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CASE REPORT

Spontaneous regression of epileptogenic pilocytic astrocytoma with *FGFR1-TACC1* fusion

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Abstract

Introduction Pilocytic astrocytoma (PA) is the most common pediatric tumor, typically located in the cerebellum, with spontaneous regression observed mainly in patients with neurofibromatosis type 1 (NF1). However, spontaneous regression of PA without NF1 is rarely reported.

Case Presentation Here, we describe a case of spontaneous regression of PA without NF1, located in the left frontal lobe with *FGFR1-TACC1* fusion, in a 14-year-old boy who presented with epilepsy. Initial MRI revealed a lesion in the left middle frontal gyrus, and subsequent follow-up MRI demonstrated spontaneous regression. Despite this regression, the patient's seizures persisted, leading to epileptic focus resection. Pathological examination confirmed PA with characteristic histological findings and *FGFR1-TACC1* fusion.

Conclusion This case suggests that *FGFR1-TACC1* fusion may be linked to spontaneous regression of PA, even in the absence of NF1. Surgical intervention may remain necessary in cases of epilepsy associated with PA, regardless of tumor regression.

Keywords Pilocytic astrocytoma · Spontaneous regression · *FGFR1-TACC1* fusion · Epilepsy

Introduction

Pilocytic astrocytoma (PA) is the most common pediatric tumor of the central nervous system, accounting for 5% of all gliomas and 15–17% of all brain tumors in children and adolescents [9]. PA occurs most frequently in the central nervous system and is located in the cerebellum (42%), followed by the supratentorial compartment (36%), optic pathway and hypothalamus (9%), brainstem (9%), and spinal cord (2%) [1]. In children, the most common site is the cerebellum (67%) and rarely the supratentorial compartment [3].

Pediatric PA rarely presents with epilepsy but may occasionally require epilepsy surgery [5]. In terms of molecular characteristics, PA often causes alterations in the mitogen-activated protein kinase (MAPK) pathways, such as *BRAF*, *NF1*, and *FGFR1*. Although the most frequent genetic change in PA is the fusion between *KIAA1549* and *BRAF* (> 70%), changes in *NF1* and *FGFR1* are rare [3, 15]. Spontaneous regression of PA has been observed and is particularly associated with neurofibromatosis type 1 (NF1) [7, 12, 13]. However, a few cases of spontaneous regression of PA have been reported even in patients without NF1 [8, 16], suggesting that genes other than *NF1* may contribute to this phenomenon.

Here, we describe a case of spontaneous regression of PA without NF1 in the frontal lobe harboring *FGFR1-TACC1* fusion that was treated with focus resection for epilepsy.

Case report

A 14-year-old right-handed boy had a tonic–clonic seizure at the age of 12 years 7 months. He had no relevant medical or family history of illness. Computed tomography performed at another hospital showed a low-density area in the left frontal lobe. Despite the administration of valproic acid, the tonic–clonic seizures persisted once a week. He was admitted to our institution with suspected tumor-related epilepsy. At the age of 12 years 8 months, the initial magnetic resonance imaging (MRI) at our institution revealed a lesion of approximately 15 mm in the left middle frontal gyrus

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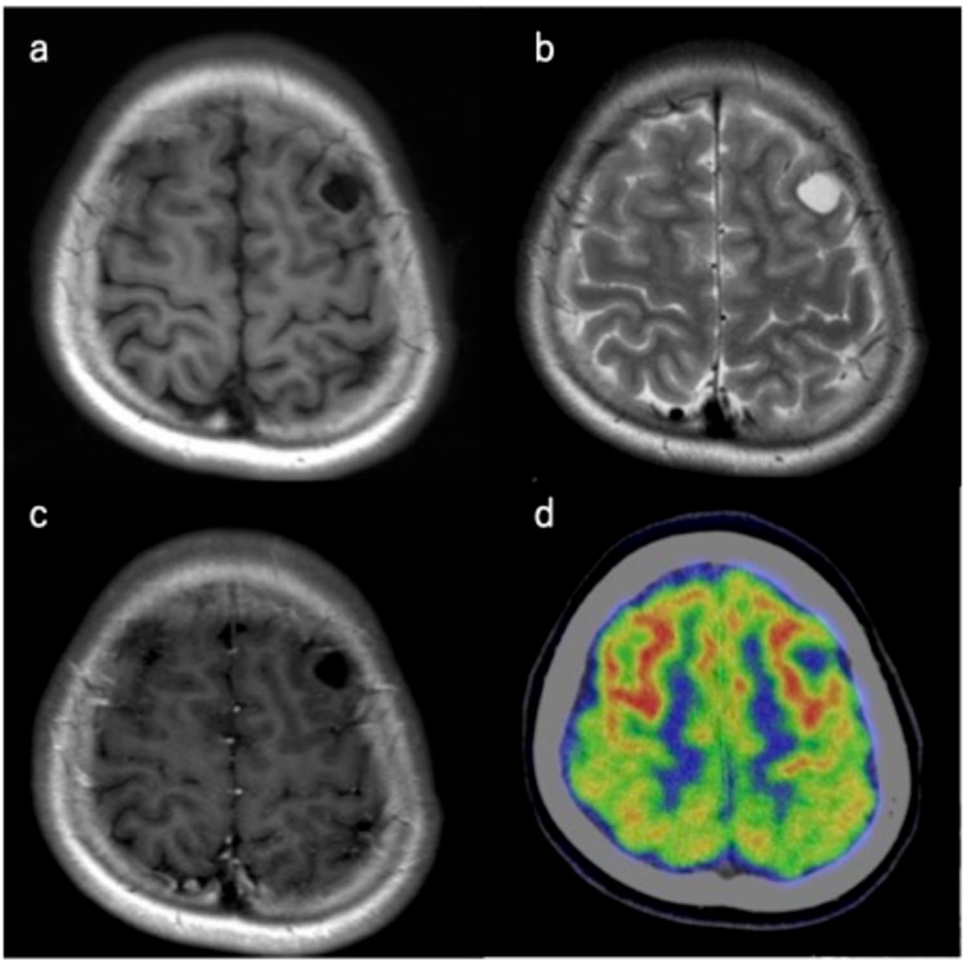

Fig. 1 Initial magnetic resonance imaging (MRI) (axial view) reveals a lesion in the left middle frontal gyrus on T1 (**a**), T2 (**b**), and Gd-enhanced T1 (**c**); fluorodeoxyglucose-positron emission tomography (axial view) demonstrates hypometabolism, in accordance with the lesion (**d**)

with T1 low, T2 high, fluid-attenuated inversion recovery (FLAIR) high intensity, and no enhancement with gadolinium on T1 (Fig. 1a–c). Fluorodeoxyglucose-positron emission tomography revealed hypometabolism in the left middle frontal gyrus, consistent with the lesion observed on MRI (Fig. 1d). Scalp electroencephalography revealed interictal epileptic discharges originating from C3 and P3. After switching from valproic acid to levetiracetam, the seizure frequency remained monthly. On prolonged scalp video electroencephalography, we observed habitual seizures that were versive to the right side, followed by focal-to-bilateral tonic–clonic seizures. Ictal and interictal epileptic discharges originated from Fp1 and F3. Follow-up MRI performed 6 and 15 months later demonstrated no changes of the size compared with the initial MRI (Fig. 2a–i). After 15 months, when the frequency of his seizures temporarily increased from monthly to weekly, the cortex around the lesion showed high intensity on FLAIR (Fig. 2i). We increased the dose of levetiracetam from 1000 to 2000 mg/day. Follow-up MRI performed 20 months after the initial MRI revealed significant spontaneous regression of the lesion (Fig. 2j–l). In spite of spontaneous regression of the lesion and increasing the dose of levetiracetam, the patient's seizures persisted at the same frequency; therefore, we decided to perform epileptic focus resection after discussions with the patient and his family. Three years after epileptic focus resection, he had no seizures or neurological deficits. Postoperative MRI revealed complete resection of the mass (Fig. 3a, b).

The removed specimen had a biphasic pattern, in which the compact area was composed of Rosenthal fibers and the loose area was composed of prominent microcysts. Eosinophilic granular bodies were observed in both areas (Fig. 4a). Based on these findings, the pathological diagnosis of PA was made. In addition, oligodendroglial clustering was observed in the cortex around the lesion (Fig. 4b). Microarray and Sanger sequencing revealed *FGFR*1-*TACC*1 fusion in the tumor (Fig. 4c).

Discussion

Spontaneous regression of PA in patients with NF1 has been reported in various studies; however, studies on PA without NF1 are limited [7, 12, 13, 16]. Parsa et al.

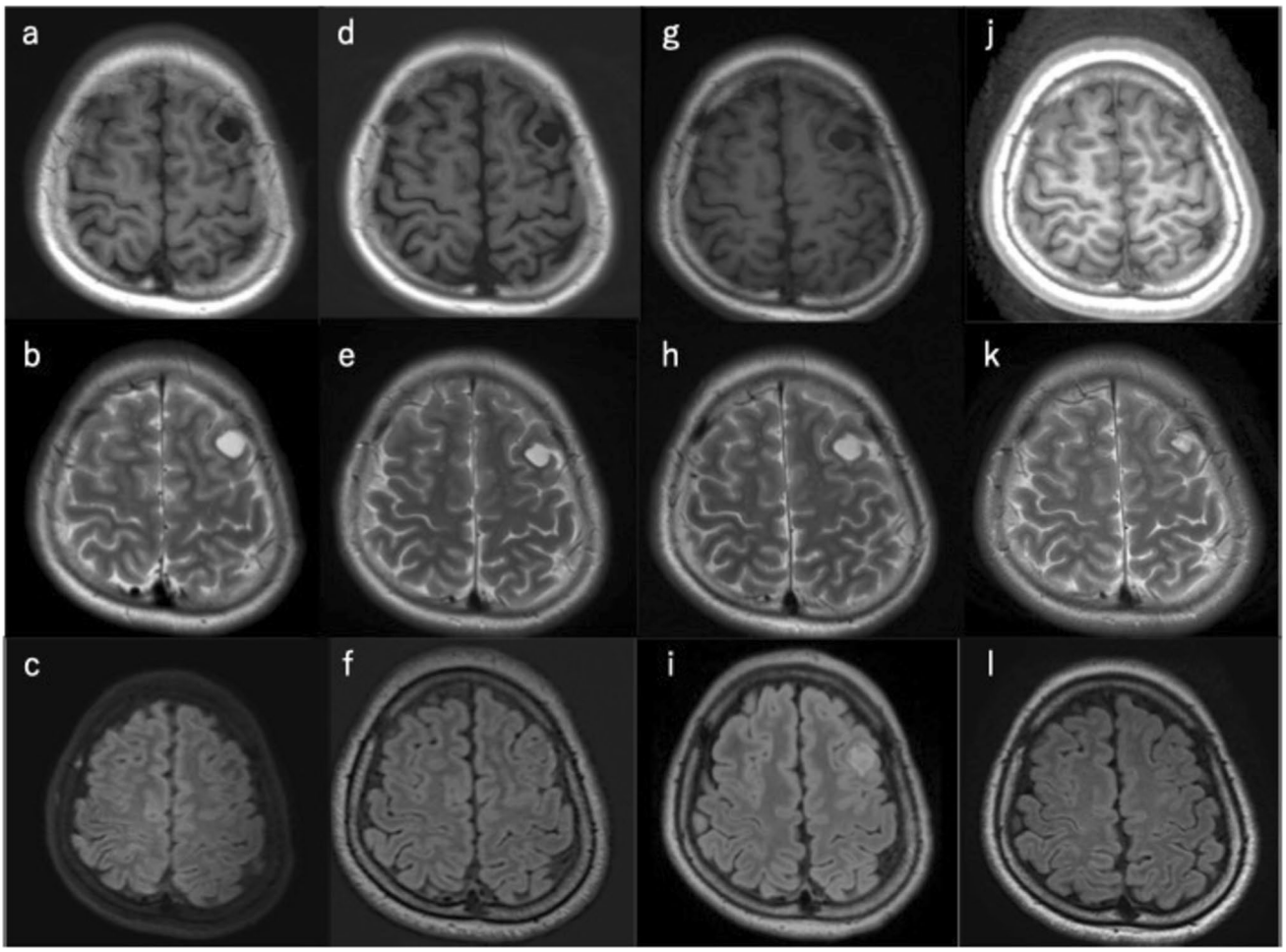

Fig. 2 MRI (axial view) shows no change at the size of the lesion between the initial MRI (**a** T1, **b** T2, **c** FLAIR), 6 months later (**d** T1, **e** T2, **f** FLAIR), and 15 months later (**g** T1, **h** T2, **i** FLAIR); however, the MRI after 20 months from the initial MRI shows spontaneous regression (**j** T1, **k** T2, **l** FLAIR)

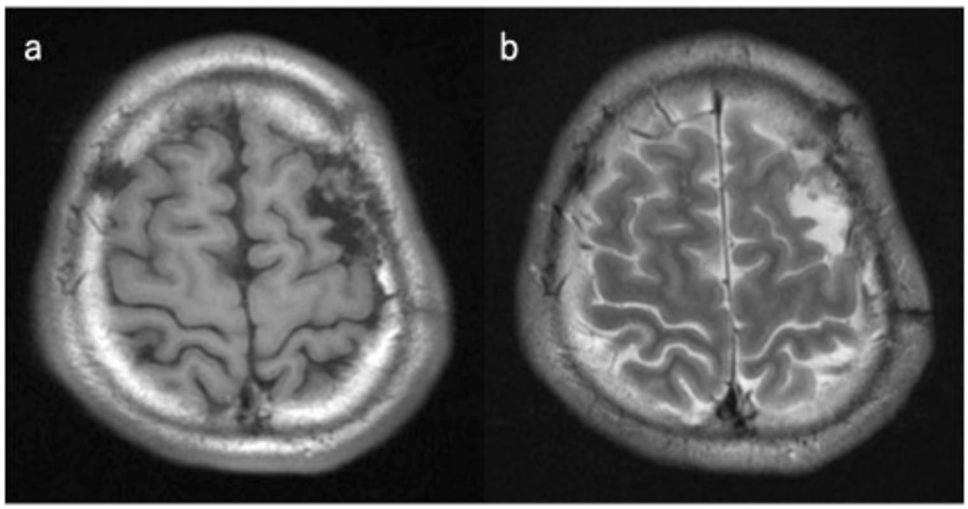

Fig. 3 Postoperative MRI (axial view) after 3 years reveals complete resection and no recurrence (**a** T1, **b** T2)

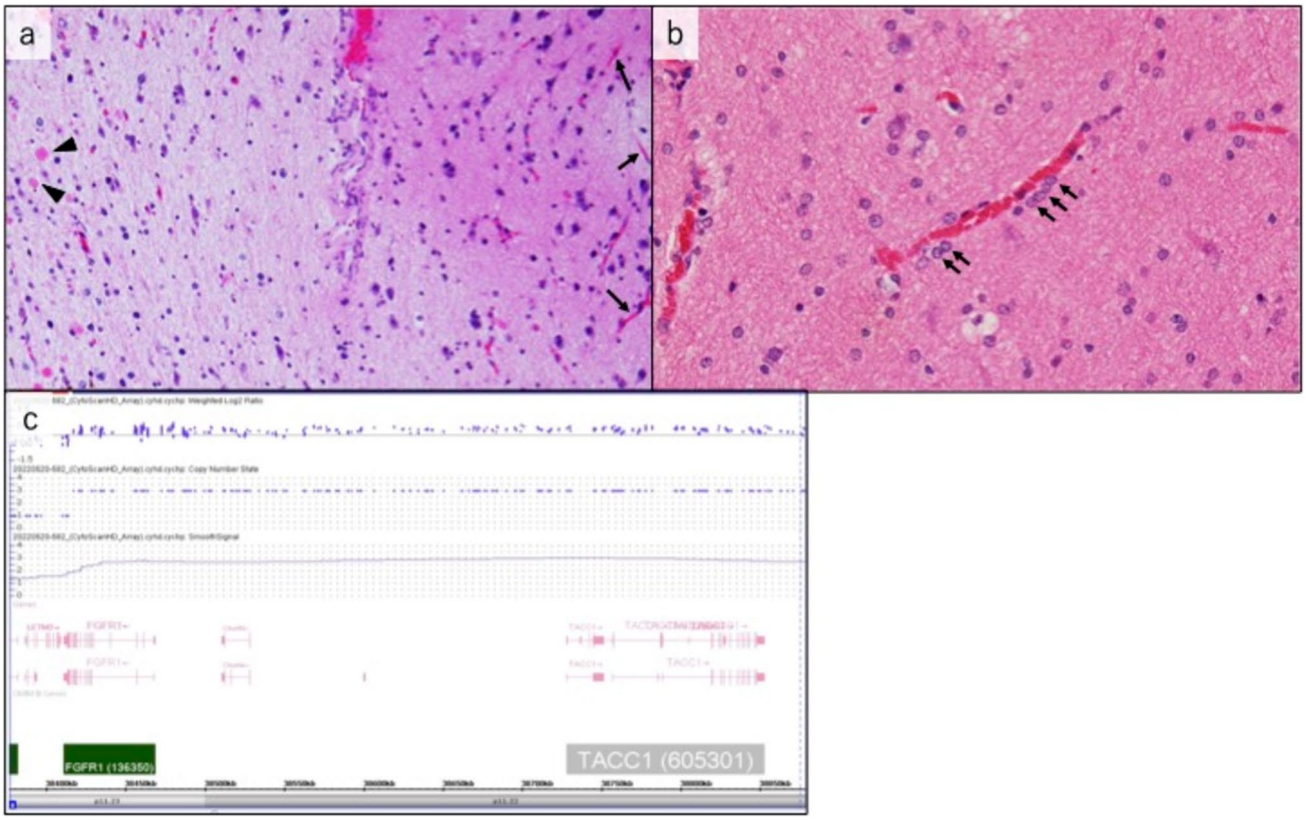

Fig. 4 Pathological features of the lesion (**a**) stained with hematoxylin and eosin (HE) in low-power (×10) field shows biphasic pattern, compact area (the right side) with Rosenthal fiber (arrow), and loose area (the left side) with eosinophilic granular bodies (arrow head); the cortex surrounding the lesion (**b**) stained with HE in high-power (×40) field shows perivascular clustering of oligodendroglia (arrow); the short arm of chromosome 8 harbors gain area, in which *FGFR*1 and *TACC*1 are lined up with microarray (**c**)

reported 12 cases of spontaneous regression of juvenile PA located in the optic pathway [12]. Of the 12 patients, 4 had NF1 and 8 did not have NF1. Rozen et al. reported cases of spontaneous regression of juvenile PA without NF1 [16]. PA was located in the optic chiasm in 10 patients, pons in 2, hypothalamus in 2, and temporal lobe in 1. To our knowledge, this is the first reported case of spontaneous regression of PA without NF1 in the frontal lobe.

The mechanisms underlying spontaneous regression of PA with or without NF1 are not fully understood. Several potential mechanisms have been proposed, based on genetic, cellular, and environmental factors. *KIAA1549-BRAF* fusion leads to activation of the MAPK pathway, which promotes cell growth and survival. However, some studies have suggested that the *KIAA1549-BRAF* fusion is associated with less aggressive tumor behavior and may even contribute to tumor regression [18]. In addition, the low level of MAPK pathway like as *BRAF/RAS*, *NF1* or $p16^{INK4a}$ pathway are related to oncogene-induced senescence [6]. *FGFR1-TACC1* fusions, which involve the MAPK pathway, are frequently found in other gliomas [2]. The *FGFR1-TACC1* fusion has been reported in cerebellar and spinal PA [4]. *FGFR1-TACC1* fusion is an oncogenic chromosomal translocation that displays oncogenic activity [19]. Spontaneous regression of pediatric PA with *FGFR1-TACC1* fusion has not yet been reported. This case suggests that the *FGFR1-TACC1* fusion may also be associated with spontaneous regression as well as the abnormalities in the MAPK pathway reported in the past.

Spontaneous regression in this case may be considered as a behavior of ghost tumors. Ghost tumors known as vanishing tumors are classified into two categories, neoplastic and nonneoplastic such as stroke and epilepsy [11, 14]. Our phenomenon was caused by the genetic abnormality in PA from the neoplastic perspective and worsen of seizure frequency from the nonneoplastic one.

Surgical resection is generally the primary treatment for PA, and the potential for spontaneous regression can influence treatment strategies. Even when treatment is deferred owing to the expectation of spontaneous regression, it is crucial to conduct regular imaging studies and neurological assessments to monitor tumor progression or changes in symptoms.

In this case, owing to the presence of tumor-related epilepsy, epileptic focus resection was performed. Patients with

intractable epilepsy show a significant increase in clustering of oligodendroglial cells in the gray and white matter regions [17]. The oligodendroglial clustering in the cortex surrounding the PA may have affected the epileptogenicity in this case. A previous report on 339 patients with tumor-related epilepsy who underwent epileptic focus resection found that the seizure recurrence rate increased by 4% for each additional year of age. Additionally, surgeries performed at sites other than the temporal lobe were associated with a twofold higher risk of seizure recurrence [10]. From an epileptogenicity perspective, surgical intervention is a viable treatment option.

Conclusion

We report a case of spontaneous regression of juvenile PA with *FGFR1-TACC1* fusion in the frontal lobe. Even in cases of spontaneous regression, surgical intervention may be an effective treatment option for tumor-related epilepsy.

Author Contribution K.H. and Y.I. wrote the main manuscript text and Hiroharu.S. prepared figures and M.S. helped the genetic analysis and Hidenori.S. and A.K. revised the manuscript critically for important intellectual content.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study was approved by the Ethics Committee of Juntendo University (No. 16–163).

Consent to participate and consent for publication The patient and his parents consented to the submission of the case report for consideration by the journal. Verbal and written consent was obtained from them for the publication of this case report and all accompanying images.

Ethical responsibilities of authors All co-authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Competing interests The authors declare no competing interests.

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