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CASE REPORT

High-grade glioneuronal tumor with an *ARHGEF2–NTRK1* fusion gene

Kazuhiko Kurozumi[1] · Yoshiko Nakano[2] · Joji Ishida[1] · Takehiro Tanaka[3] · Masatomo Doi[4] · Junko Hirato[5] · Akihiko Yoshida[6] · Kana Washio[7] · Akira Shimada[7] · Takashi Kohno[8] · Koichi Ichimura[2] · Hiroyuki Yanai[9] · Isao Date[1]

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Abstract

Here, we report a highly unusual case of high-grade glioneuronal tumor with a *neurotrophic tropomyosin receptor kinase* (*NTRK*) fusion gene. A 13-year-old girl presented with headache and vomiting and MRI detected two cystic lesions bilaterally in the frontal areas with surrounding edema. The left larger tumor was removed by left frontal craniotomy. The tumor was diagnosed as a high-grade glioneuronal tumor, unclassified. Methylation profiling classified it as a diffuse leptomeningeal glioneuronal tumor (DLGNT) with low confidence. This tumor showed genotypes frequently found in DLGNT such as 1p/19q codeletion without IDH mutation and, however, did not have the typical DLGNT clinical and histological features. RNA sequencing identified an *ARHGEF2* (encoding Rho/Rac guanine nucleotide exchange factor 2)–*NTRK1* fusion gene. The presence of recurrent NTRK fusion in glioneuronal tumors has an important implication in the clinical decision making and opens up a possibility of novel targeted therapy.

Keywords Pediatric brain tumor · *1p19qLOH* · RNA sequencing · *NTRK1*

Introduction

Mixed glioneuronal tumors are rare group of brain tumors that consist of glial and neuronal components. These tumors include gangliogliomas (GG), papillary glioneuronal tumors (PGNT), rosette-forming glioneuronal tumors (RFGNT), diffuse leptomeningeal glioneuronal (DLGNT) tumors, angiocentric gliomas, and others [1–5]. Making histological diagnosis of glioneuronal tumors has been sometimes challenging. However, unique molecular signatures have recently been identified, enabling creation of classification schemes that assign tumors to subtypes based on similarity to defined methylation signatures [6].

Gene fusions resulting from chromosomal rearrangements are an important class of somatic alterations that contribute to development of cancer [7]. For example, *ALK* fusions have been detected in a subset of non-small cell lung cancer and ALK inhibitors have been shown to improve outcomes of patients with *EML4-ALK*-positive tumors [8]. Recently oncogenic and drug-sensitive

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✉ Kazuhiko Kurozumi
kkuro@md.okayama-u.ac.jp

[1] Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

[2] Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan

[3] Department of Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[4] Division of Pathology, St. Marianna University School of Medicine, Kawasaki, Japan

[5] Clinical Department of Pathology, Gunma University Hospital, Gunma, Japan

[6] Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan

[7] Department of Pediatrics, Okayama University Hospital, Okayama, Japan

[8] Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan

[9] Department of Pathology, Okayama University Hospital, Okayama, Japan

Neurotrophic tropomyosin receptor kinase type 1 (*NTRK1*) rearrangements have been identified in lung cancers [9].

We here describe an unusual case of high-grade glioneuronal tumor with *NTRK1* fusion. This fusion is likely to be an oncogenic driver and may serve as a therapeutic target.

Case report

Clinical history and image presentation

A 13-year-old girl presented with headache and vomiting. CT scan revealed hydrocephalus and multiple cystic lesions with calcification in the left and right frontal lobes (Fig. 1a, b). The patient had a history of epilepsy from age of 1 to 6, which had been controlled with phenobarbital, and the CT scan obtained at the age of 3 showed no abnormal lesion.

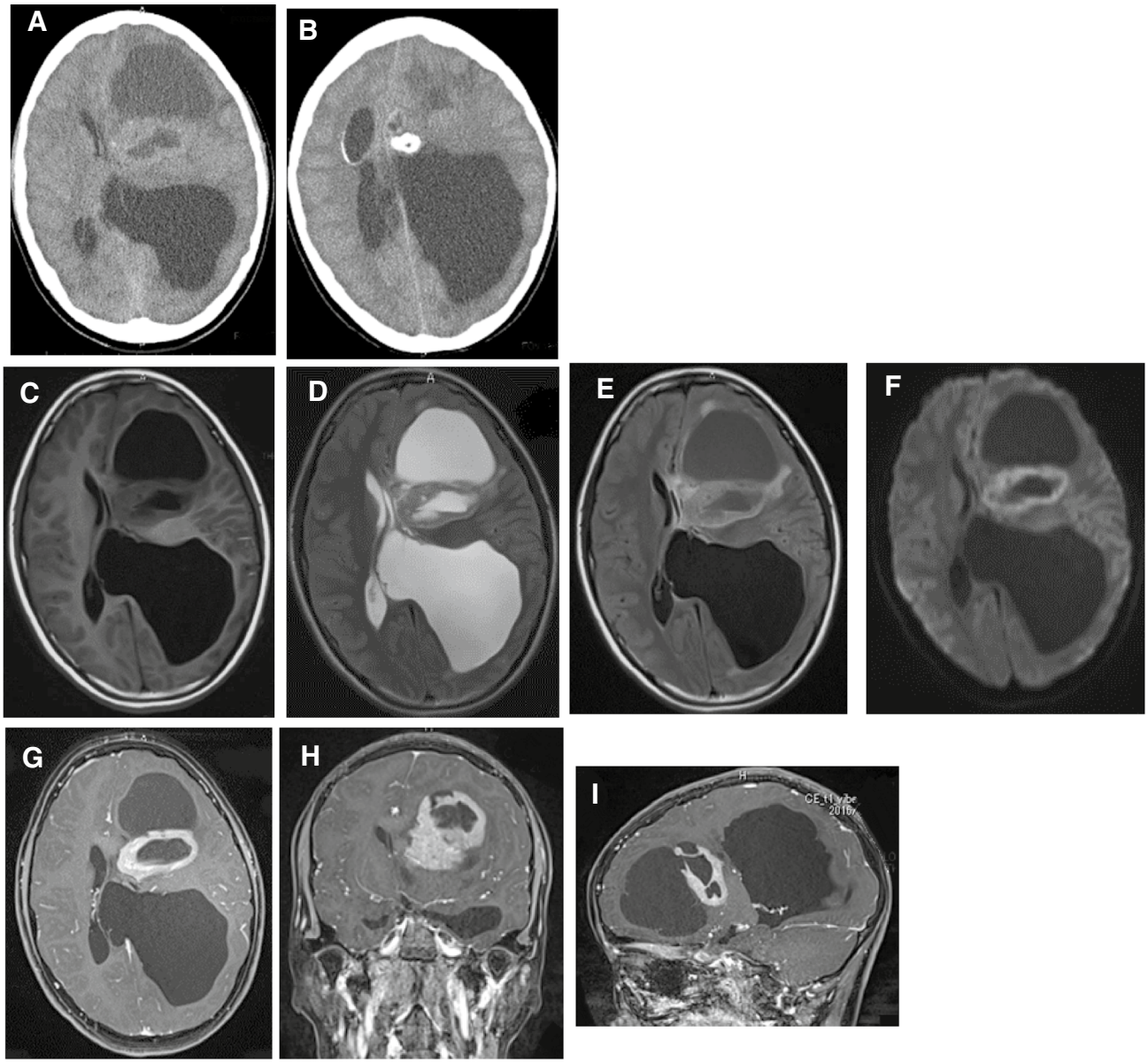


Fig. 1 Computed tomography (CT), magnetic resonance imaging (MRI), and angiography images. **a** Preoperative axial CT image showing a cystic tumor with calcification **b** in the left frontal area and hydrocephalus; brain shift has occurred. Another cystic tumor is visible in the right frontal area. **c** T1- and **d** T2-weighted images showing a well-delineated cystic tumor in the left frontal lobe. **e** Fluid-attenuated inversion recovery magnetic resonance image showing perilesional edema. **f** Diffusion-weighted image showing a hyperintense mass. Preoperative **g** axial, **h** coronal, and **i** sagittal MRI images showing a cystic tumor with ring enhancement in the frontal lobe

MRI detected a solid lesion with an enhancing cystic component in the left frontal area (Fig. 1c–i). Angiography showed feeding arteries from the left lateral thalamostriate artery. Ependymoma, neurocytoma, pilocytic astrocytoma, and anaplastic astrocytoma were considered as our differential diagnosis.

Operative procedure and postoperative course

Left frontal craniotomy was performed, and the left-sided tumor was only partially removed because of copious bleeding; left ventricular drainage was established which lead to consequent reduction in ventricular size (Fig. 2a–c). Because the patient had multiple lesions and was a child, she was treated with temozolomide without radiation therapy on the basis of a local diagnosis of anaplastic oligodendroglioma. The remaining tumor initially decreased in size (Fig. 2d). However, 9 months after the first operation, MRI showed areas of recurrence and reoperation was undertaken (Fig. 2e–h). Intraoperative MRI was used to facilitate maximum resection (Fig. 2i). The removal rate was estimated as > 95% (Fig. 2j). Postoperatively, the patient underwent radiation therapy and chemotherapy with temozolomide. Nine months after the second surgery, she was in good health with normal development and no neurological deficits. MRI showed no recurrence of tumor.

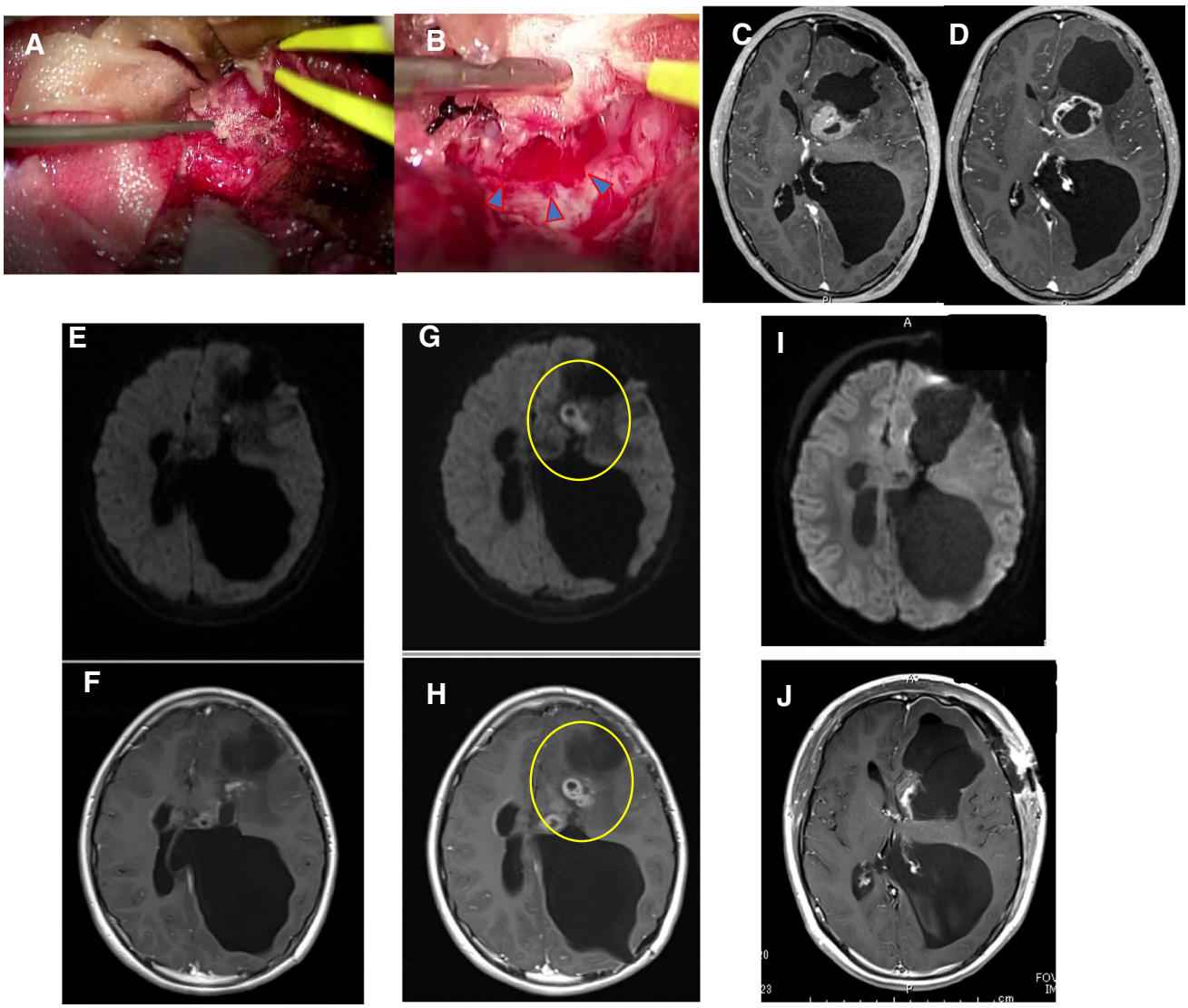


Fig. 2 **a** Intraoperative photograph showed boundary of tumor and skin incision in the left frontal area. Intraoperative image showing **a** reddish lesion and **b** that the lesion is well-demarcated. **c** Postoperative MRI showing residual tumor in the left frontal lobe. **d**–**f** Follow-up MRI showing shrinkage of the residual tumor (**d**, **f**: Gd-enhanced MRI, **e**: DWI). **g** DWI and **h** Gd-enhanced MRI showing a new lesion in the upper frontal area. **i** Intraoperative MRI showing total removal of the recurrence in the left frontal lobe and **j** subtotal removal of residual tumor

Pathological findings

The tumor was sharply demarcated from normal tissue and consisted of small spindle or round cells arranged in dense fibrillary or fascicular patterns with long spindle cells. The nuclei were oval with faint chromatin; however, a few cells with large nuclei and increased chromatin were present. Vascular structures were prominent; however, there was no endothelial proliferation or necrosis. Part of the lesion contained round cells with perinuclear halos (Fig. 3a–e).

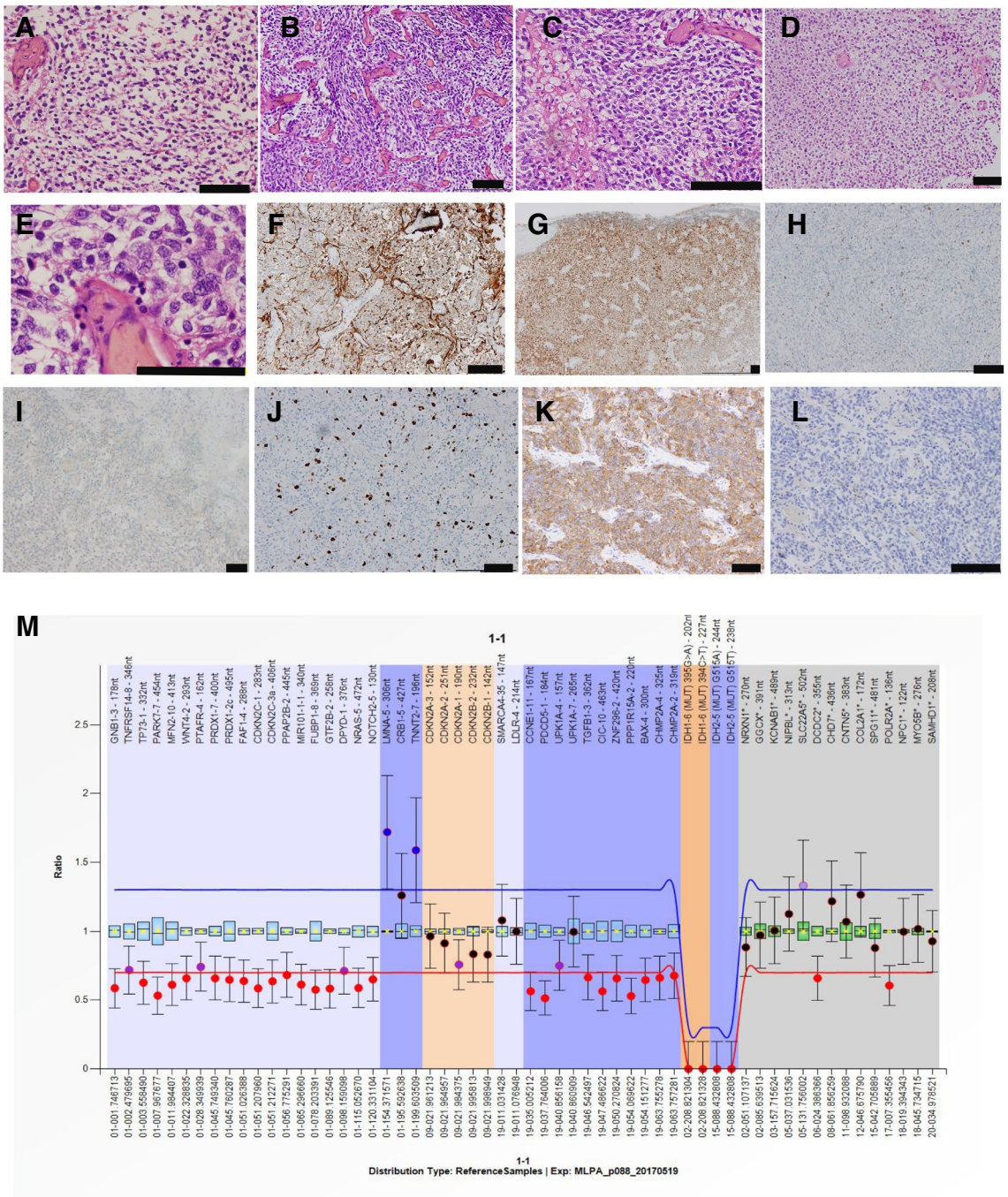


Fig. 3 Pathological findings. Photomicrographs **a**, **b** showing small hypervascular, spindle-shaped astrocytic components and **c**, **d** round cells with perinuclear halos (H&E stain). **e** Mitotic figures are evident. Immunohistochemistry showing some of the cells are **f** GFAP+, **g** ATRX retained, **h** P53 weakly positive, **i** mIDH1−. **j** MIB-1 labelling index is approximately 20%. **k** Synaptophysin+, **l** NeuN−. Bar = 100 µm, **m** Presence of *1p/19q* codeletion shown by MLPA

On immunohistochemical investigation (Fig. 3f–l), some of the tumor cells were positive for glial fibrillary acidic protein, whereas in the less dense areas, they were focally positive for only oligodendrocyte transcription factor 2. The cells were NeuN, isocitrate dehydrogenase R132H, and H3 K27M negative and synaptophysin positive. The Ki-67 index was approximately 20%. p53 protein was only focally positive (< 5% of tumor cells), and alpha-thalassemia/mental retardation syndrome X-linked protein expression was retained. Initially, this tumor was diagnosed as oligodendroglioma.

During the second operation, two specimens were resected, comprising a newly developed and a residual lesion. The new lesion consisted of diffusely arranged tumor cells with perinuclear halos, small, round, granular, chromatin-rich nuclei, and eosinophilic cytoplasm. Those tumor cells had atypical nuclei that varied in size and shape. There were more than 50 mitotic figures per 10 high-power fields. Microvascular proliferation was also identified.

The residual lesion had large, round, eosinophilic tumor cells with irregular granular nuclei and sparsely distributed chromatin and also contained atypical astrocytes in reticulated small vessels. Ganglion cells with cytoplasm of unclear eosinophilic Nissl were also found. In this area, no mitotic figures were clearly identified.

On immunohistochemical investigation, GFAP was negative in the recurrence, but positive in atypical astrocytes and some of the mid-to-large tumor cells in the residual tumor. Nestin and Olig2 were positive in both lesions. A few tumor cells in the recurrence were weakly positive for synaptophysin and neurofilament protein, whereas most of the residual tumor cells were positive for these proteins. NeuN was negative in both lesions.

Central pathology review for this tumor resulted in a final diagnosis of high-grade glioneuronal tumor, which consisted of small spindle or round cells arranged in dense fibrillary or fascicular patterns with long spindle cells and contained round cells with perinuclear halos. Immunohistochemistry staining showed that some of the tumor was positive for synaptophysin and neurofilament protein, but contained oligodendrocyte-like cells, which are often present in glioneuronal tumors. Our differential diagnoses of the tumor with neuronal component were extraventricular neurocytomas and oligodendroglioma with neuronal differentiation. Our patient's tumors were not well-differentiated into small neuronal cells and had cells of various other morphologies, indicating that it was not an extraventricular neurocytoma. The presence of immature ganglion-like cells indicated that they were not oligodendrogliomas with neuronal differentiation. The tumor was finally diagnosed as a high-grade glioneuronal tumor, unclassified.

Genetic analysis

In both initial and recurrent specimens, pyrosequencing showed no hotspot mutations in *IDH1/2*, *BRAF*, *H3F3A*, *HIST1H3B*, *TERTpromoter* [10, 11], or *FGFR1*. *KIAA1549–BRAF* fusion was not detected by RT-PCR [12]. 1p/19q codeletion was detected by fluorescence in situ hybridization (FISH, Abbott Molecular) and multiplex ligation-dependent probe amplification (SALSA MLPA probemix P088-C2 Oligodendroglioma 1p-19q, MRC-Holland) (Fig. 3m).

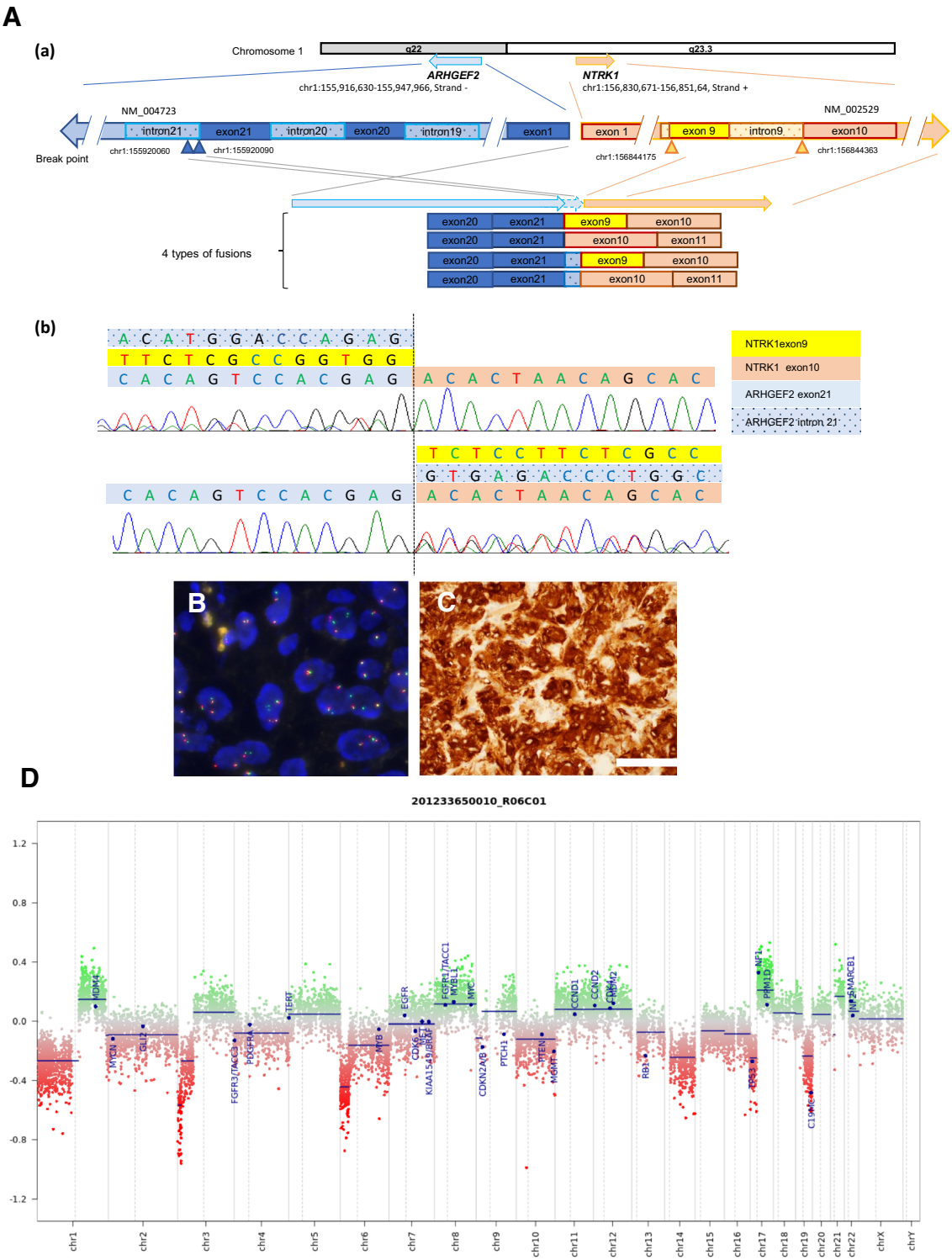
In initial specimen, target sequencing using the Brain Tumor Panel 93 (Ion Torrent) (Supplementary M&M) showed no significant pathogenic variants. These genotypes were not compatible with any tumor type defined in the revised WHO classification [13].

RNA sequencing identified a fusion gene, *ARHGEF2–NTRK1* fusion (Exon21–Exon10, Exon20–Exon10). This fusion was validated by RT-PCR and Sanger sequencing (Fig. 4a). FISH analysis demonstrated a signal pattern that did not meet the pre-determined criteria for NTRK1 rearrangement. However, the signal pattern was atypical, because the majority (57%) of tumor cells harbored isolated 5′ (green) signals in addition to mildly increased (up to 6) copies of fused 3′/5′signals. Pan-TRK and TRKA immunohistochemistry showed strong staining in the tumor cells. (Fig. 4b, c).

Methylation profiling was performed using an Infinium HumanMethylation EPIC BeadChip (Illumina, San Diego, CA, USA), and the methylation classifier developed by German Cancer Research Center (DKFZ)/University Hospital Heidelberg/German Consortium for Translational Cancer Research (DKTK) (the DKFZ classifier, molecularneuropathology.org) was performed by uploading the idat files of the sample to their website as instructed. It was matched as methylation class family member of "methylation class diffuse leptomeningeal glioneuronal tumor (DLGNT)", with a calibrated score 0.61. However, the interpretation was no match (score < 0.9). The copy number variation profile of the methylation array data confirmed a combined loss of 1p/19q, among numerous other copy number alterations affecting whole chromosomes/chromosomal arms (Fig. 4d). There was no evidence of BRAF duplication, the finding consistent with the absence of BRAF fusion, which are frequent changes observed in DLGNT, determined by RT-PCR as above.

Discussion

We present a case of a histologically unclassifiable glioneuronal tumor with an *ARHGEF2–NTRK1* fusion that developed in a pediatric patient. This tumor shared genotypes



frequently found in DLGNT such as codeletion of 1p/19q with wild-type IDH and, nevertheless, did not have the typical DLGNT histological features. The identification of this rare fusion opens a new possibility of targeted therapy for this rare subset of pediatric brain tumors.

The Trk receptor family comprises three transmembrane proteins referred to as TrkA, TrkB, and TrkC that are encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively [14]. These receptor tyrosine kinases are expressed in human neuronal tissue and play an essential role in the development and function of the nervous system

◂**Fig. 4** RNA sequencing and validation with RT-PCR, FISH, and immunohistochemistry. **a** Scheme of the ARHGEF2 (1q22) and NTRK1 (1q23.3) fusion. Two break points (△) were identified in each gene and resulted in four types of fusions: ARHGEF2 exon 21–NTRK1 exon 9; ARHGEF2 exon 21–NTRK1 exon 10; ARHGEF2 intron 21 (30 bases adjacent to exon 21)–NTRK1 exon 9; and ARHGEF2 intron 21 (30 bases adjacent to exon 21)–NTRK1 intron 10. **b** Results of Sanger sequencing of the RT-PCR product using the forward primer (upper panel) and the reverse primer (lower panel). The mixed sequences observed before or after the break points were due to the coexistence of multiple fusion transcripts as schematically presented in (**a**). Mixed sequences are dissolved and indicated above the electropherograms. **b** FISH: the signal pattern was atypical, because the majority (57%) of tumor cells harbored isolated 5′ (green) signals in addition to mildly increased (up to 6) copies of fused 3′/5′signals. **c** Immunohistochemistry: The tumor cells showed diffuse strong reactivity to Pan-TRK antibody in the cytoplasm. Bar = 100 µm. **d** Copy number variation profile provided in the report from the DKFZ methylation classifier. It confirmed 1p/19q codeletion as well as presence of other copy number variations

through activation by neurotrophins. Gene fusions involving *NTRK* genes lead to transcription of chimeric Trk proteins with constitutively activated or overexpressed kinase function, conferring oncogenic potential [14].

The Trk receptor abnormalities have recently emerged as targets for cancer therapy. There is a limited number of reported Trk receptor tyrosine-kinase inhibitors in the literature and only a few of these have been tested in clinical trials [14–16]. Entrectinib is an orally bioavailable inhibitor of the TK TrkA, TrkB, and TrkC, as well as of C-ros oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) [15, 17]. LOXO-101 is a pan-Trk inhibitor with highly selective activity against the Trk kinase family [18]. Altiratinib (DCC-2701) [19] and sitravatinib (MGCD516) [20] are multikinase inhibitors with reported in vitro activity against TrkA and TrkB, and were both recently tested in phase I clinical trials.

NTRK1 fusions have been identified in several types of pediatric brain tumors. Zheng et al. [21] reported one in-frame fusion involving exon 21 of *ARHGEF2* (encoding Rho/Rac guanine nucleotide exchange factor 2) in glioblastomas and exon 10 of *NTRK1*. Structural variants generating fusion genes were found in 47% of diffuse intrinsic pontine gliomas (DIPGs) and non-brainstem high-grade gliomas (NBS-HGGs), with recurrent fusions involving the neurotrophin receptor genes NTRK1, NTRK2, and NTRK3 in 40% of NBS-HGGs in infants [22]. These series were infant, whereas our case was an adolescent. In addition, the fusions involving *NTRK1,NTRK2,* or *NTRK3* with undetermined fusion partners have been reported in single cases of DLGNT [5].

DLGNT presents as a plaque-like subarachnoid tumor, commonly involving the basal cisterns and interhemispheric fissure of children but lacking intraparenchymal tumor [23]. DLGNT is one of the rare tumor entities presenting as primary malignant meningitis with less than 100 cases reported to date [24]. The imaging of DLGNT shows predominantly spinal and infratentorial leptomeningeal thickening, that is, T2-hyperintense and usually non-contrast enhancing [25]. Our case did not present meningitis nor have diffuse leptomeningeal dissemination.

Our patient's tumor showed an intriguing genotype: *IDH* wild-type and 1p/19q codeletion. Codeletion of the entire arms of 1p/19q is typically observed in oligodendrogliomas and, however, always accompanied by IDH1/2 mutations. No tumor with this genotype is defined in the WHO2016 classification. Interestingly, *TERT* mutation, which is almost always found in 1p/19q codeleted oligodendroglioma, was not identified in this tumor. Tabouret et al. reported that anaplastic oligodendrogliomas with codeletion of *1p/19q* with wild-type *IDH* are exceptional [26]. Extraventricular neurocytoma has certainly been reported to harbor wild-type *IDH1/2* and *1p/19q* codeletion[13]. However, histologically, these tumors were not extraventricular neurocytomas. Thus, this tumor did not match any entity defined in the WHO 2016 classification.

By means of methylation-based molecular classification, Deng et al. [5] recently proposed that DLGNT comprises two molecularly defined subgroups (DLGNT methylation class [MC]-1 and DLGNT MC-2) with distinct clinical and genetic features. They reported that codeletion of 1p/19q with wild-type IDH was frequently detected in DLGNT-MC-1. The genotype of our tumor was consistent with DLGNT-MC-1, although histologically not compatible with DLGNT. Interestingly, NTRK fusions (see above) were observed only in the DLGNT-MC-1 group. The DKFZ methylation classifier reported that it matched to methylation class family member of DLGNT, however, with low calibrated score was low (0.61). Based on the above genotype/epigenotype, the tumor may be considered either as an atypical DLGNT or a novel subset. The diagnosis of tumors, where genotypes and histology do not agree with the established entity, is a challenging problem. Our case may be useful to re-define the entity in the future WHO Classification.

Conclusions

Here, we present a case of high-grade glioneuronal tumor with *NTRK1* fusion. The tumor was considered highly unusual that 1) it developed in an adolescent patient and 2) it shared genotypes frequently found in DLGNT such as 1p/19q codeletion without IDH mutation and, however, did not have the typical DLGNT histological features. Methylation classification confirmed that it belonged to a member of glioneuronal tumor, but did not match any existing tumor entity. Our experience of this case strongly suggested that glioneuronal tumors need to be screened for *NTRK1* fusion,

regardless of histological subtypes or patients' age. Detecting this fusion gene may lead to a better understanding of oncogenesis and development of new therapeutic options.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

1. Nagaishi M, Nobusawa S, Matsumura N et al (2016) SLC44A1–PRKCA fusion in papillary and rosette-forming glioneuronal tumors. J Clin Neurosci 23:73–75
2. Bandopadhayay P, Ramkissoon LA, Jain P et al (2016) MYB-QKI rearrangements in angiocentric glioma drive tumorigenicity through a tripartite mechanism. Nat Genet 48:273
3. Louis DN (2007) WHO classification of tumours of the central nervous system. Copenhagen, WHO Regional Office Europe
4. Momota H, Shimoyama Y (2015) Recurrent papillary glioneuronal tumor presenting as a ganglioglioma with the BRAF V600E mutation. Neuropathology 35:603–605
5. Deng MY, Sill M, Chiang J et al (2018) Molecularly defined diffuse leptomeningeal glioneuronal tumor (DLGNT) comprises two subgroups with distinct clinical and genetic features. Acta neuropathologica 136:239–253
6. Capper D, Jones DT, Sill M et al (2018) DNA methylation-based classification of central nervous system tumours. Nature 555:469
7. Yoshihara K, Wang Q, Torres-Garcia W et al (2015) The landscape and therapeutic relevance of cancer-associated transcript fusions. Oncogene 34:4845
8. Shaw AT, Kim D-W, Nakagawa K et al (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394
9. Vaishnavi A, Capelletti M, Le AT et al (2013) Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med 19:1469
10. Arita H, Yamasaki K, Matsushita Y et al (2016) A combination of TERT promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas. Acta Neuropathol Commun 4:79
11. Arita H, Narita Y, Fukushima S et al (2013) Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol 126:267–276
12. Jones DTW, Kocialkowski S, Liu L et al (2008) Tandem duplication producing a novel oncogenic *BRAF* fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68:8673–8677
13. Louis DN, Perry A, Reifenberger G et al (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820
14. Amatu A, Sartore-Bianchi A, Siena S (2016) NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open 1:e000023
15. Rolfo C, Ruiz R, Giovannetti E et al (2015) Entrectinib: a potent new TRK, ROS1, and ALK inhibitor. Expert Opin Investig Drugs 24:1493–1500
16. Lange AM, Lo H-W (2018) Inhibiting TRK proteins in clinical Cancer therapy. Cancers 10:105
17. Alvarez-Breckenridge C, Miller JJ, Nayyar N et al (2017) Clinical and radiographic response following targeting of BCAN-NTRK1 fusion in glioneuronal tumor. NPJ Precis Oncol 1:5
18. Burris HA, Shaw AT, Bauer TM et al (2015) Pharmacokinetics (PK) of LOXO-101 during the first-in-human phase I study in patients with advanced solid tumors: interim update. In: AACR-2015 2015, Abstract No. 4529
19. Smith BD, Kaufman MD, Leary CB et al (2015) Altiratinib inhibits tumor growth, invasion, angiogenesis, and microenvironment-mediated drug resistance via balanced inhibition of MET, TIE2, and VEGFR2. Mol Cancer Ther 14:2023–2034
20. Patwardhan PP, Ivy KS, Musi E et al (2016) Significant blockade of multiple receptor tyrosine kinases by MGCD516 (Sitravatinib), a novel small molecule inhibitor, shows potent anti-tumor activity in preclinical models of sarcoma. Oncotarget 7:4093
21. Zheng Z, Liebers M, Zhelyazkova B et al (2014) Anchored multiplex PCR for targeted next-generation sequencing. Nat Med 20:1479
22. Wu G, Diaz AK, Paugh BS et al (2014) The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet 46:444
23. Southwell DG, Garcia PA, Berger MS et al (2012) Long-term seizure control outcomes after resection of gangliogliomas. Neurosurgery 70:1406–1414
24. Reifenberger G, Rodriguez F, Burger P et al (2016) Diffuse leptomeningeal glioneuronal tumour. WHO Classification of Tumours of the Central Nervous System, Revised. 4th edn. International Agency for Research Centre, Lyon, pp 152–155.
25. Schwetye KE, Kansagra AP, McEachern J et al (2017) Unusual high-grade features in pediatric diffuse leptomeningeal glioneuronal tumor: comparison with a typical low-grade example. Hum Pathol 70:105–112
26. Tabouret E, Nguyen AT, Dehais C et al (2016) Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort. Acta Neuropathol 132:625–634