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CASE REPORT

Concomitant KIAA1549-BRAF fusion and IDH mutation in Pediatric spinal cord astrocytoma: a case report and literature review

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Abstract

Primary tumors of the spinal cord are rare, accounting for 3–6% of tumors in the central nervous system, particularly in children. KIAA1549-BRAF fusion is more common in pilocytic astrocytoma (PA) and IDH1 R132H mutation is rare in infratentorial tumors. Here, we report a 10-year-old male patient who presented with weakness in lower limbs that progressed to difficulty walking. Magnetic resonance imaging (MRI) revealed an intramedullary solid-cystic lesion from the medulla oblongata to the thoracic spin 4 level, with the expansion of the spinal cord. The lesion exhibited patchy enhancement at C4-T1, indicating a tentative diagnosis of astrocytoma. The patient underwent resection of the lesion in the spinal canal from the cervical 6 level to the thoracic 2 level. Histopathology confirmed diagnosis of astrocytoma, WHO grade 2. Genetic analysis showed both IDH1 R132H mutation and KIAA1549-BRAF fusion. Therefore, our integrated diagnosis was astrocytoma, IDH mutation, WHO grade 2. Its molecular analyses include IDH1 R132H mutation and KIAA1549-BRAF fusion. After the operation, the patient did not receive chemo- or radiotherapy, and underwent an aggressive rehabilitation regiment. Follow up 10 months later, symptoms improved. To our best knowledge, this is the first case of concomitant IDH mutation and BRAF fusion in pediatric spinal cord astrocytoma.

Keywords Spinal cord · Astrocytoma · IDH1 R132H mutation · KIAA1549-BRAF fusion

Introduction

Primary tumors of the spinal cord are rare, accounting for 3–6% of tumors in the central nervous system, and their incidence in children is lower than in adults [8, 17, 21]. B-Raf is an intracellular serine/threonine kinase component of the mitogen-activated protein kinase (MAPK) pathway [24], which regulates cell growth, proliferation, and differentiation [7]. BRAF fusion causes a loss of the BRAF N-terminal auto-inhibitory domain, which can lead to tumorigenesis [25]. KIAA1549-BRAF is the most common form of BRAF fusion, commonly occurring in low-grade gliomas, such as pilocytic astrocytoma (PA), pilomyxoid astrocytoma (PMA) and diffuse leptomeningeal glioneuronal tumors (DLGNT) [18]. Furthermore, KIAA1549-BRAF is an accepted marker of a good prognosis [27]. Examination of isocitrate dehydrogenase (IDH) in diffuse glioma is essential for accurate diagnosis based on the updated 2016 World Health Organization (WHO) classification of brain tumors [13]. IDH1 mutations are found in up to 75% of grade 2 and 3 diffuse glioma, most of which are supratentorial [11, 26], and rarely infratentorial [5]. Moreover, most patients with tumors harboring IDH1 mutations are adults, while pediatric gliomas do not typically harbor IDH mutations [2]. Notably, patients with IDH mutation have longer survival than patients with IDH wild-type tumors [11, 26].IDH mutations are rarely found in spinal cord astrocytoma, with only one case report of an IDH1 R132S mutation in spinal cord astrocytoma reported to date [23]. To our best knowledge, there are no cases of concomitant IDH 1 mutation and KIAA1549-BRAF fusion in glioma has been reported, and the effect of this double alteration on prognosis is unknown. Here, we report a case of pediatric spinal cord astrocytoma with concomitant IDH1 R132H mutation and KIAA1549-BRAF fusion.

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Clinical summary

A 10-year-old male patient presented with weakness in lower limbs and an unsteady gait for 2 months. There was no obvious relief to symptoms after rest. The MRI revealed an intramedullary solid-cystic lesion from the medulla oblongata to thoracic spine 4 level (Fig. 1). The lesion displayed patchy enhancement at C4-T1. The tentative diagnosis of this case was astrocytoma.

The patient underwent resection of the intramedullary lesion. During the operation, the surgeon extracted the cyst fluid and relived the spinal cord swelling. Because the tumor was multilayered, only partial resection (C6-T2) was achieved. The pathohistological diagnosis was astrocytoma. After the operation, the patient received no other oncological intervention but underwent active rehabilitation. At the 10-month follow-up, the patient had recovered from limb weakness and was able to walk a few steps.

Histopathological findings

Hematoxylin and eosin (HE) staining showed diffuse proliferation of tumor cells with round, ovoid, or fusiform nuclei, but no obvious cytoplasmic staining. No bipolar cells or piloid neurites were observed. Rosenthal fibers and eosinophilic granular bodies were visible in a large proportion of the cells (Fig. 2a-d). There was no evidence of necrosis, mitosis or microvascular proliferation. Immunohistochemical staining demonstrated that the tumor cells were positive for GFAP and IDH1 R132H (Fig. 2e, g). Some glial cells exhibited oligodendrocyte lineage transcription factor 2 (OLIG2) (Fig. 2f) positivity in their nuclei. The Ki-67 index was approximately 2% (Fig. 2). BRAF V600E (Fig. 2j), P53 (Fig. 2i), and H3K27M (Fig. 2k) were negative, while ATRX (Fig. 2h) was positive.

Genetic analysis

Genomic DNA was extracted from the formalin-fixed, paraffin-embedded (FFPE) tumor samples and then amplified

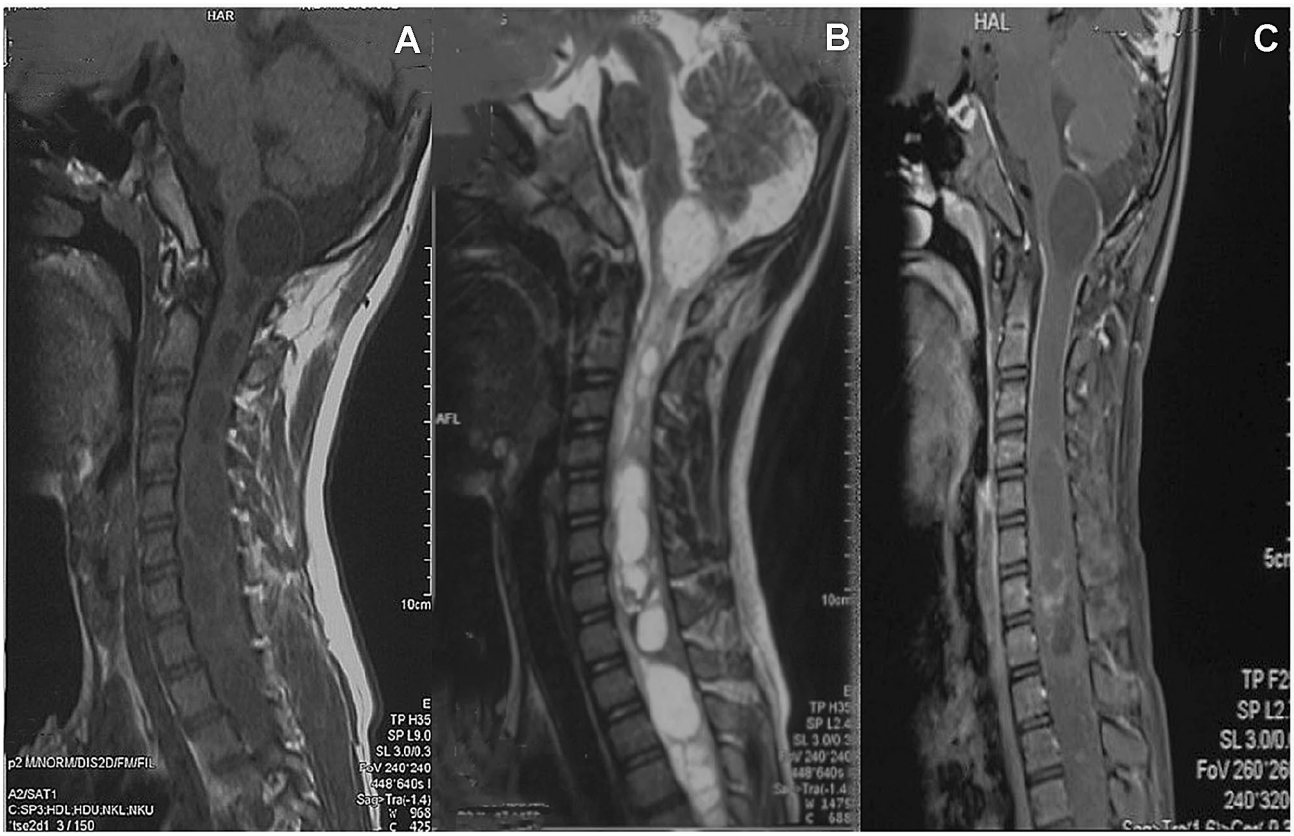

Fig. 1 Sagittal T1- **a** and T2-weighted **b** images revealing a longitudinally extending intramedullary mass from the medulla to the T4 level, with multi-cystic changes throughout the mass. **c** Sagittal contrast-enhanced T1-weighted image showing slightly heterogeneous enhancement in the mass, with peripherally enhanced superior cystic changes and solidly enhanced inferior T2-isointense tumor

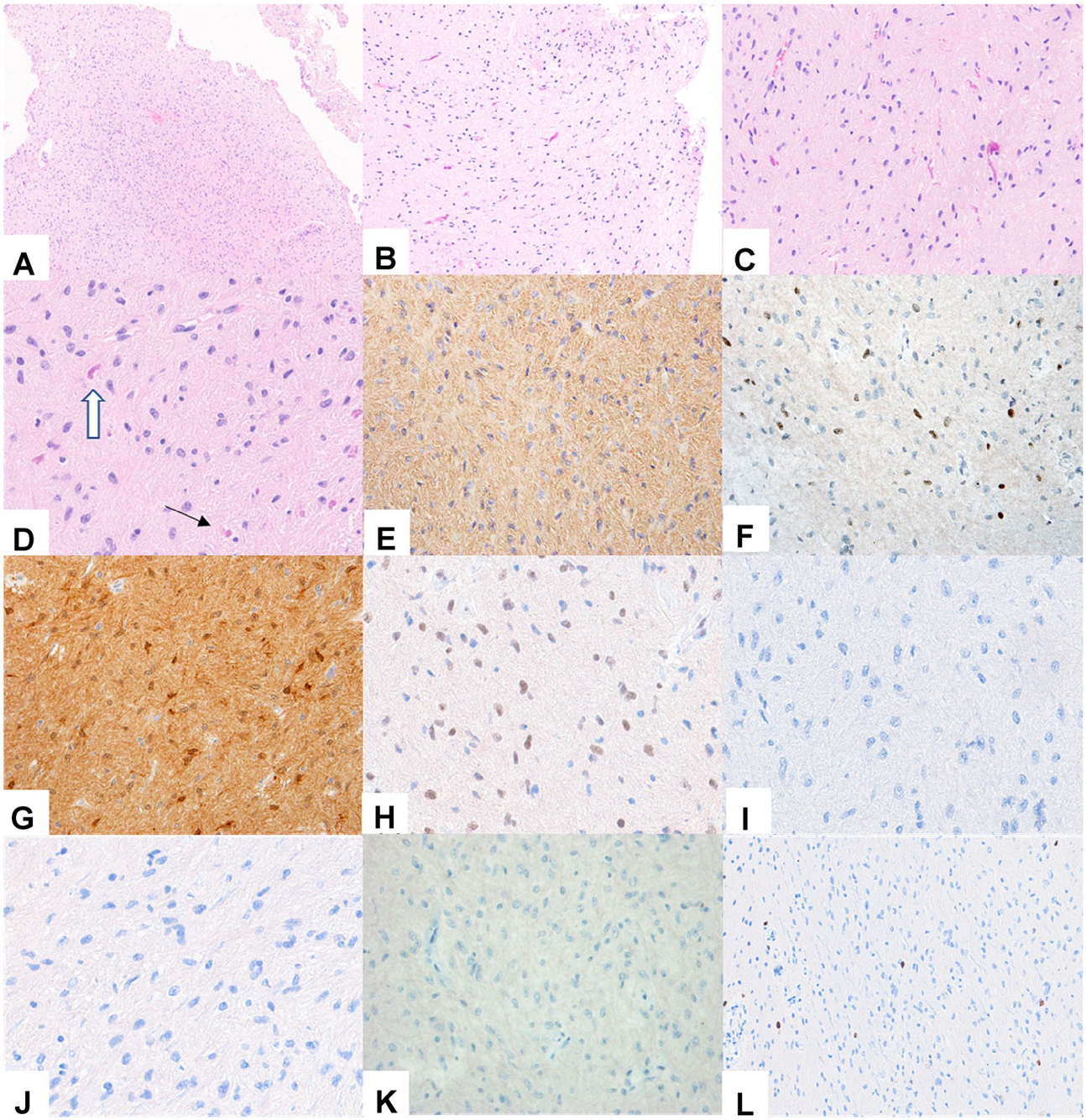

Fig. 2 Histopathological features. HE staining showing diffusely proliferating tumor cells with round, ovoid, or fusiform nuclei (**a**–**d**). Rosenthal fibers (**d** thick arrow) and eosinophilic granular bodies (**d** thin arrow) were frequent. Immunohistochemical staining showing that the tumor cells are positive for Glial fibrillary acidic protein (GFAP) (**e**). OLIG-2 expression was evident in some glial cells (**f**). Tumor cells were also positive for isocitrate dehydrogenase 1 R132H (IDH1 R132H) (**g**) and ATRX(H), but negative for P53 (**i**). BRAF V600E (**j**) and H3K27M (**k**) is also negative. The Ki-67 index was approximately2% **l**)

by Polymerase Chain Reaction (PCR) using appropriate primer pairs. The mutation hotspots at codon 132 of IDH1 and 172 of IDH2 were screened by Sanger sequencing. IDH1 and IDH2 was sequenced after amplification by polymerase chain reaction (PCR) using the IDH1 forward primer 5′-ACC AAATGGCACCATACGA-3′ and reverse primer 5′TTC ATACCTTGCTTAATGGGTGT-3′), and the IDH2 forward primer 5′-GCTGCAGTGGGACCACTATT-3′ and reverse primer 5′-TGTGGCCTTGTACTGCAGAG-3′, respectively. The results revealed the presence of the IDH-1 R132H mutation (Fig. 3a). The KIAA1549-BRAF fusion was confirmed by Fluorescence In Situ Hybridization (FISH) (Fig. 3b) and

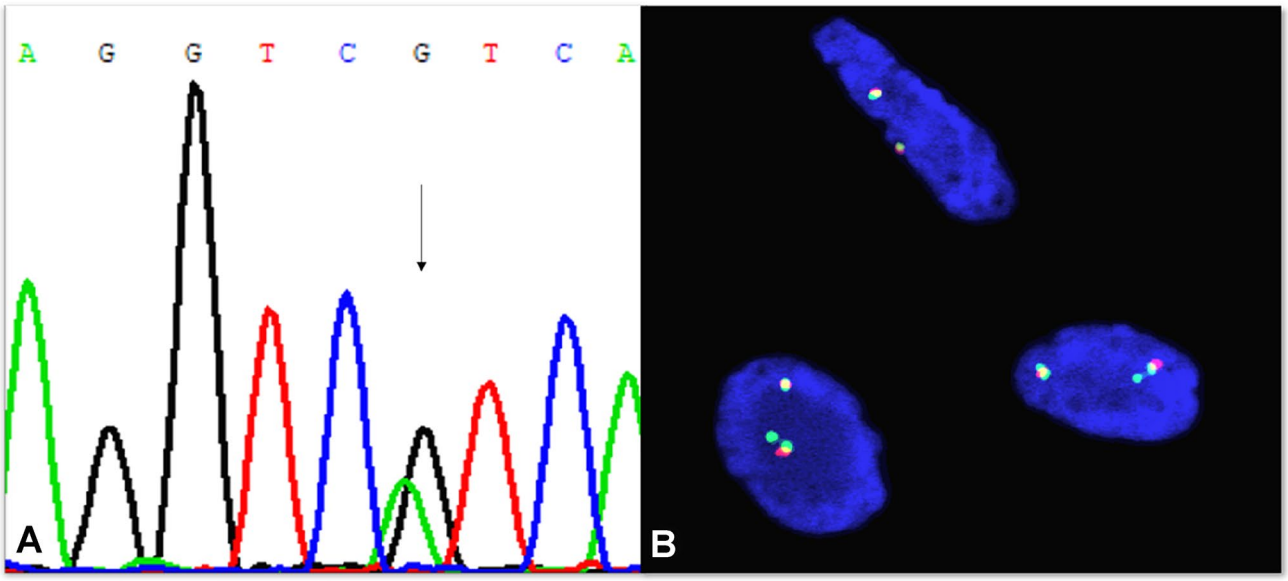

Fig. 3 Genetic features of the tumor. Sanger sequencing revealed the presence of the isocitrate dehydrogenase 1 R132H (IDH1 R132H) mutation (395: G-A) (A) and Fluorescence In Situ Hybridization (FISH) revealed the presence of the KIAA1549-BRAF fusion: Using BRAF Break probes that encompassed the entire BRAF gene on 7q34, the normal and fusion-negative nuclei displayed two pairs of merged(yellow) or adjacent signals red/green (5′/3′), representing the two wild type(wt) BRAF alleles. Fusion-positive nuclei in tumor sections display the BRAF break apart pattern; two pairs of merged(yellow) or adjacent signals red/green (representing 5′/3′ wt BRAF alleles), and one additional split green (3′) signal indicating a duplicated copy of the 3′ BRAF region (B)

next-generation sequencing (NGS). No other mutations were detected.

Discussion

To the best of our knowledge, this is the first case of pediatric spinal cord astrocytoma with concomitant BRAF fusion and IDH mutation. IDH mutations are mainly reported in adult supratentorial glioma, and is rare in infratentorial or pediatric low-grade gliomas [5, 11, 26]. Accordingly, there are few reports on infratentorial gliomas harboring IDH mutations (Table 1). In fact, we are aware of only a single report on spinal cord astrocytoma with IDH1 mutation, and the 44-year-old patient harbored the IDH1 R132S rather than the R132H mutation [2]. Shankar et al. analyzed 17 spinal cord gliomas, which no case of IDH mutation [22]. Hidehiro et al. did not identify an IDH mutation among 25 cases of brainstem glioma [16]. We, therefore, believe that most spinal cord gliomas harbor the wild-type IDH gene.

The KIAA 1549-BRAF fusion was first reported in 2008. The authors found a tandem duplication of 7q34 leading to a fusion between KIAA1549 and BRAF in most PA. This event can activate the ERK/MEK/MAPK pathway and result

Table 1 Summary of previously reported IDH mutations in infratentorial gliomas

First author and year	Frequency of IDH mutation	Age (years) and sex	Tumor location	Histological diagnosis	IDH mutation
Keisuke et al. 2017 [23]	Case report	44/F	Spinal cord	DA	IDH1 R132S
Javadi et al. 2018 [9]	Case report	22/F	Brain stem	DA	IDH1 R132H
Matsumura et al. 2018 [14]	Case report	83/M	Cerebellum	AA	IDH1 R132H
		75/F	Cerebellum	AA	IDH2 R172K
Ellezam et al. 2012 [5]	4/44	40/M	Medulla	DA	IDH1 R132H
		24/M	Medulla	DA	IDH1 R132H
		56/M	Pons	AA	IDH1 R132H
		53/M	Cerebellum	AA	IDH1 R132G
Porkholm et al. 2017 [19]	1/23	13/Not descried	Brain stem	DA	IDH1 R132S

DA diffuse astrocytoma, *AA* anaplastic astrocytoma

in proliferation, survival, and tumorigenesis, but can also trigger cell differentiation and senescence [10, 15]. It occurs frequently in PA (> 70%) and DLGNT (75%), while the incidence of the KIAA1549-BRAF fusion in diffuse astrocytoma was found to be low [3, 18]. In our case, the cells were round and ovoid, with inconspicuous cytoplasm, no bipolar cells or piloid neurites. The pathohistological diagnosis was therefore consistent with diffuse astrocytoma.

Initially, KIAA1549-BRAF fusion and IDH mutation were thought to be exclusive genetic events that could distinguish pilocytic astrocytoma from diffuse astrocytoma [12]. However, Badiali et al. found that IDH mutation and KIAA1549-BRAF fusion were both present in 11 of 180 adult gliomas, suggesting that these are two independent genetic events [1]. Cruz et al. demonstrated the presence of KIAA1549-BRAF fusion in 39 of 82 pediatric low-grade gliomas, 4 of which also had IDH1 G105G polymorphism but no IDH mutation [4]. Gierke et al. reported no coexistence of KIAA1549-BRAF fusion and IDH mutation in 765 cases of central nervous system gliomas [6]. Among 1037 pediatric low-grade gliomas (PA in 321 cases, diffuse astrocytoma in 16 cases), 671 cases underwent molecular detection that did not find KIAA1549-BRAF fusion concomitantly with IDH 1 mutation [20]. Hence, our case is the first report of pediatric spinal cord astrocytoma harboring both KIAA1549-BRAF fusion and IDH1 R132H mutation. There are still no case reports on KIAA1549-BRAF fusion together with IDH mutation in PA.

In adult supratentorial glioma, the prognosis of IDH mutant tumors is better than that of IDH wild-type cases [11, 26]. KIAA1549-BRAF is also considered a good prognostic factor [27]. However, the only known case of IDH mutant spinal cord astrocytoma survived for only 11 months [23]. Given the very rare incidence of spinal cord astrocytoma harboring IDH mutation as well as KIAA1549-BRAF fusion, a prognosis of gliomas with both alterations cannot be made without additional case reports.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interests.

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