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Clinical study

Clinical relevance of *BRAF* status in glial and glioneuronal tumors: A systematic review

Yoshiki Sugiura, Masaya Nagaishi *

Department of Neurosurgery, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minami-Koshigaya, Koshigaya-shi, Saitama 343-8555, Japan

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ABSTRACT

Alterations in the BRAF gene have been reported to play a key role in the tumorigenesis of various tumors. Recent studies have shown the existence of BRAF alterations in ganglioglioma (GG), pilocytic astrocytoma (PA), pleomorphic xanthoastrocytomas (PXA), and epithelioid glioblastoma (eGBM). The focus of this review was the association between the clinical characteristics and BRAF status in these glial and glioneuronal tumors. The BRAF abnormalities, KIAA1549-BRAF fusion and BRAF mutation, were detected in approximately 50% of the analyzed tumors regardless of the tumor location, and there were site-specific BRAF abnormalities that became more remarkable on analysis by each tumor subtype. The median age of patients with KIAA1549-BRAF fusion was much lesser than that of those with BRAF mutations. Histological analysis indicates that the existence of KIAA1549-BRAF fusion is related to pilocytic morphology. The review of imaging features indicated that cyst formation is associated with the existence of KIAA1549-BRAF fusion in PA and GG and the lack of BRAF mutation in GG. Hemorrhage was significantly present in cases of GG with KIAA1549-BRAF fusion, but no relevance was shown in cases with BRAF mutations. No significant relevance was detected between the presence of calcification and BRAF alterations. Our clinical and genetic review of BRAF-related tumors indicated that the KIAA1549-BRAF fusion was strongly associated with PA, but not with other glial and glioneuronal tumors.

1. Introduction

The mitogen-activated protein kinase (MAPK) pathway comprises various molecules, including Ras, Raf, MEK, and MAPK. The genetic alterations in these molecules lead to activation of the MAPK pathway and are related with tumorigenesis in many types of malignant tumors [1]. An activated MAPK pathway is found in 30% of human cancers and is mainly due to alterations of the *Ras* and *Raf* genes [2]. Three Raf kinase family members (i.e., A-Raf, B-Raf, and C-Raf) are included in the MAPK pathway and are all related with tumorigenesis. The B-Raf kinase is encoded by the *BRAF* gene, which is known as the major oncogenic gene among the three. The *BRAF* gene activation that is related to the tumorigenesis of brain tumors commonly occurs via activating mutations or duplication of the *BRAF* gene.

The *BRAF* gene on the long arm of chromosome 7q34 consists of 18 exons. The tandem duplications on chromosome 7q34 lead to a fusion gene between *KIAA1549* and *BRAF*. The duplications result in loss of the N-terminal autoinhibitory domain of the *BRAF*, which triggers the constitutive kinase activity [3]. Various *KIAA1549–BRAF* mRNA fusion junctions have been identified. The most common fusion junction is between exon16 of *KIAA1549* and exon 9 of *BRAF* (16–9 fusion), followed by *KIAA1549* exon 15–*BRAF* exon 9 (15–9 fusion), *KIAA1549* exon 16–*BRAF* exon 11 (16–11 fusion), *KIAA1549* exon 16–*BRAF* exon 10 (16–10 fusion), *KIAA1549* exon 15–*BRAF* exon 11 (15–11 fusion), *KIAA1549* exon 17–*BRAF* exon 10 (17–10 fusion), and *KIAA1549* exon 18–*BRAF* exon 10 (18–10 fusion). *KIAA1549–BRAF* fusion is frequently found in pilocytic astrocytoma (PA) and pilomyxoid astrocytoma (PMA), which is an aggressive variant of PA. The mutational hotspot of the *BRAF* gene is in the amino acid position 600, where valine is substituted by glutamic acid (V600E). The point mutation converts *BRAF* into an active state that causes constitutive activation of the MAPK pathway [4]. In intracranial tumors, *BRAF* V600E mutation has been reported in pleomorphic xanthoastrocytomas (PXA), ganglioglioma (GG), desmoplastic infantile ganglioglioma and desmoplastic infantile astrocytoma, PA, epithelioid glioblastomas (eGBM), and craniopharyngiomas [5,6].

The glial tumors related to *BRAF* alterations often share common histopathological traits, such as the presence of eosinophilic granular body, Rosenthal fiber, cortical dysplasia of the surrounding normal tissue, and pilocytic differentiation in the glial component of GG. GG cases with a prominent pilocytic glial component

* Corresponding author.
E-mail address: nagaishi-nsu@umin.ac.jp (M. Nagaishi).

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are often difficult to distinguish from PA. In addition, the presence of a small number of neuronal cells, which are morphologically hard to distinguish from dysplastic or reactive neuronal cells, may confuse the diagnosis of these cases. Composite PXA–GG and eGBM arising from PXA have been reported. The most recent updates on the histopathological diagnosis of several subtypes of brain tumor emphasized the use of molecular profiling for categorization [7]. Although *BRAF* profiling in the molecular diagnosis for tumor categorization is not included in the fourth edition of the World Health Organization classification of central nervous system tumors, its diagnostic value has been mentioned by several reports [8]. In the present study, we reviewed the current literature to identify the clinical features related with the presence and absence of *BRAF* abnormalities in *BRAF*-related gliomas.

2. Materials and methods

2.1. Search strategy

Relevant studies published in English were identified by PubMed search using the keyword "*BRAF* fusion" or "*BRAF* mutation" in combination with "ganglioglioma", "pilocytic astrocytoma", "pleomorphic xanthoastrocytoma", "glioneuronal tumor", and "epithelioid glioblastoma". This review included PA, PMA, GG, PXA, or eGBM cases that underwent analysis of the *BRAF* status and had available clinical data, including tumor location and the presence of cyst formation, calcification, and hemorrhage, but excluded cases without *BRAF* status or all of clinical data mentioned above. The searched literatures included case reports, case series, case-control studies, systematic reviews, and metaanalyses. The tumor locations reviewed were in the cerebral hemisphere, encephalon/optic tract, cerebellum, and brainstem/spine. Notably, PA in the hypothalamic-chiasmatic region and optic chiasm are genetically homogeneous tumors and originate from glial cells on the floor of the third ventricle [9]. We summarized all tumors that originated from these regions as "encephalon/optic tract".

2.2. Statistical analysis

The Chi-square test or Fisher's exact test was used to analyze the differences in the qualitative features among the groups. Student's *t*-test or the Mann–Whitney *U* test was performed to analyze the differences in the variables. *P*-values < 0.05 were considered statistically significant.

3. Results

Our search resulted in 174 literatures. After review, 119 articles were excluded because of the lack of clinical data and 52 studies met the inclusion criteria; 32 were published as case reports and 20 were case series. In the 52 available literatures, a total of 512 patients were included in this study [10–61]. PA was the most common subtype analyzed and comprised 225 cases, including four cases of anaplastic PA. There were 115 cases of GG; 105 cases of PXA (WHO grade II = 81 cases, Grade III = 24 cases); 40 cases of eGBM; and 27 cases of PMA. The overall mean sex ratio (male/female) was 1.1; 1.1 for PA, 1.0 for GG, 0.9 for PXA, 1.7 for eGBM, and 0.9 for PMA. The clinical characteristics by the BRAF status are summarized in Table 1. The median age of the cases with PA, GG, PXA, eGBM, and PMA was 10, 15, 26.5, 21.5, and 2 years, respectively. The *KIAA1549–BRAF* fusion was detected in 139 cases, which included 120 cases (63%) of PA, 10 cases (77%) of PMA, and nine cases (18%) of GG (Fig. 1). The *KIAA1549–BRAF* fusion was assessed using real-time PCR in 141 cases, fluorescent *in situ* hybridization (FISH) in 84 cases, and whole-genome or whole-exome sequencing in 24 cases. Four cases were not available for analysis. In these cases, the sex ratio (male/female) was 1.2, and the median age was 8 years. No cases of PXA and eGBM were analyzed for *KIAA1549–BRAF* fusion. This fusion was more common in patients who were ≤10 years old than in those >10 years old ($P = 0.0002$). The cases with *BRAF* fusion were significantly younger than those without the fusion ($P = 0.0004$). Fusion variants were identified in 80 cases of PA, 1 case of PMA, and nine cases of GG.

Table 1
The clinical characteristics by BRAF status in glial and glioneuronal tumors.

	BRAF mutation +	KIAA1549-BRAF fusion+	BRAF mutation – and/or duplication –
Gender (510)			
Male	80	75	110
Female	74	64	107
Age (503)			
≧18	63	26	74
<18	90	113	137
Location (514)			
Infratentrial	36	93	87
Supratentrial	122	46	130
Cyst formation (78)			
Present	12	12	8
Absent	28	0	18
Bleeding (65)			
Present	4	5	0
Absent	32	4	20
Calcification (37)			
Present	5	NA	0
Absent	23	NA	9
Histological subtype (514)			
PA	24	120	83
PMA	0	10	17
GG	54	9	52
PXA	58	NA	47
eGBM	22	NA	18

The culmulative number of cases available was shown in parentheses by each clinical characteristics, and the maximum culmulative number is 514 including 2 cases with simultaneous presence of BRAF mutation and duplication. aPXA, anaplastic pleomorphic xanthoastrocytoma; eGBM, epithelioid glioblastoma; GG, ganglioglioma; PA, pilocytic astrocytoma; PXA, plemorphic xanthoastrocytoma.

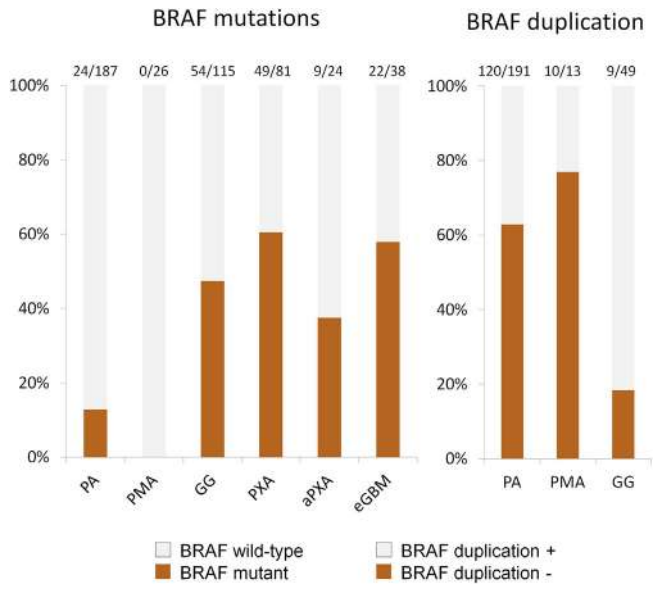

Fig. 1. Frequency of the BRAF alteration by tumor subtypes. The number and frequency of the mutations and duplication of BRAF were illustrated according to tumor subtypes.

Of the 81 cases of PA and PMA, 67% (n = 54) had 16–9 fusion, 22% (n = 18) had 15–9 fusion, 7% (n = 6) had 16–11 fusion, 1% (n = 1) had 19–9 fusion, 1% (n = 1) had 16–10 fusion, and 1% (n = 1) had 18–10 fusion. On the other hand, in the 99 cases of GG, the most common fusion was 15–9 in (56%, n = 5), followed by 16–9 (22%, n = 2) and 16–11 (22%, n = 2). Fusion variants were not identified in remaining 49 cases, and most of them were analyzed using FISH. The distribution of fusion variants was significantly different between the GG and PA cases ($P = 0.03$). Simultaneous presence of *BRAF* mutation and duplication was detected in two cases of PA, but there were none in the other tumor subtypes.

BRAF mutations within exon 18 was detected in 158 cases, which included 24 cases (13%) of PA, 54 cases (47%) of GG, 58 cases (55%) of PXA, 22 cases (58%) of eGBM, and no case of PMA (Fig. 1). The *BRAF* mutation was assessed using sequence analysis including pyrosequencing, Sanger sequencing, and whole-genome and whole-exome sequencing in 404 cases; immunohistochemical analysis in 34 cases; and single-nucleotide polymorphisms genotyping analysis in 27 cases. Five cases were not available for analysis. The overall sex ratio (male/female) was 1.1, and the median age was 18 years. In patients with an average age of >4.7 years, *BRAF* mutations were more common than *BRAF* duplication ($P < 0.0001$). The *BRAF* mutation was frequently observed in cases over the age of 10 years than those 10 years and under ($P < 0.0001$).

3.1. Localization

In this series, *BRAF* alteration was observed in 58% (103/179) of tumors in the cerebral hemisphere, 49% (45/91) of tumors in the encephalon/optic tract, 60% (80/133) of tumors in the cerebellum, and 46% (27/59) of tumors in the brainstem/spine. Of the tumors with *BRAF* mutations, 55% (99/179) arose in the cerebral hemisphere, 13% (11/84) in the encephalon/optic tract, 16% (16/100) in the cerebellum, and 28% (16/58) in the brainstem/spine. Of the brain tumors with *KIAA1549–BRAF* fusion, 16% (4/25) arose in the cerebral hemisphere, 63% (35/56) in the encephalon/optic tract, 61% (64/105) in the cerebellum, and 31% (11/35) in the brainstem/spine (Fig. 2). The common location of tumors was the cerebral hemisphere for *BRAF* mutation and the encephalon/optic nerve and cerebellum for *KIAA1549–BRAF* fusion. Interestingly, tumors with *BRAF* mutations and those with *KIAA1549–BRAF* fusion showed similar incidence rates between the encephalon/optic tract and the cerebellum. The sites of tumors with *BRAF* abnormalities according to tumor subtypes are illustrated in Fig. 3. The distribution of the site of tumors with *BRAF* mutation or duplication was different among the tumor subtypes. In PA, the distributions of *BRAF* mutation and *BRAF* duplication were similar between tumors located on the encephalon/optic tract and those on the cerebellum. On the other hand, similarities in the occurrence rate of *BRAF* abnormalities in GG were seen in two infratentorial sites (brainstem/spine and cerebellum) and in two supratentorial sites (cerebral hemisphere and encephalon). The distribution of *BRAF* mutations on the cerebral hemisphere was similar between PXA and eGBM (61% and 63%, respectively). The number of cases with PXA and eGBM located on the other sites was not sufficient for analysis. *BRAF* mutations were more frequently detected in PXA tumors located on the temporal lobe than in those on the other cerebral hemisphere locations (68%, 26/38 vs. 32%, 8/25; $P = 0.009$).

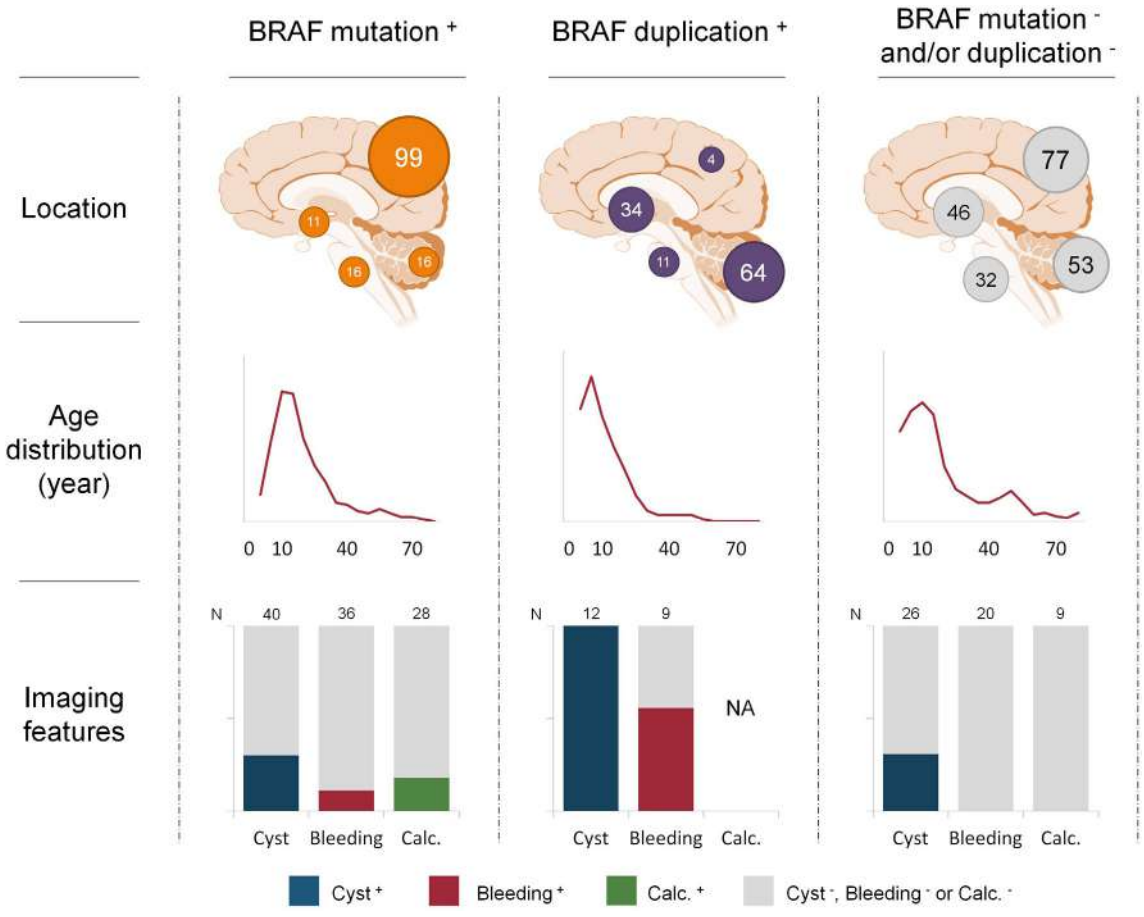

Fig. 2. Simplified summary of clinical characteristics by the BRAF status. Location, age distribution, and imaging features by the BRAF status illustrated with simplified schema. The number of cases is indicated within the circles. Calc.; calcification.

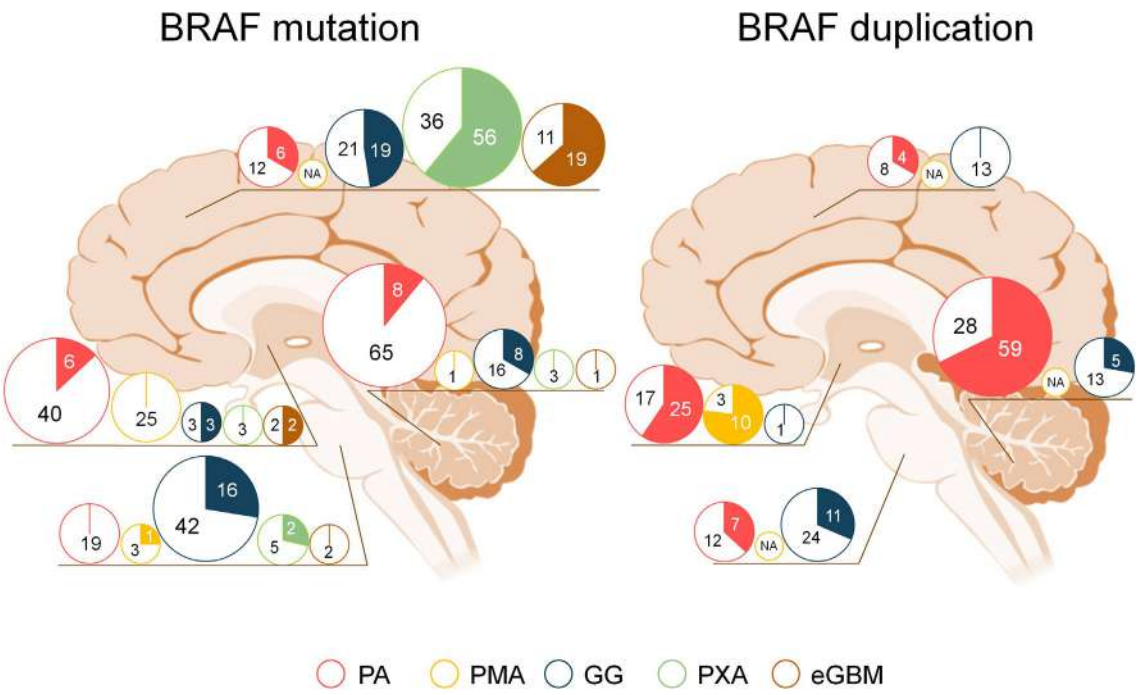

Fig. 3. Distribution of BRAF alterations across tumor locations and glioma subtypes. Case distribution with BRAF mutations or BRAF duplication illustrated with simplified schema by tumor locations. Colored circle indicates BRAF alterations; blank indicates no BRAF alterations. The number of cases is indicated within the circles. Circles with NA indicate no available cases in the location.

3.2. Imaging features

Cyst formation was observed in 32 of 78 cases, including 5/5 (100%) cases of PA, 16/40 (40%) cases of GG, 9/23 (39%) cases of PXA, and 2/10 (20%) cases of eGBM. *BRAF* mutations were detected in 28 of 46 cases (61%) without cyst formation and in 12 of 32 cases (38%) with cyst formation ($P = 0.04$). In the analysis of each tumor subtype, the lack of cyst formation was significantly associated with the existence of *BRAF* mutation in GG ($P = 0.02$), but not in PA, PXA, and eGBM. In 34 cases with available data on both *KIAA1549–BRAF* fusion and cyst formation, the *KIAA1549–BRAF* fusion was detected in 13 of 16 cases with cyst formation, including three cases of PA and 10 cases of GG, but it was not detected in all 18 cases without cyst formation ($P < 0.0001$). This analysis indicated that cyst formation was associated with the existence of *KIAA1549–BRAF* fusion in PA and GG and the lack of *BRAF* mutation in GG.

Thirty-seven cases had available data on the status of calcification. Of these, five cases had calcification, including two cases of PXA and three cases of eGBM. *BRAF* mutations were observed in 5/5 (100%) cases with calcification and in 23/31 (74%) cases without calcification ($P = 0.57$). The presence of calcification and *KIAA1549–BRAF* fusion was investigated in only four cases, and all showed lack of both the calcification and the *KIAA1549–BRAF* fusion. Hemorrhage was observed in 9 of 65 cases, including 0/2 case of PA, 6/40 (15%) cases of GG, 1/13 (8%) cases of PXA, and 2/10 (20%) cases of eGBM. Similar to the analysis of calcification, the presence of hemorrhage was not associated with the presence of *BRAF* mutation. Mutations of *BRAF* were observed in 4/9 (44%) cases with hemorrhage and in 33/55 (60%) cases without hemorrhage ($P = 0.49$). On the other hand, *KIAA1549–BRAF* fusion was seen in 5/6 (83%) cases with hemorrhage but in only 4/25 (16%) cases without hemorrhage ($P = 0.004$). Only 31 cases with GG had available data for both *KIAA1549–BRAF* fusion and the presence of hemorrhage. No cases of PMA had available data on cyst formation, calcification, and hemorrhage.

4. Discussion

Review of all the cases, indicated that *BRAF* alterations were associated with tumorigenesis in approximately half of the tumors, regardless of the location. On the other hand, there were site-specific differences in the rate of *BRAF* mutations and *KIAA1549–BRAF* fusion. The site-specificity became more remarkable in the analysis by each tumor subtype. PA tumors from the cerebellum and encephalon/optic tract had more frequent *KIAA1549–BRAF* fusion, compared with tumors in the other locations, but had rare *BRAF* mutations. In addition, among PA tumors, 16–9 fusion was frequent in the cerebellum and 15–9 fusion was frequent in the midline location (i.e., encephalon and brainstem). Likewise, GG with 15–9 fusion was commonly observed in the midline location (i.e., brainstem). In GG cases, *BRAF* mutations were more frequent in tumors from supratentorial sites than in those from infratentorial sites. In PXA cases, the temporal location was associated with *BRAF* mutations. PA arising in the neurofibromatosis type 1 generally originates from the optic tracts, which are commonly associated with defects in the *NF1* gene. Several studies identified the relationship between *BRAF* alterations and histopathological findings, such as reticulin deposition and CD34 expression in PXA with *BRAF* mutations [62] and myxoid histopathology in PA with the *KIAA1549–BRAF* (15–9) fusion [63]. These site-specific genetic alterations and histopathological appearance related to *BRAF* alterations suggested the existence of region-specific cells of origin, regardless of tumor subtype.

GG comprised glial and neuronal elements, and the spectrum of each element differs according to the tumors. Gupta analyzed the *BRAF* status in GG cases that largely exhibited PA with foci of gangliocytic differentiation on the posterior fossa or spinal cord and detected *KIAA1549–BRAF* fusion in 82% and *BRAF* mutation in none [18]. In contrast with the nine cases with prominent pilocytic component in the report by Gupta, no GG case (0/40) showed *BRAF* duplication in our review. Although 15–9 is the most common gene fusion in GG, most of the cases with GG and this fusion pat-

tern were in the midline location, which was similar to PA. In addition, these 9 GG cases with *BRAF* duplication frequently revealed cyst formation (9/9, 100%) and hemorrhage (5/9, 56%), whereas infratentorial GG without *BRAF* duplication showed cyst formation in only 18% (4/22) and hemorrhage in only 5% (1/22). Therefore, infratentorial GG with prominent pilocytic component clinically and genetically appears similar to PA, suggesting that GG and PA have common molecular mechanisms for pathogenesis. In our review, all tumors with *KIAA1549–BRAF* were PA or PMA, when these nine cases of GG were categorized to PA. Although the existence of *KIAA1549–BRAF* fusion had been rarely reported in cases with lower grade glial and glioneuronal tumors, except PA or PMA [64,65], the presence of prominent pilocytic component in the tumor specimens of these cases needs to be reassessed. Our review confirmed that the existence of *KIAA1549–BRAF* fusion was strongly associated with pilocytic morphology and had a diagnostic value for PA, PMA, and GG with prominent pilocytic component.

Cyst formation is frequently observed in PMA, GG, PXA, and PA and is rarely seen in eGBM. Our review indicated that cyst formation was associated with the existence of *KIAA1549–BRAF* fusion in PA and GG and the lack of *BRAF* mutation in GG. All GG cases that demonstrated both *BRAF* duplication and cyst formation were from the report by Gupta and showed prominent pilocytic component and infratentorial location. In this review, calcification was not significantly associated with *BRAF* status, but the small sample size and the unavailability of data on some tumor subtypes may have led to these results.

In summary, *BRAF* alterations were seen in approximately half of the *BRAF*-related tumors, regardless of the tumor location. The frequency and distribution pattern of *BRAF* alterations illustrated in the figures of this review are characteristic of the tumor subtypes, and the evaluation of *BRAF* status is valuable for diagnosis especially in diagnostically challenging cases. In addition, the presence of cyst formation and bleeding is a useful clinical information that indicates the existence of *BRAF* abnormalities.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2019.05.014.

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