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CASE REPORT

A long-term survivor of pediatric midline glioma with *H3F3A* K27M and *BRAF* V600E double mutations

Yoshiko Nakano[1,2] · Kai Yamasaki[1,2] · Hiroaki Sakamoto[3] · Yasuhiro Matsusaka[3] · Noritsugu Kunihiro[3] · Hiroko Fukushima[4] · Takeshi Inoue[4] · Mai Honda-Kitahara[1] · Junichi Hara[2] · Akihiko Yoshida[5] · Koichi Ichimura[1]

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Abstract

We report a case of 2-year-old female with lateral ventricular glioma harboring both *H3F3A* K27M and *BRAF* V600E mutations. By the methylation analysis, the tumor was classified as a diffuse midline glioma H3 K27M mutant, WHO grade IV. However, the tumor was pathologically low-grade and likely localized rather than diffusely infiltrating. Further, the patient has survived more than 8 years after gross total resection of the tumor. Whereas both *H3F3A* K27M and *BRAF* V600E have been reported as poor prognostic markers in pediatric glioma, our case, along with several other reported cases, suggests that the coexistence of these two mutations might not indicate poor prognosis. The case emphasizes the importance of comprehensive assessment based on pathological, genetic and clinical findings and calls for further investigations of non-diffuse glioma with *H3F3A* K27M and glioma with *H3F3A* K27M and *BRAF* V600E.

Keywords *BRAF* V600E · *H3F3A* K27M · Pediatric glioma · Double mutations · Prognosis

Introduction

The importance of genetic analysis of pediatric brain tumors has dramatically increased in recent years. First, diagnosis based on the revised 2016 WHO classification of tumors of the central nervous system requires the analysis of certain missense mutations, fusion genes, and amplifications/deletions of certain chromosome regions [1, 2]. Second, for medulloblastomas, a molecular classification is used both as a prognostic marker and for stratification into risk groups [3]. Third, some genetic abnormalities, such as the *BRAF* V600E mutation, and the *NTRK*, *MET*, and *ALK/ROS1* fusion genes, can be effective therapeutic targets [4–7]. In addition, methylation-based classification has become a powerful tool [8]. For example, posterior fossa ependymoma is molecularly classified into the PFA and PFB subgroups, which have distinct clinical features [9–11]. Strum et al. reported that CNS–PNET could be reclassified into several novel subgroups [12]. Further, in 2018, the German Cancer Research Center (DKFZ) demonstrated the utility and accuracy of methylation-based classification of all brain tumor entities, and this classification tool is now available on their website [13].

Here, we report a case of pediatric midline low-grade glioma (LGG) in the lateral ventricle harboring both the *H3F3A* K27M and *BRAF* V600E mutations. Based on the methylation analysis, the tumor was classified as a "diffuse midline glioma with an H3 K27M mutant." However, the pathological and clinical features were distinct from those of this entity.

Yoshiko Nakano and Kai Yamasaki contributed equally to this work.

✉ Yoshiko Nakano
yonakano@ncc.go.jp

1 Division of Brain Tumor Translational Research, National Cancer Center Research Institute, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

2 Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan

3 Department of Pediatric Neurosurgery, Osaka City General Hospital, Osaka, Japan

4 Department of Pathology, Osaka City General Hospital, Osaka, Japan

5 Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan

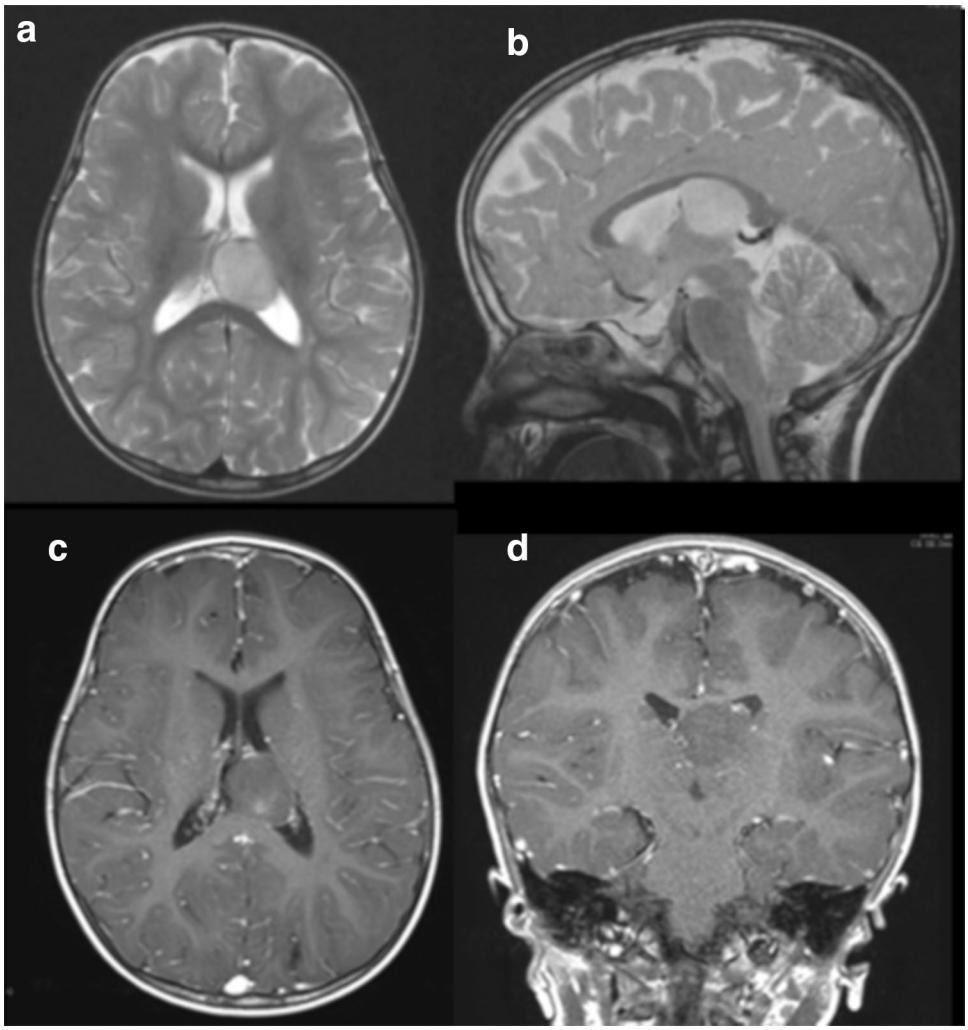

Fig. 1 Radiological imaging of the case. **a**–**d** T2-weighted (**a**, **b**) and contrast-enhanced T1-weighted MRI (**c**, **d**) demonstrating a circumscribed, partially enhanced mass in the left ventricle

Clinical summary

A 2-year-old female was referred to our hospital because of an intraventricular mass. The patient was born at 33 weeks gestation and she stayed in the hospital for 1 month because of her low birth weight. At the age of 1 year, she presented with epilepsy, which was controlled with an antiepileptic drug. MRI showed a nodular mass in the left ventricle (Fig. 1a–d). The patient underwent gross total resection of the mass because it was slowly growing. Based on the intraoperative findings, the border between the tumor and the normal thalamic tissues was partially unclear, whereas that between the tumor and ventricular lumen was clear. The local pathological diagnosis based on the 2007 WHO classification was oligoastrocytoma. She received no chemotherapy or radiotherapy and has survived without the evidence of disease for more than 8.5 years. After the publication of the revised fourth edition of the WHO classification in 2016, a molecular analysis and a review of the central pathology were performed (Fig. 2, 3a–f).

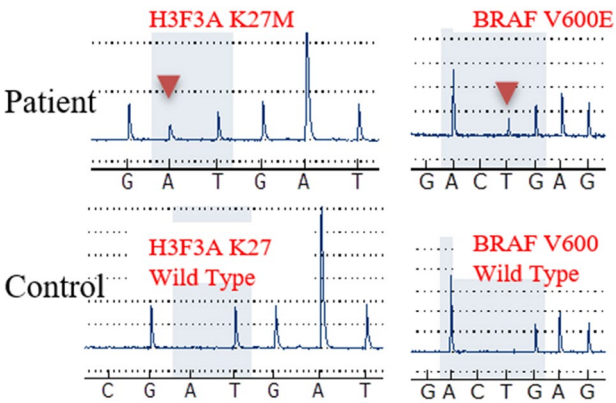

Fig. 2 Pyrosequencing results showing the *BRAF* V600E and *H3F3A* K27M mutations

Pathological findings

The tumor consisted of moderately cellular glial proliferation within a fibrillary background. The lesional cells

were relatively uniform in appearance and were round, oval, and spindle shaped. Pleomorphic, giant, epithelioid, rhabdoid, and piloid cells were lacking. The round cell component was associated with a perinuclear halo and resembled oligodendroglial tumors, whereas the spindle cells resembled the astrocytic lineage (Fig. 3a, b). There were a small number of rosette-like glial structures (Fig. 3c). Dysmorphic ganglion cells were absent. Mitotic figures were not detected. Necrosis, microvascular proliferation, Rosenthal fibers, and eosinophilic granular bodies were not observed. Focal microcalcification was present. Immunohistochemically, the tumor cells were positive for glial fibrillary acidic protein and S100 protein but were negative for epithelial membrane antigen and synaptophysin. In agreement with the molecular findings, they were immunopositive for H3 K27M, with a concomitant loss of H3K27me3 expression (Fig. 3d, e). BRAF V600E immunohistochemistry was positive (Fig. 3f), and H3 K27M and BRAF V600E staining appeared to be present in the same cells. The tumor retained ATRX expression, and p53 staining showed wild-type labeling. The MIB1 labeling index was 6.8%. The tumor mostly lacked transgressing neurofilament–positive fibers, and there was no evidence of diffuse infiltration.

Molecular analysis

DNA and RNA were extracted from frozen tumor tissue using the DNeasy Blood and Tissue Kit (Qiagen, Tokyo, Japan) and the miRNeasy Mini Kit (Qiagen, Tokyo, Japan), respectively. Hot spot mutations, including *IDH1* R132, *IDH2* R172, *BRAF* T599, *BRAF* V600, *H3F3A* K27, *H3F3A* G34, *TERT p*romoter C250, *TERT* promoter C228, *FGFR1* N546, and *FGFR1* K656, were analyzed by pyrosequencing using the AQ assay with a PyroMark Q96 (Qiagen, Tokyo, Japan). The polymerase chain reaction (PCR) for pyrosequencing and the pyrosequencing assay were performed as previously described [14]. Primer sequences are listed in supplementary Table 1. The *BRAF* V600E and *H3F3A*

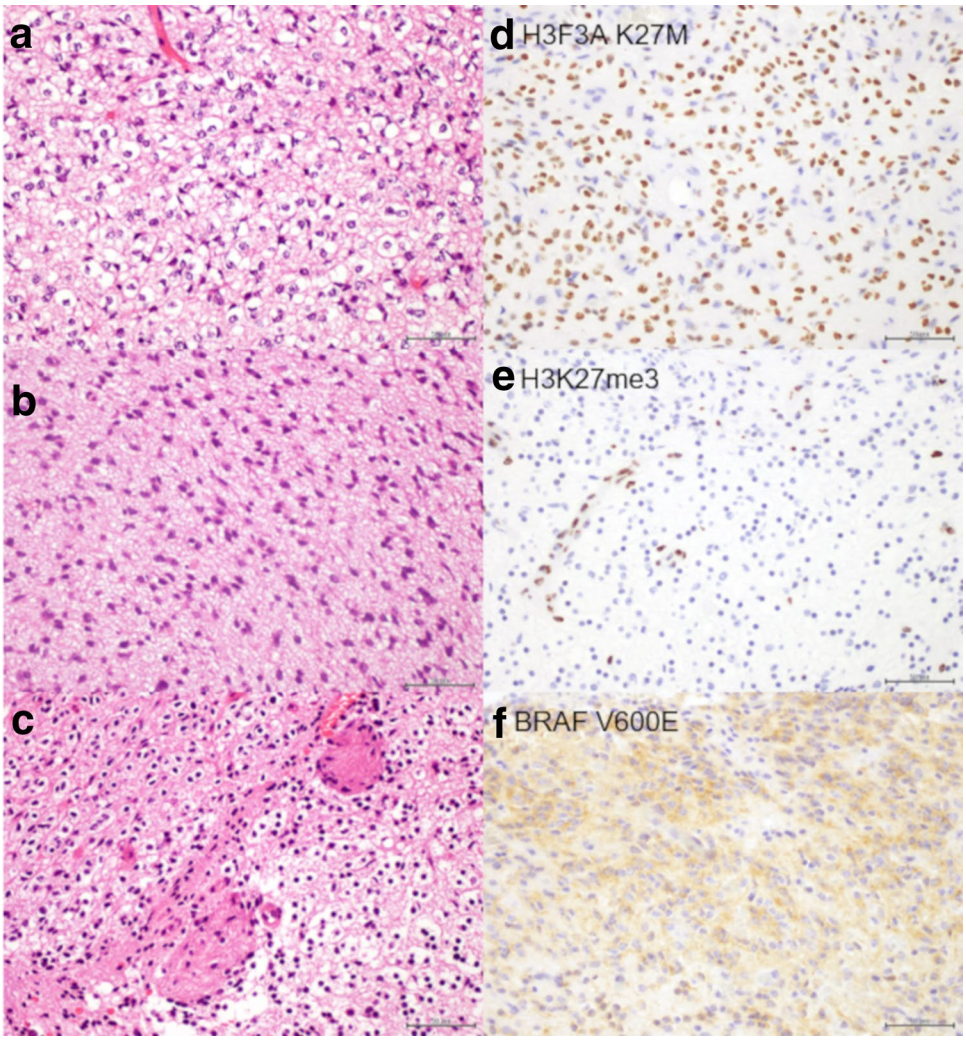

Fig. 3 Histological and immunohistochemical findings. The tumor consisted of glial proliferation with oligodendroglial (**a**) and astrocytic (**b**) morphology. There were a small number of rosette-like glial structures (**c**). Immunohistochemically, the tumor cells were positive for H3 K27M (**d**), with a concomitant loss of H3K27me3 expression (**e**). BRAF (V600E) immunohistochemistry was also diffusely positive (**f**)

K27M mutations were detected at frequencies of 40% and 46%, respectively (Fig. 2). The hot spot mutation in other analyzed genes was not detected. Multiplex ligation-dependent probe amplification (MLPA) using the SALSA MLPA probemix P088-C2 (MRC-Holland, Amsterdam, the Netherlands) revealed no *CDKN2A* deletion. The existence of *KIAA1549-BRAF* fusion was assessed by reverse transcriptase PCR using previously reported primers and it was not detected [15].

A methylation classifier assay was then performed. DNA methylation was analyzed using an Infinium HumanMethylation450 BeadChip array (Illumina, San Diego, CA, USA), and the IDAT-files from the sample were uploaded to the online classifier developed by the DKFZ (https://www.molecularneuropathology.org/mnp). The tumor was classified as a "diffuse midline glioma, H3 K27M mutant" with a calibrated score of 0.98.

Discussion

Here, we report a case of midline glioma harboring concurrent *H3F3A* K27M and *BRAF* V600E mutations. The tumor was classified as a "diffuse midline glioma, H3 K27M mutant, WHO grade IV" by methylation analysis. However, in several aspects, the case was not entirely compatible with typical diffuse midline gliomas with *H3F3A* K27M mutations. Importantly, the present

Table 1 Reported cases of pediatric intracranial tumors harboring the *H3F3A* K27M and *BRAF* V600E double mutations

Age (y/o)	Location	Histology	Sugrery (extent of resection)	Chemotherapy	Radiotherapy	Outcome (foll-low-up period)	References
Infant	Pons	AA grade3	Yes (NA)	NA	NA	Alive (>9 years)	Karremann [20]
2	Ventricle	LGG, NOS	Yes (GTR)	No	No	Alive (>8.5 years)	Present case
2	Pons	Diffuse LGG, NOS	Yes	No	No	Alive (>5.2 years)	Nguyen [36]
5	Thalamus	Diffuse glioma with focal PXA like	NA	NA	NA	NA	Solomon [37]
6	Pons	GG	Yes (residual tumor+)	No	No	Alive (>0.8 years)	Pagès [35]
7	Thalamus	Low grade astroc-toma	Biopsy	Yes	Yes	Dead (1.2 years)	Ryall [38]
8	Thalamus	GG	Yes (residual tumor+)	No	No	Alive (>7 years)	Pagès [35]
10	Peduncle	GG	Yes (residual tumor+)	No	No	Alive (NA)	Pagès [35]
10	Diencephalon	DA	NA	NA	NA	NA	Zhang [34]
10	Brainstem	PA with aggres-sive features vs diffuse HGG, NOS	Yes (N/A)	Yes	No	Dead (1.0 years)	Nguyen [36]
10	Midline	GBM	NA	NA	NA	Dead (5.3 years)	Mackay [22], Wu [7]
12	Thalaus	GG	Yes (residual tumor+)	No	No	Dead (8 years)	Pagès [35]
14	Spinal	GG	Yes (residual tumor+)	No	No	Alive (>1 years)	Pagès [35]
16	Pineal	PXA with aggres-sive features, grade III GG	Yes (NA)	No	No	Dead (3 years)	Nguyen [36]
17	Thalamus	Glioblastoma	NA	No	No	Dead (1.4 years)	Ryall [38]
Pediatric, >5 y/o	Midline	GG → AGG (malingnant transformation)	NA	NA	NA	NA	Mistry [35]

AA anaplastic astrocytoma, *NA* no data available, *LGG* low grade glioma, *NOS* no otherwise specified, *GTR* gross total resection, *GG* ganglioglioma, *DA* diffuse astrocytoma, *PA* pilocytic astrocytoma, *HGG* high grade glioma, *GBM* glioblastoma, *PXA* pleomorphic xanthoastrocytoma, *AGG* anaplastic ganglioglioma

tumor was likely localized rather than diffusely infiltrating. Radiologically, it seemed well circumscribed; that is most of the tumor surface being surrounded by cerebral fluid. However, the border between tumor and normal thalamic tissue was partly unclear. Histologically, there was a paucity of transgressing neurofilament, suggesting a non-diffuse process, although this finding needs to be interpreted with caution because it may simply reflect the intra-ventricular growth. "Diffuse midline glioma with H3 K27M mutant WHO grade IV" was introduced as a new entity of WHO classification 2016, based on the knowledge at that time that recurrent mutation at K27 in *H3F3A, HIST1H3B,* and *HIST1H3C* is detected in high-grade glioma (HGG) from the pons, thalamus and spinal cord and that these mutations occur exclusively in diffuse midline gliomas, as stated in WHO blue book [2, 16]. However, some cases of non-diffuse glioma with H3F3A K27M were subsequently reported [17, 18]. Accordingly, Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO (cIMPACT-NOW) up date 2 emphasizes that "diffuse," "midline," "glioma" and "H3 K27M-mutant" are requirements for the diagnosis of diffuse midline glioma with H3 K27M [16]. Therefore, based on the cIMPACT-NOW-modified view of the WHO Classification, the present case seems incompatible with the "diffuse mid-line glioma with H3 K27M" designation. Whereas some of the reported localized gliomas with H3 K27M demonstrated the histology of well-established entities, the present case was difficult to classify histologically. The original diagnosis of oligoastrocytoma is likely invalid due to its mostly localized nature. Although histological findings, along with the presence of the *BRAF* mutation, may suggest a possibility of pilocytic astrocytoma, characteristic features of that entity were mostly lacking, including piloid or microcystic loose tissues, Rosenthal fibers, eosinophilic granular bodies, and microvascular proliferation. The morphology did not fit well with other *BRAF*-mutant localized gliomas either, such as gangliogioma and pleomorphic xanthoastrocytoma. Taken together, the present case would be best labeled descriptively as low-grade glioma, likely localized, not elsewhere classified as per the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO cIMPACT-NOW update 1 [16, 19].

Classification based on methylation profiles is a highly robust method for facilitating diagnosis and subgrouping brain tumors. However, the interpretation of methylation-based classification may sometimes require caution. H3 K27M would cause a considerable change in the tumor's epigenetic landscape, which may mask fine differences among K27M-harboring tumors, some of which are not compatible with the definition of diffuse midline glioma with H3 K27M mutation, as in our case. Other mutations, such as *BRAF,* may on the other hand less affect epigenetic landscape, which could make them more difficult to distinguish by methylation profiling alone. The principle of defining a tumor entity, whether using should histology, genetics, methylation, or their combination, warrants further discussion.

In addition to the location and histological findings presented above, the patient's age at diagnosis and her relatively long survival of the present case are also unusual for H3F3A K27M–positive glioma. The *H3F3A* K27M mutation is characteristically detected in pediatric gliomas. The mean age at diagnosis is 6–10 years [6, 20–22]. Most *H3F3A* K27M -positive gliomas arise in the pons or thalamus, and only approximately 5% arise in the ventricle [6, 20]. In most cases, the histological grade is high. The median overall survival of *H3F3A* K27M-positive midline glioma is less than 1 year, which is significantly worse than that of *H3F3A* K27 wild-type glioma. Based on an analysis of 77 pediatric patients with diffuse midline glioma over the age of 3 years, Karremman et al. reported that H3 K27M status has a negative impact on survival, regardless of tumor location or pathological grade [20]. There is a case report of pediatric LGG in the thalamus harboring H3 K27M transformed to HGG [23]. Pratt et al. also reported that H3 K27M has a negative impact on survival in circumscribed/non-diffuse glioma [24].

In contrast to *H3F3A* K27M, *BRAF* V600E is detected in a variety of tumors arising in patients of all ages, including thyroid and colorectal cancers as well as Langerhans cell histiocytosis [3, 25–31]. It is also detected in various glioma subtypes arising in any location, and the frequency is high in some subtypes, such as pleomorphic xanthoastrocytoma. The prognostic implications of *BRAF* V600E are dependent on various factors, including patient age, patient gender, tumor type, and the presence of other concurrent molecular abnormalities [3, 25–32]. For pediatric LGG, several reports suggest that *BRAF* V600E is associated with an aggressive clinical course, although this is somewhat controversial [3, 28, 32, 33]. Lassaletta et al. reported that the progression-free survival of patients with *BRAF* V600E–positive LGG is significantly worse than that of patients with wild-type *BRAF* LGG [3]. Mistry et al. reported that the frequency of *BRAF* V600E in pediatric LGG that underwent malignant transformation was higher than the frequency in non-transformed LGG (44% vs. 6%) [31].

Although the coexistence of *H3F3A* K27M and *BRAF* V600E mutations is rare, there have been several reported cases of pediatric glioma harboring these concurrent mutations (Table 1) [20, 22, 32, 34–38]. Interestingly, these include both diffuse midline glioma and non-diffuse glioma. In view of the diagnostic and prognostic information of this alternation, the recently published cIMPACT-NOW update 4 proposed the new classification name "Diffuse glioma, *BRAF* V600E mutant." The diagnosis of some cases shown in Table 1 may warrant further discussion [39]. It is also noteworthy that the

prognosis of these patients was not necessarily dismal but instead appeared to be somewhat better than that of patients with midline glioma harboring only the *H3F3A* K27M mutation, and that no patients died within the first year after the initial diagnosis. Notably, four patients, including all three patients under the age of 3 years, survived for more than 5 years. However, the number of reported cases with concurrent mutations is small and histological diagnosis, grading and age of diagnosis are variable. The follow-up periods are too short and recent widespread application of BRAF-targeted therapy may change their survival [40]. Therefore, further analysis of more cases is required to clarify these points.

In summary, we report a case of a relatively long-term survivor of pediatric midline glioma harboring concurrent *BRAF* V600E and *H3F3A* K27M. Although the tumor was classified as "diffuse midline glioma with H3K27M mt, WHO grade IV" based on methylation analysis, the pathological and clinical features of this case did not fit those of "diffuse midline glioma with H3 K27M mt" as defined in the current WHO classification (2016). Our case points to certain limitation of the current methylation classifier and it calls for further discussion of the integrated diagnosis of brain tumor. Further investigations of non-diffuse glioma with *H3F3A* K27M and glioma with both *BRAF* V600E and *H3F3A* K27 M are warranted.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest associated with this manuscript.

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