative results are obtained for (b) smooth muscle antigen, but (c) myogenin, and (d) desmin are positive. Immunohistochemical studies also show negative results for (e) S-100 and (f) integrase interactor 1, excluding the diagnoses of malignant peripheral sheath tumor and atypical teratoid/rhabdoid tumor (AT/RT). Magnification, ×400; scale bar, 100 μm.

diagnosis and treatment are essential, but early diagnosis remains difficult.

Whereas previous classifications have divided tumors into embryonal and alveolar subtypes based on histomorphology, the 2020 Classification of Soft-Tissue Tumors by the World Health Organization now divides RMS into embryonal (including the former botryoid category), sclerosing and spindle cell (with myogenic differentiation one mutation or nuclear receptor coactivator two rearrangements), alveolar (with forkhead in RMS rearrangements), and pleomorphic subtypes.[2] ARMS is a malignant neoplasm consisting of a monomorphic population of primitive round cells with skeletal muscle differentiation.[2] Myogenin immunostaining has been described as a useful marker for the alveolar subtype of RMS and as a tool to distinguish this entity from the more common embryonal subtype.[12] The clinical and histological criteria currently in use to classify RMS are complex, but the predictive power remains limited. However, the role of molecular testing in subclassifying patients with ARMS by associating distinctive clinical patterns with common and variant gene fusions has been shown to be helpful. For example, ARMS is characterized by consistent chromosomal translocations and chimeric genes, with PAX3-FOXO1 and PAX7-FOXO1 expressed as novel fusion transcripts.[10]

The majority of case reports have described secondary brain RMS with primaries in the extremities, lungs, scalp, or genital tract. A few cases of primary intracranial ARMS have been reported. A review of the literature identified 48 cases of primary cerebral RMS, among which 33 involved children and the majority of tumor lesions were embedded in the cerebral surface and only rarely entirely intraparenchymal or intraventricular.[3,11] The present case showed primary brain ARMS with multiple disseminated lesions in the CNS. Further, molecular analysis revealed that this tumor had the H3F3A p.Lys28Met mutation but no formation of PAX3-FOXO1 or PAX7-FOXO1 fusion genes. This case thus appears to represent ARMS with an extremely rare molecular pattern.

The optimal treatment strategy following histological diagnosis and staging of primary brain ARMS remains contentious. The inherent difficulty in identifying the cell of origin in RMS makes the selection of appropriate chemotherapy difficult and the attendant benefits controversial.[13] In addition, given the rarity of intracranial RMS and the heterogeneity of treatments, little has been learned about the optimal therapeutic approach. The most common approach is to perform surgery first, followed by adjuvant radiotherapy and chemotherapy. Surgery remains the mainstay of treatment. Patients who undergo gross total resection achieve a 5-year overall survival rate of 55.7%.[7] However, in our case, biopsy with piece resection for diagnostic purposes was the only option due to the surrounding anatomy. Some form of treatment for residual tumor is required in such cases. The combination of vincristine, adriamycin, and cyclophosphamide, as the so-called VAC regimen, is recognized as the standard treatment for ARMS. Radiotherapy is also used in some cases.[17] However, data from randomized clinical trials to identify the optimal combination therapy remains lacking. Early, aggressive chemotherapy is associated with the best prognosis.[15] Complete removal was difficult in this case, and the only way to remove the multiple tumor lesions was by biopsy, but the early intervention was still possible, despite the extreme rarity of this case, as only 7 days elapsed from diagnosis to treatment initiation. However, despite

the relatively timely chemotherapy and radiotherapy, the treatment proved ineffective, and the patient died within about 6 months. Further, experience with therapy for this pathological entity and longer patient follow-up is required.

CONCLUSION

The present case describes one of the few adult cases of primary brain ARMS. Given the rarity of this pathology, a multidisciplinary approach is indispensable. At present, surgical resection of the tumor followed by adjuvant chemotherapy and radiotherapy remains the logical approach to tumor management to maximize long-term survival. While multidisciplinary treatment with chemotherapy and radiotherapy in addition to surgery was performed as early as possible in the present case, good clinical results were not obtained. Further studies and accumulation of cases are therefore needed to understand the behavior of these tumors better, identify an optimal therapeutic plan, and standardize diagnostic immunohistochemical and genetic analyses.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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