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Case Report

Molecular analyses of rosette-forming glioneuronal tumor of the midbrain tegmentum: A report of two cases and a review of the FGFR1 status in unusual tumor locations

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ABSTRACT

Background: Rosette-forming glioneuronal tumor (RGNT) is a rare tumor that arises primarily in the posterior fossa, with molecular features of *FGFR1* mutation. A previous study reported that brainstem RGNT accounts for only 2.7% cases; therefore, midbrain RGNT is infrequent.

Case Description: The authors encountered two cases of RGNT located in the midbrain tegmentum (Case 1: 23-year-old woman and Case 2: 18-year-old boy), both exhibiting similar cystic components with gadolinium-enhanced cyst walls on preoperative magnetic resonance imaging, surgically resected through the occipital transtentorial approach. Histological findings in both cases comprised two characteristic architectures of neurocytic and glial components, typical of RGNT. Molecular assessment revealed no *FGFR1* mutation in the initial specimen, but revealed *FGFR1* K656E mutation in the recurrent specimen in Case 1 and showed no *FGFR1* mutation but showed *TERT* C228T mutation in Case 2. Neither case revealed *IDH1/2*, *BRAF*, *H3F3A* K27, *H3F3A* G34, or *HIST1H3B* K27 mutations. DNA methylation-based classification (molecularneuropathology.org) categorized both cases as RGNT, whose calibrated scores were 0.99 and 0.47 in Cases 1 and 2, respectively.

Conclusion: Midbrain tegmentum RGNTs exhibited typical histological features but varied *FGFR1* statuses with *TERT* mutation. RGNT in rare locations may carry different molecular alterations than those in other common locations, such as the posterior fossa.

Keywords: FGFR1, Midbrain, Rosette-forming glioneuronal tumor, Tegmentum, TERT

INTRODUCTION

Rosette-forming glioneuronal tumor (RGNT) is a rare tumor that arises primarily in the posterior fossa[21] with a hallmark of *FGFR1* mutation.[4,12,13,25,29] This tumor entity was first described in 2002,[21] and classified as the World Health Organization Grade I in 2007. In addition to the posterior fossa, RGNT arises throughout the central nervous system, such as in the

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supratentorial region, pineal region, basal ganglia, and spinal cord;[2,7,9,14,20,22,30,31] its incidence in the brain stem is 2.7%.[31]

We encountered two cases of RGNT located in the midbrain tegmentum, both of which demonstrated a gadolinium-enhanced cyst wall and were radically resected using the occipital transtentorial approach. Molecular analyses of the rare midbrain tegmentum RGNT included *FGFR1, TERT*, *IDH1*, *IDH2*, *H3F3A*, *HIST1H3B*, *BRAF*, KIAA1549-BRAF fusion, and DNA methylation-based classifiers provided by MolecularNeuropathology.org.[8] Moreover, in a literature review, we illustrate the *FGFR1* status in unusual tumor locations of RGNT.

CASE DESCRIPTION

Clinical summary

Case 1

A 23-year-old woman presented with sensory disturbances in the left face and hand. Gadolinium-enhanced T1-weighted (GdT1WI) magnetic resonance imaging (MRI) revealed enhancement suggestive of a thin cystic wall without nodule formation on the right side of the midbrain tegmentum [Figure 1a]. The patient underwent partial tumor resection through the occipital transtentorial approach without developing postoperative neurological deficits [Figure 1b]. GdT1WI MRI obtained 15-month postsurgery revealed spontaneous regression of the enhanced cystic tumor [Figure 1c]; however, GdT1WI MRI obtained 30-month postsurgery revealed regrowth of the enhanced tumor [Figure 1d]. She underwent a second surgery through the occipital transtentorial approach, subsequently achieving gross total tumor resection [Figure 1e]. No additional neurological deficits were noted. A central pathological review diagnosed both the initial and recurrent tumors as RGNT. Follow-up GdT1WI MRI 3 years after the second surgery revealed good local tumor control [Figure 1f] without neurological deficits.

Case 2

An 18-year-old boy presented with a tremor in the right hand. GdT1WI MRI revealed a cystic tumor with thin-wall enhancement on the left side of the midbrain tegmentum [Figure 1g]. The patient underwent subtotal tumor resection through an occipital transtentorial approach [Figure 1h]. Transient right oculomotor nerve palsy was observed postoperatively, with complete recovery. A central pathological review diagnosed the patient with RGNT. Follow-up MRI 3 years postsurgery revealed no tumor recurrence [Figure 1i].

Tumor specimens, DNA extraction, and pyrosequencing

Surgical tumor specimens of the initial and recurrent tissue samples of Case 1 and the initial tissue sample of Case 2 were subjected to the central pathological review by the Japan Children's Cancer Group. Due to the tumor location in the

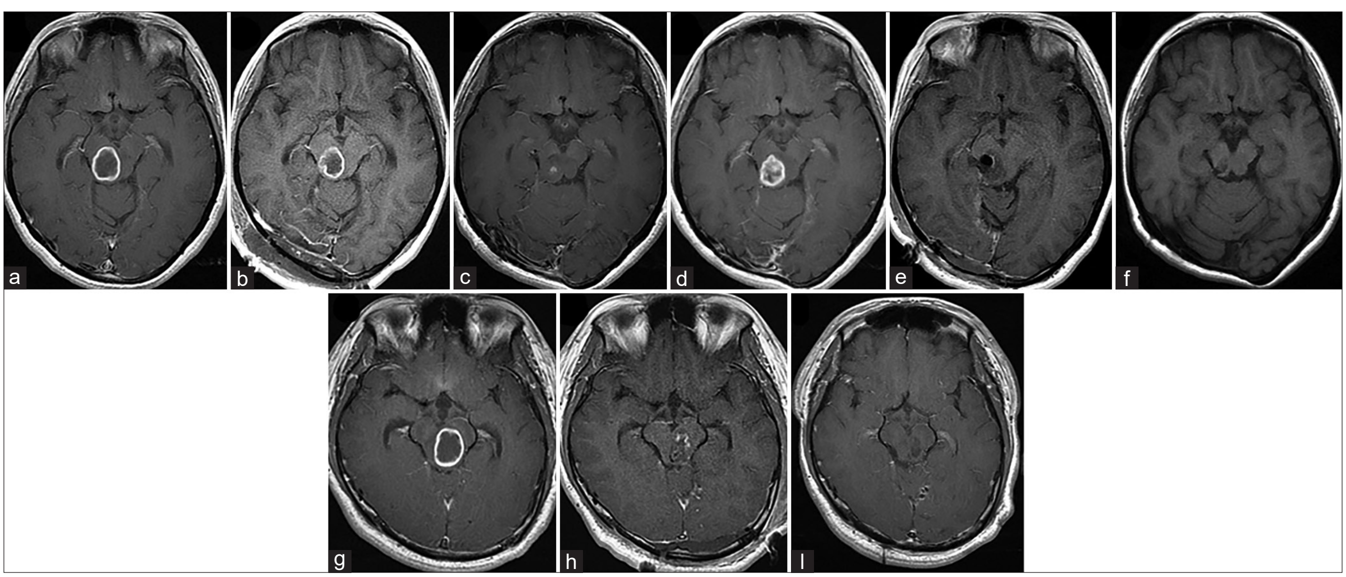

Figure 1: Gadolinium-enhanced T1-weighted magnetic resonance imaging (GdT1WI) of Cases 1 and 2. Case 1: Preoperative GdT1WI reveals an enhanced cystic tumor on the right side of the midbrain tegmentum (a). Postoperative magnetic resonance imaging indicates partial resection of the tumor (b). GdT1WI obtained 15 months after the initial surgery reveals tumor regression (c). After 30 months, follow-up GdT1WI reveals regrowth of the enhanced tumor (d). GdT1WI obtained immediately after the second surgery indicates gross total tumor resection (e). GdT1WI obtained 3 years after the second surgery reveals no recurrence (f). Case 2: Preoperative GdT1WI reveals an enhanced cystic tumor on the left side of the midbrain tegmentum (g). Postoperative GdT1WI indicates subtotal resection of the tumor (h). GdT1WI obtained 2 years after the second surgery reveals no recurrence (i).

midbrain, the tumor specimens were small. We were only able to obtain fresh frozen tissue from the recurrent tumor in Case 1, while paraffin-embedded specimens were available for the others. DNA from the frozen tumor tissue was extracted using a DNeasy Blood and Tissue Kit (Qiagen, Tokyo, Japan), and DNA from paraffin-embedded tumor tissue was extracted using a QIAamp DNA FFPE Tissue Kit (Qiagen, Tokyo, Japan). Hotspot mutations, including *IDH1* R132, *IDH2* R172, *BRAF* T599, *BRAF* V600, *H3F3A* K27, *H3F3A* G34, *HIST1H3B* K27, *FGFR1* N546, *FGFR1* K656, and C228T or C250T mutations in the promoter region of *TERT* (*TERT*p), were assessed through pyrosequencing[5] using the AQ assay of PyroMark Q96 (version 2.5.7) on a PyroMark ID pyrosequencer (Qiagen, Tokyo, Japan), according to the manufacturer's instructions. Real-time polymerase chain reaction was performed to identify KIAA1549-BRAF fusion in Case 1. Sanger sequencing was conducted for *FGFR1*. The central nervous system tumor classification based on methylation profiling was performed using the methylation profiling classifier developed by the German Cancer Research Center (DKFZ)/University Hospital Heidelberg/German Consortium for Translational Cancer Research (DKTK) (the DKFZ classifier, molecularneuropathology.org).[8] We used an Infinium MethylationEPIC BeadChip array (Illumina, San Diego, CA, USA) and uploaded the IDAT files of the samples to their website to obtain the classification and copy-number profiles.

Histological findings

Cases 1 [Figure 2a-f] and 2 [Figure 3a-e] revealed similar histological findings. Hematoxylin and Eosin (HE) staining demonstrated a biphasic pattern of glial and neurocytic architecture [Figures 2a-c and 3a-c]. The former component, comprising an astrocyte-like structure, was positive for GFAP [Figure 2d and 3d], and the latter component, comprising neurocytic rosettes and perivascular pseudorosettes, was positive for synaptophysin [Figure 2e and 3e]. [Figure 2f] shows the HE staining of the recurrent tissue in Case 1 without malignant changes. Other immunohistochemical staining methods demonstrated IDH1 R132H-negativity, O6-methylguanine DNA methyltransferase-negativity, TP53 sparse positivity, and 2–3% on the MIB-1 labeling index; thus, RGNT was diagnosed.

Molecular analysis

The results of molecular analyses are summarized in [Table 1].

Case 1

FGFR1 mutation was assessed using the initial FFPE specimen, but neither N546 nor K656 mutations were detected [Table 1]. Molecular analysis of fresh frozen tissue from the recurrent tumor specimen revealed *FGFR1* K656E mutation [Figure 4a], but no other mutations in *IDH1, IDH2, BRAF, H3F3A, H3F3A, HIST1H3B, TERT*p, or KIAA1549-BRAF fusion [Table 1]. DNA methylation-based classifier using the recurrent tissue specimen indicated that the case matched RGNT with a calibrated score of 0.99. The analysis of copy-number variations calculated from the DNA methylation array showed a balanced profile [Figure 4b].

Case 2

Molecular analyses using the initial FFPE specimen revealed no *FGFR1* mutations but revealed *TERT*p C228T mutation [Table 1 and Figure 4c]. DNA methylation-based classifier classified the case as RGNT, but the calibration score was 0.47 (<0.5). The analysis of copy-number variations calculated from the DNA methylation array revealed a balanced profile [Figure 4d].

DISCUSSION

We have reported two cases of histologically confirmed RGNT located in the midbrain tegmentum using molecular analyses. Brainstem RGNT has a prevalence of 2.7%,[31] and RGNT extending to the tectum has a prevalence of 4.1%.[17] Only one RGNT case located in the midbrain tegmentum has been reported in the literature;[20] thus, our cases are second and third. These two cases demonstrated radiologically similar appearances with gadolinium-enhanced cyst walls and were radically resected using the occipital transtentorial approach. In general, midbrain tumors are challenging for neurosurgeons to operate on,[10] and a cystic tumor is not an optimal target for stereotactic biopsy. Therefore, sufficient tumor tissue cannot be obtained.

Diffuse midline gliomas or tectal gliomas can be differential diagnoses due to the midline, brainstem, or midbrain locations. A report of adult brainstem gliomas included nine lesions located in the midbrain tectum and two in the midbrain tegmentum. One case each exhibited H3K27M positivity on immunohistochemistry,[10] indicating that diffuse midline glioma can be observed in the midbrain. However, the present RGNT cases did not exhibit diffuse infiltrating features or harbor H3K27M mutations, which are prerequisites for diagnosing diffuse midline gliomas.[24] Another report of 22 cases of tectal gliomas found three cases (14%) that presented with a cystic component, and eight (36%) that exhibited contrast enhancement.[23] Although tectal gliomas radiologically resemble midbrain tectal RGNT,[14,28,31] DNA methylation profiling can differentiate tectal gliomas from RGNT.[23]

The initial tumors in Cases 1 and 2 did not harbor *FGFR1* mutations, in contrast to the findings of Sievers *et al*., all of whose RGNT cases carried *FGFR1* hotspot mutations.[29] The unique histological features of RGNT include the presence of neurocytic and glial components.[26] Kitamura *et al*.

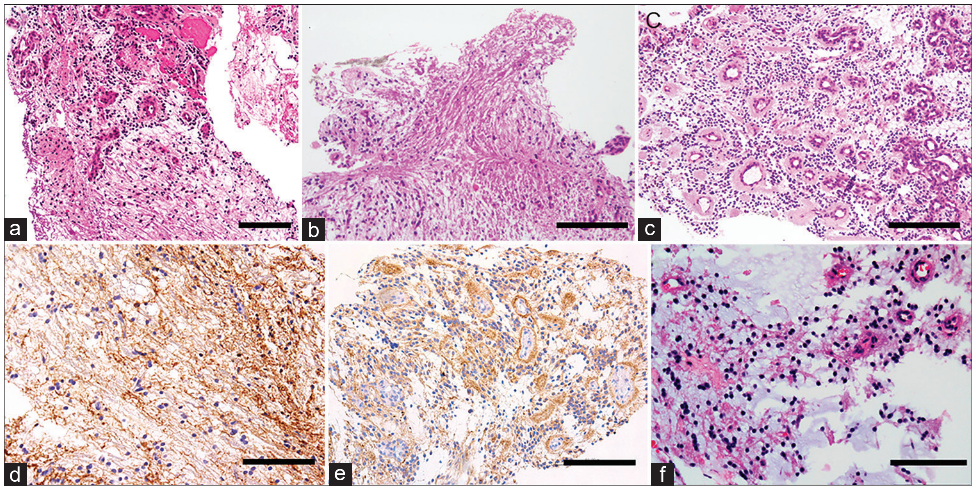

Figure 2: Histological findings of Case 1. Hematoxylin and Eosin (HE) staining demonstrate coexistence of glial and neurocytic components (a). Higher magnification reveals the glial component (b) and neurocytic component (c). The glial component is GFAP positive (d) and the neurocytic component is synaptophysin positive (e). HE staining of the recurrent tissue does not reveal malignant changes (f). The black bar indicates 100 um.

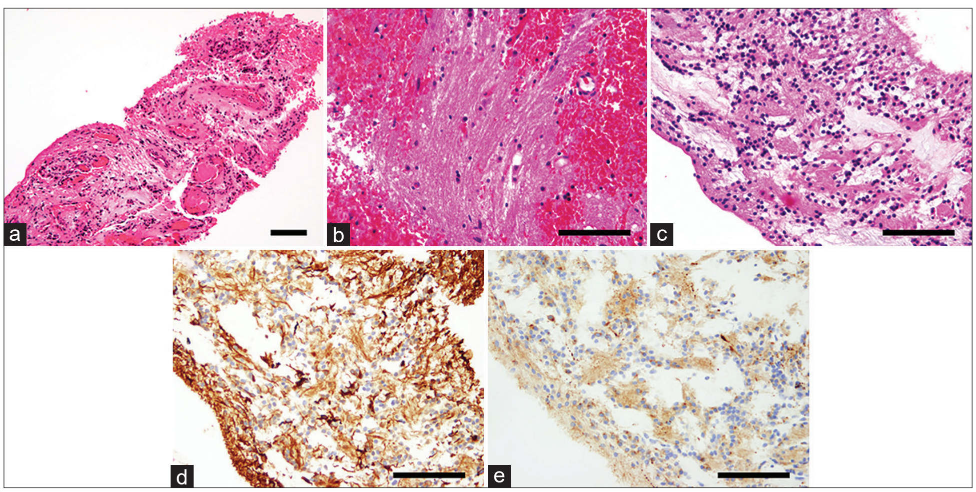

Figure 3: Histological findings of Case 2. Hematoxylin and Eosin staining (a-c) demonstrates glial (b) and neurocytic (c) components, confirmed by GFAP (d) and synaptophysin (e) staining, respectively. The black bar indicates 100 um.

Table 1: Summary of molecular analyses of two cases.

	Status	Tissue	Pyrosequence									RT-PCR
			***FGFR1* N546**	***FGFR1* K656**	***TERT* C228**	***TERT* C250**	***IDH1* R132**	***IDH2* R172**	***H3F3A* K27, G34**	***HIST1H3B* K27**	***BRAF* T599, V600**	**KIAA1549 -BRAF fusion**
Case 1	Initial	FFPE	wt[a]	wt[a]	NA	NA	NA	NA	NA	NA	NA	NA
	Recurrence	Fresh frozen	wt[a]	K656E[a]	wt	wt	wt	Wt	wt	wt	wt	No fusion
Case 2	Initial	FFPE	wt	wt	C228T	wt	wt	Wt	wt	wt	wt	NA

RT-PCR: Real-time PCR, FFPE: Formalin-fixed paraffin-embedded, wt: Wild type, NA: Not applicable, Additional sanger sequencing[a]

microdissected these two components separately and found two patients who harbored *FGFR1* mutations in both components, whereas one harbored an *FGFR1* mutation only in the glial component.[20] Of note, the case with discordance in *FGFR1* mutation was located at the midbrain tegmentum. This case and our study indicate that the location in the midbrain tegmentum and the tumor component affected the *FGFR1* status because a limited amount of tumor tissue might affect the proportion of the two components. Moreover, in 30 RGNT cases in Sievers's study, 14 cases were located in the fourth ventricle, ten in the cerebellum, five in the diencephalon, and one in the mesencephalon (midbrain tectum),[29] but none were located in the midbrain tegmentum. Kitamura's study included cases of RGNT without *FGFR1* mutations located in the lateral ventricle, midbrain tectum, and frontal lobe. Furthermore, Bidinotto *et al.*,[7] Hamauchi *et al.*,[15] and Shibayama *et al.*[27] reported cases of spinal RGNT without *FGFR1* mutations. Therefore, RGNT in rare tumor locations may present with various *FGFR1* mutation statuses [Table 2]. In terms of copy-number variations calculated from the DNA methylation array, both cases presented balanced profiles corresponding to Sievers' series.

We found a *TERT*p mutation in the RGNT cases. Duan *et al.* analyzed *TERT*p mutations in spinal RGNTs found no mutations.[11] Our second case with *TERT*p mutation was classified as RGNT through DNA methylation profiling, but the calibration score was only 0.47. One interpretation is that the small tumor specimen resulted in a disproportion amount of glial and neurocytic components and might have affected the score. An alternative interpretation is that an atypical subset of RGNT with *TERT*p mutation was differentiated from a typical RGNT. In lower grade gliomas, *TERT*p mutation is a poor prognostic factor in IDH-wildtype gliomas, but not in IDH-mutated gliomas.[3] Moreover, *TERT*p mutation is a poor prognostic factor for glioblastoma.[6,19] At present,

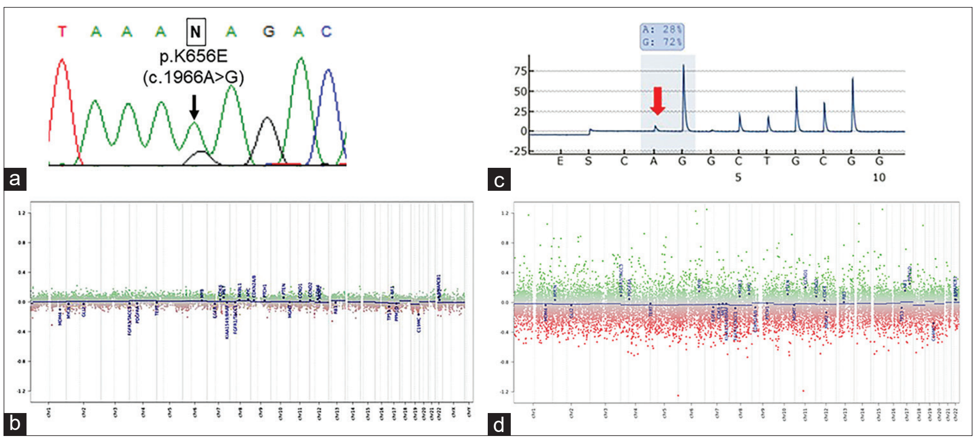

Figure 4: Molecular analysis of Case 1 (a and b) and Case 2 (c and d). Sanger sequencing reveals *FGFR1* K656E mutation (c.1966A>G, arrow) in the recurrent specimen (a), and the DNA methylation-based classification reveals flattened copy-number alterations corresponding to those of RGNT (b). Pyrosequencing reveals a mutation at the C228T of *TERT* promoter (c, red arrow) and the DNA methylation-based classification reveals flattened copy-number alterations corresponding to those of RGNT (d).

Table 2: Summary of RGNT cases without the FGFR1 mutation in unusual tumor locations.

Reference (First Author, Year)	Cases (Age/Sex)	Tumor Location	FGFR1 Status
Bidinotto *et al.*, 2015	33/M	Spine (C6-T3)	wt
Kitamura *et al.*, 2018	30/F	Tegmentum	Glial component: mutation N545K Neurocytic component: wt
Kitamura *et al.*, 2018	67/F	Tectum	wt
Kitamura *et al.*, 2018	55/M	Lateral ventricle	Glial component: wt Neurocytic component: wt
Kitamura *et al.*, 2018	19/M	Frontal lobe	Glial component: wt Neurocytic component: wt
Hamauchi *et al.*, 2019	37/F	Spine (C2-C5)	wt
Shibayama *et al.*, 2021	4/F	Spine (C3-T4)	wt
Present cases	23/F (Initial, case 1)	Tegmentum	wt
	23/F (Recurrence, case 1)	Tegmentum	K656E
Present cases	18/M (Case 2)	Tegmentum	wt

RGNT: Rosette-forming glioneuronal tumor, wt: wild-type the clinical significance of *TERT*p mutation is unknown in RGNT. RGNT occasionally presents with spontaneous shrinkage,[16] as observed in Case 1 of the present study. However, RGNT also presents a malignant clinical course with dissemination[1] and malignant transformation to glioblastoma[18] which may be affected by *TERT*p mutation. Further molecular investigations and clinical follow-ups are required.

CONCLUSION

We have reported two cases of cystic tumor in the midbrain tegmentum, histologically diagnosed as RGNTs. Molecular analyses showed that both cases were negative for *FGFR1* mutation in the initial tumor specimens, and one case presented with *TERT*p mutation. The present cases indicate that RGNT in uncommon tumor locations, including the midbrain tegmentum, may molecularly differ from RGNTs in other common tumor locations, and demonstrate the importance of molecular analyses for understanding the pathophysiology of RGNTs.

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Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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