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IDH-mutant Astrocytoma Arising in the Brainstem with Symptom Improvement by Foramen Magnum Decompression: A Case Report

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Abstract

Diffusely infiltrative midline gliomas are known to have a poor prognosis. The standard treatment for typical diffuse midline glioma in the pons is local radiotherapy as surgical resection is inappropriate. This case reports a brainstem glioma in which stereotactic biopsy and foramen magnum decompression were concomitantly performed to confirm the diagnosis and improve symptoms. A 23-year-old woman was referred to our department with a chief complaint of headache for six months. Magnetic resonance imaging (MRI) showed diffuse T2 hyperintense swelling of the brainstem with the pons as the main locus. Enlargement of the lateral ventricles was observed because of cerebrospinal fluid obstruction out of the posterior fossa. This was atypical for a diffuse midline glioma in terms of the longstanding slow progression of symptoms and patient age. Stereotactic biopsy was performed for diagnosis, and foramen magnum decompression (FMD) was concomitantly performed to treat the obstructive hydrocephalus. The histological diagnosis was astrocytoma, IDH-mutant. Post-surgery, the patient's symptoms were relieved, and she was discharged on the fifth day after surgery. The hydrocephalus was resolved, and the patient returned to normal life without any symptoms. The tumor size follow-up with MRI demonstrated no marked change for 12 months. Even though diffuse midline glioma is considered to have a poor prognosis, clinicians should contemplate if it is atypical. In atypical cases like the one described herein, surgical treatment may contribute to pathological diagnosis and symptom improvement.

Keywords: brainstem glioma, IDH mutant, foramen magnum decompression

Introduction

Gliomas occurring on the midline, such as diffuse midline glioma, H3 K27-altered (DMG), are known to have a poor prognosis, with a median overall survival of 8 months to 19.7 months.[1-3] Surgical treatment like tumor resection is inappropriate, and focal radiotherapy is the only standard treatment at present because none of the current chemotherapies have demonstrated improved patient survival.[4-6]

There is a high risk in diagnosing brainstem gliomas using biopsy because the result does not affect the treatment plan and is not necessarily representative of the entire tumor.[7,8] However, some researchers in recent years have reported that stereotactic biopsy should be performed in cases with atypical findings, such as a focal appearance and/or abnormal contrast enhancement in radiological images.[9,10]

We have experienced a case of astrocytoma, isocitrate dehydrogenase (IDH)-mutant, World Health Organization (WHO) grade 2 arising in the brainstem in which the symptoms were improved by foramen magnum decompression (FMD) following stereotactic biopsy.

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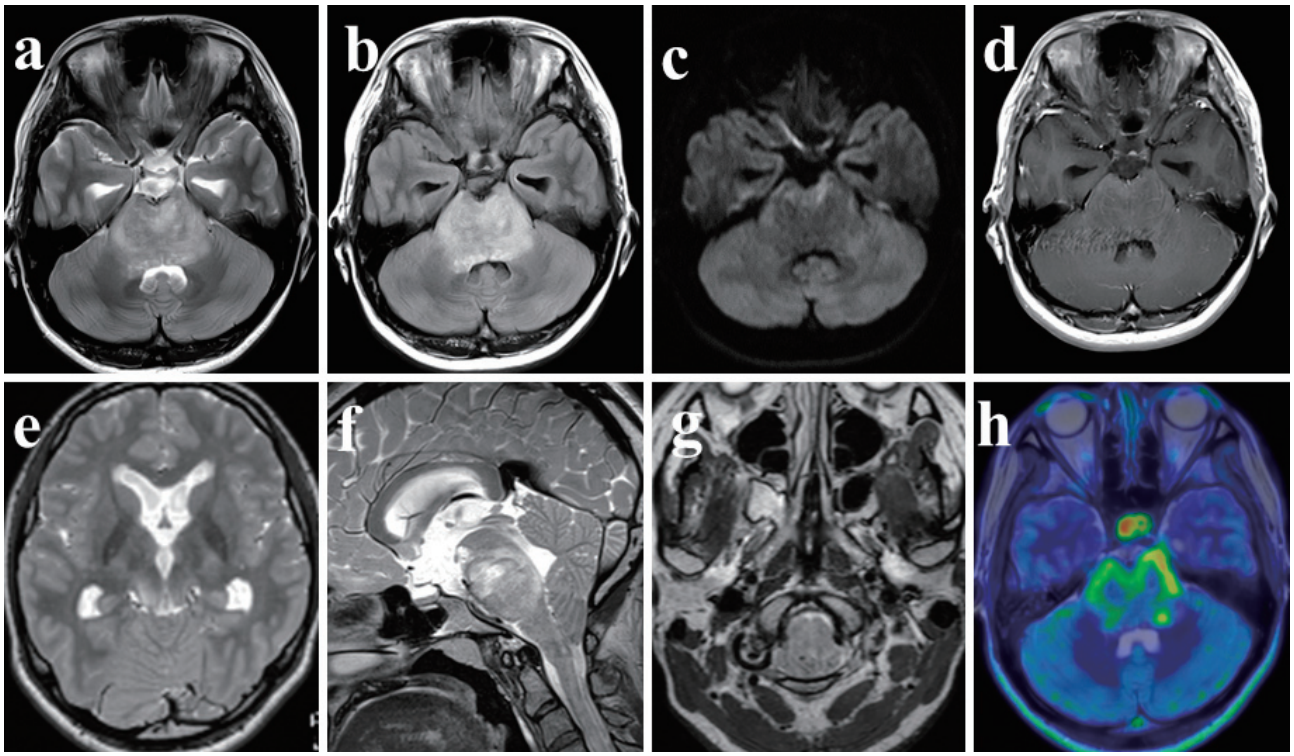

Fig. 1 Preoperative magnetic resonance imaging (MRI). a, b: Axial images of the T2-weighted and T2-FLAIR (fluid-attenuated inversion recovery) showing diffuse hyperintense swelling of the brainstem c: Diffusion-weighted image showing spotty high intensity in the ventral pons. d: T1-weighted gadolinium (Gd)-enhanced MRI showing no apparent contrast enhancement in the tumor. e-g: T2-weighted MRI showing enlarged lateral ventricles due to CSF obstruction with tonsillar herniation in the posterior fossa. h: ^{11}C-methionine was partially concentrated in the sites of the pons on position emission tomography (PET) scan.

Case Report

A 23-year-old woman was referred to our hospital with a chief complaint of headache for the past six months. Magnetic resonance imaging (MRI) suggested a brainstem-infiltrating tumor within the entire pontine expansion. The headache was aggravated by nodding, and she also presented with impaired visual function. Fundus examination revealed congested papillae. However, there was no evidence of palsy of the cranial nerves, including the abducens nerve and facial nerve. MRI showed an intramedullary tumor expanding infiltratively surrounding the pons and lateral ventricles enlarged due to cerebrospinal fluid (CSF) obstruction with tonsillar herniation in the posterior fossa (Fig. 1a-g). No contrast enhancement was observed in the T1-gadlinium image, although partial high uptake on a ^{11}C-methionine positron emission tomography (PET) scan was observed (Fig. 1h), which indicated the possibility of an aggressive feature. The ratio of uptake in lesion to normal was 3.43. The time since onset was approximately six months, which was relatively long, and the symptoms (the lack of cranial nerve palsy) were discrepant with DMG, considering the size of the lesion. Against this background, we opted for surgical intervention. Stereotactic biopsy for diagnosis was performed using a Leksell frame in the right lateral decubitus position. A biopsy site was planned to avoid neurological damage, especially to the cranial nerves. First, when targeting the strong hot spot of the ^{11}C-methionine PET, the biopsy needle protruded into the cistern, resulting in a puncture through the arachnoid into the brainstem. However, the tumorized brainstem was very firm and it was infeasible to perform a biopsy from this site. Therefore, the tissue of T2 high signal and normal signal of ^{11}C-methionine at the left dorsolateral safe point of the pons was biopsied. After the biopsy, FMD was performed to improve the symptoms of occlusive hydrocephalus following the narrowing of the posterior fossa with brainstem expansion. When the external ventricular drainage was inserted through the posterior horn of the lateral ventricle, the pressure was high (400 mm H_2O). To avoid upward herniation, the drainage was restricted to measuring CSF pressure. Chronologically, a CSF reservoir was placed under the galea, and a midline suboccipital craniotomy (3 cm × 3 cm) with a C1 laminectomy of 20 mm length was performed in the prone position (Fig. 2a-e). A dura-splitting decompression was carried out to minimize surgical invasiveness. The patient's headache and visual acuity promptly improved, and she was discharged without any complications on the fifth postoperative day. Hematoxylin and eosin staining showed moderately in-

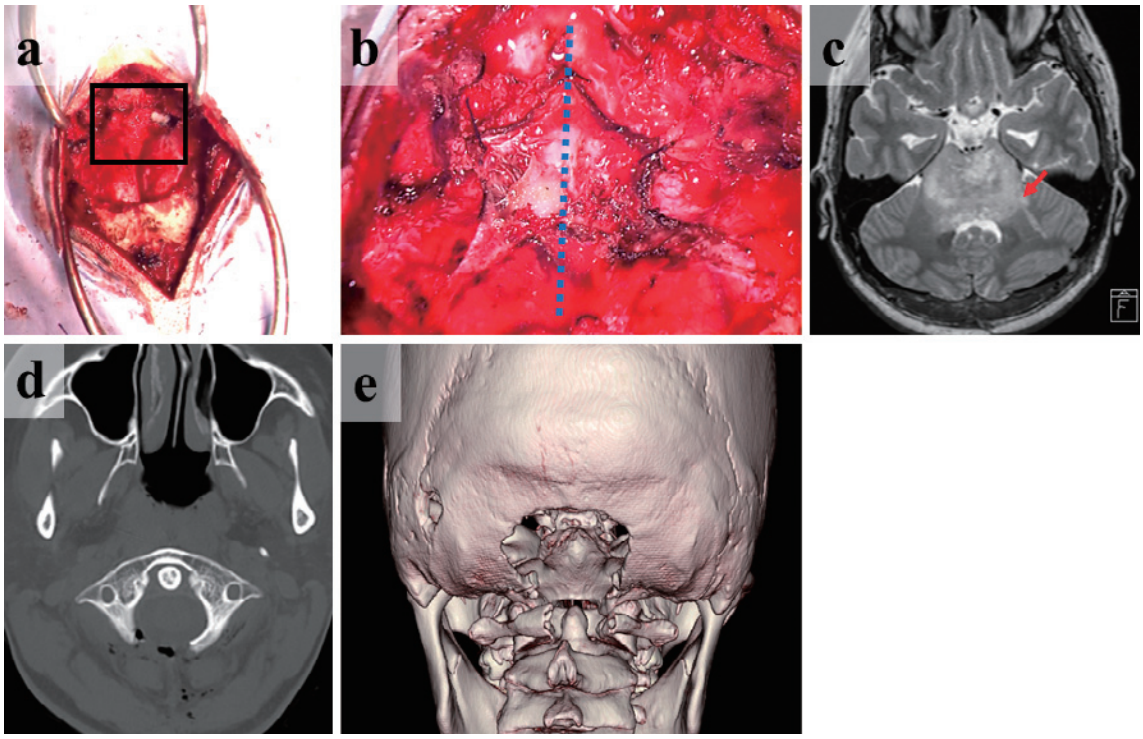

Fig. 2 Intraoperative findings and postoperative images. a: A midline suboccipital craniotomy was performed in the supine position and the C1 vertebral arch was resected. The square indicates the area Fig. 2b indicates. b: The epidural layer was decompressed through a midline incision as much as possible. The blue dotted line indicates the median line. c: Postoperative MRI image of T2-weighted. The arrow indicates the biopsied area. d, e: Postoperative CT and CT reconstruction showing the minimal extent of craniectomy and laminectomy.

creased cellularity and cells with irregularly shaped nuclei. However, there was no mitotic activity or anaplasia (Fig. 3a-b). Immunohistochemical analysis showed positive staining of IDH1R132H and ATRX. The Ki-67-positive rate was low, and the p53-positive rate was approximately 25% (Fig. 3c-f). Target assay revealed the mutation of *IDH1*R132 H. There were no alterations in *TERT* promotor, *H3F3A*, and *HIST1H3B*. The codeletion of 1p/19q was not examined because the sample amount was small. The tumor was diagnosed as astrocytoma IDH-mutant, WHO grade 2, not otherwise specified in the 2021 WHO Classification of Tumors of the Central Nervous System.[11] Postoperative MRI visualized the CSF space at the foramen magnum, followed by improvement of the hydrocephalus and periventricular edema (Fig. 4). Postoperative treatment is currently postponed because the tumor size follow-up with MRI demonstrated no marked change for 12 months. Radiation therapy will be planned when the tumor shows signs of growth or becomes symptomatic. She returned to work in good condition with a 100% Karnofsky performance score.

Discussion

Gliomas arising on the midline, such as DMG, are known to have a poor prognosis and surgical biopsy and treatment are considered inappropriate.[1-5] We present a case of adult brainstem glioma that had a non-stereotypical clinical course as a malignant brainstem glioma, such as a pediatric-type diffuse high-grade glioma; therefore, we performed stereotactic brainstem biopsy. We concomitantly performed FMD, and the symptoms caused by the hydrocephalus improved. The histological diagnosis was astrocytoma, IDH-mutant, which is rare in brainstem gliomas.

Surgical brain biopsy is a standard diagnostic method for brain lesions. However, biopsy for brainstem lesions is contraindicated because the small sample obtained from stereotactic biopsy is not necessarily representative of the entire tumor and can result in a low diagnostic yield. Additionally, Since radiation therapy remains the standard treatment option for these patients regardless of the grade of the tumor, the risks of biopsy are considered to be unwarranted by some clinicians. However, in recent years, the significance of this procedure is being re-evaluated due to the development of biopsy techniques.[10,12] Hersh et al. uncovered a complication rate of 7.7% in 65 patients who underwent surgical brain biopsy for brainstem glioma.[7-9] Rachinger et al. reported that the diagnostic value of conventional MRI in the treatment planning of brainstem

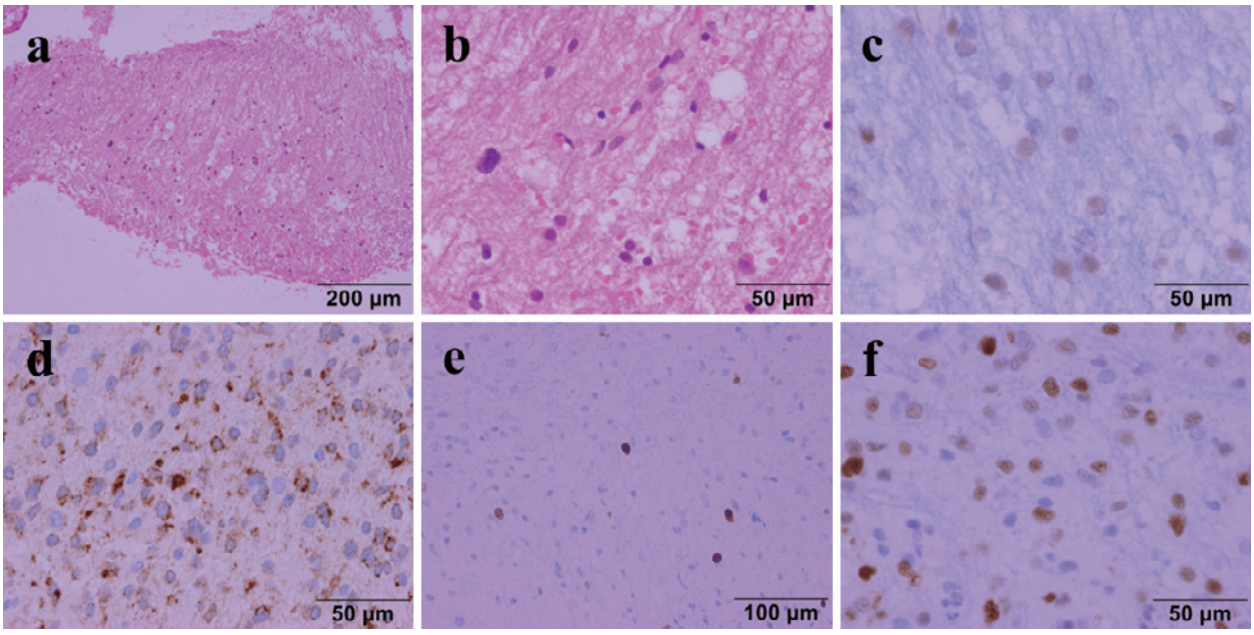

Fig. 3 Pathological findings. a, b: Hematoxylin and eosin staining shows moderately increased cellularity. c: Immunohistochemical analyses show positive staining for ATRX. d: IDH1 R132H was positive. e: Ki-67-positive rate was low. f: p53-positive rate was approximately 25%.

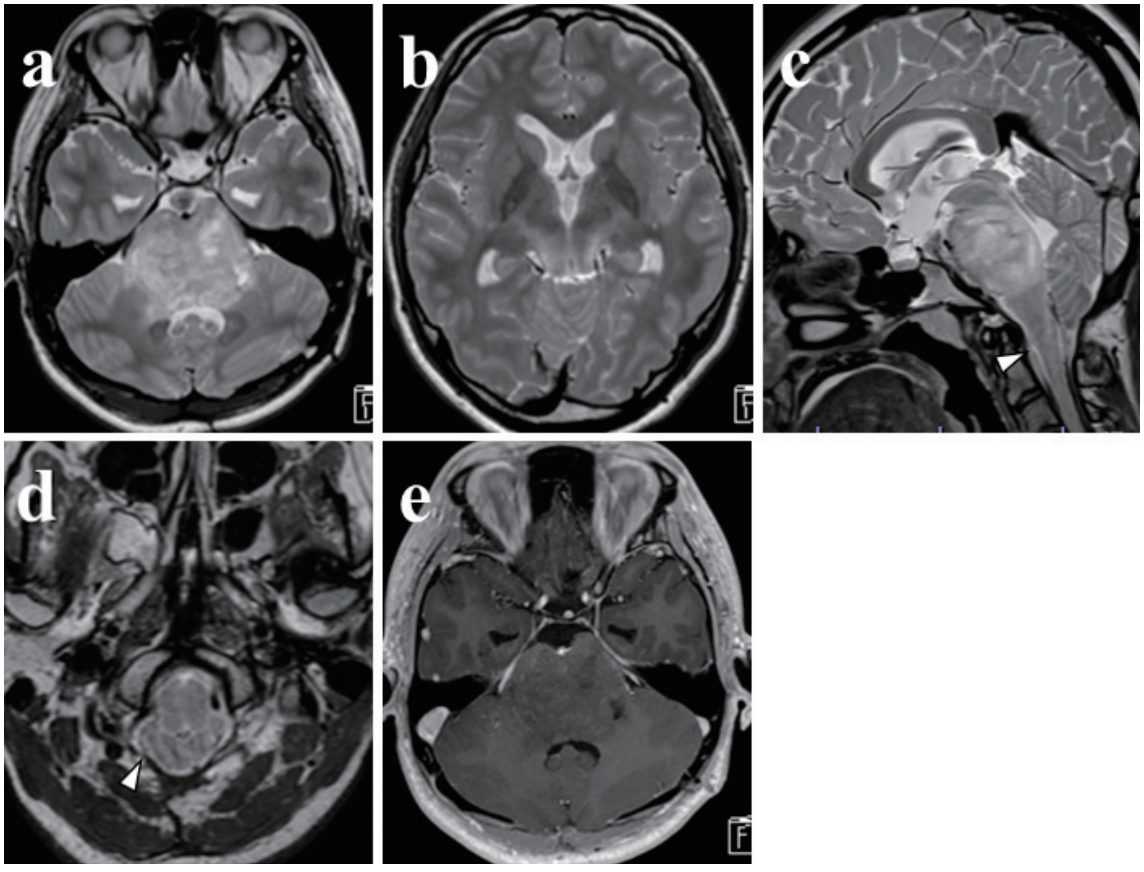

Fig. 4 MRI follow-up post-surgery. a, b: Postoperative T2-weighted image indicating improvement of hydrocephalus and periventricular edema. c, d: Images indicating that a space and a flow void of the CSF at the foramen magnum were visualized (white arrowhead). e: T1-weighted gadolinium (Gd)-enhanced MRI showing no apparent contrast enhancement in the tumor.

gliomas is insufficient, and the multimodally guided stereotactic biopsy should be a standard in adult patients with brainstem lesions.[13] In the present case, stereotactic biopsy revealed the diagnosis of astrocytoma, IDH-mutant, which was helpful in predicting the future prognosis.

IDH mutations are often found in young adults with diffuse and lower-grade gliomas, but they are low in infratentorial gliomas.[14,15] In infratentorial diffuse gliomas, the frequency of IDH mutations is rare, with approximately 5 to 7% of diffuse gliomas arising in the brainstem.[14] It has been revealed that, like supratentorial lesions, IDH-mutant lesions in the infratentorial area tend to have a better prognosis than wild-type lesions, although no significant difference has been observed.[16,17] The mutation of *IDH1*R 132H was identified in more than 80% of supratentorial IDH-mutant astrocytomas, whereas it was present in only 24% in infratentorial IDH-mutant astrocytomas, with the others more frequently being *IDH1*R132C/G mutation.[18] In the same report, loss of ATRX is also described in different frequencies in supratentorial and infratentorial IDH-mutant astrocytomas. Loss of ATRX was observed in 94% of supratentorial IDH-mutant astrocytoma, whereas less than half of infratentorial IDH-mutant astrocytomas had loss of ATRX; this case also did not have ATRX mutation. As reported in 42 cases of infratentorial IDH-mutant astrocytoma, it is distinct in subtype from supratentorial astrocytomas, and the overall survival of infratentorial IDH-mutant astrocytomas is significantly poorer than that for supratentorial IDH-mutant astrocytomas.[18]

Previous reports have only discussed 20 cases of IDH-mutant brainstem glioma.[17,19,20] Of these cases, 18 cases discussed treatment: 11 cases were receiving chemoradiation therapy, 5 cases were receiving only radiation therapy, and 2 cases were receiving only chemotherapy. In one case, debulking was performed as a surgical treatment. Radiotherapy with 54 Gy in 30 fractions was mainly used, and temozolomide was mainly used for chemotherapy. Median overall survival was 36 months. Among the cases, there have been four reports of diffuse astrocytoma, and chemoradiation was the main treatment.[19,21-23] While these treatments should be considered in terms of tumor control, the long-term effects of treatments including radiation and chemotherapy need to be examined.[24] The patient described herein is being kept under observation, considering the slow rate of tumor progression and the fact that she is currently asymptomatic and willing to be observed. Yamasaki et al. uncovered that the T2-FLAIR mismatch sign in DIPG may be an indicator for better response to radiotherapy,[25] but this sign was not observed in our case. Genomic profiling assays to identify CDKN2A/B were unable to be performed due to the lack of biopsy volume. The promising establishment of a liquid biopsy method in the near future will help overcome the limitations of tumor sampling in critical locations.[26]

Surgical treatment for brainstem glioma is considered to have a high complication rate and is to be avoided for poor prognosis diseases.[7,13] However, the present case, as mentioned above, was not a typical DMG. Since of the slow symptomatic course, we considered that the prognosis of the disease may not be as poor as a DMG, and the symptoms were definitely associated with hydrocephalus. We expected that FMD would improve the symptoms and help the patient return to her normal quality of life without any complications such as cranial nerve damage The biopsy and FMD were performed minimally invasively. Postoperative pain was very minor, and the cosmetic result was satisfactory. The patient was discharged promptly and resumed her daily life. Aihara et al. revealed that FMD was effective when neurological symptoms were due to narrowing of the fourth ventricle caused by brainstem enlargement and obstructive hydrocephalus.[27] FMD is usually performed in syringomyelia associated with Chiari I malformation, to free the CSF pathways. Isu et al. advocated that FMD dividing the outer layer of the dura mater is sufficient because the circulatory disturbance of CSF is corrected by the procedure.[28] In the present case, FMD without a dural patch was employed to sufficiently dilate around the foramen magnum in accordance with the slow tumor growth to avoid drastic changes in the pressure of the posterior fossa. The patient's symptoms immediately and satisfactorily improved without any complications, including CSF leakage. Her quality of life was well maintained for at least a year in a brainstem tumor through the gradual enlargement of the posterior fossa.

Stereotactic biopsy and foramen magnum decompression were performed concomitantly for a symptomatic brainstem glioma. As in the present case, surgical treatment may contribute to symptomatic improvement in cases where tumor progression is expected to be slow. Even in cases of brainstem glioma, it is important to make a definite pathological diagnosis in atypical cases and to perform surgical treatment according to the clinical symptoms. Adjuvant therapy such as radiation therapy will be considered for future tumor growth.

Acknowledgments

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Ethics Approval

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee (IRB#1911-023, #1608-026) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The consent of the participant was obtained.

Conflicts of Interest Disclosure

The authors declare that we have no conflicts of interest related to this case report.

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