Clinical Case Report

Medicine®

OPEN

Dysembryoplastic neuroepithelial tumor-like pilocytic astrocytoma

A case report

Jia-Ming Liao, PhD[a], Wei Wang, PhD[b], Jing Xie, MD[c], Hai-Bo Wu, MD[c,*]

Abstract

Rationale: Pilocytic astrocytoma (PA) typically shows biphasic pattern with a mixture of loose microcystic and compact regions, in which it is not uncommon to see heterogeneous morphology. However, there has not been reported in the literatures of the PA type that shows similarity to dysembryoplastic neuroepithelial tumor (DNT) in both histological morphology and immunophenotype.

Patient concerns: The present study described a case of PA affecting the right temporal-occipital lobe in a 22-year-old male patient. Morphologically, it composed of totally distinctive microcystic pattern. The classical biphasic pattern of PA was not observed. Immunohistochemically, neuronal marker NeuN was expressed in tumor cells scattered in the background which simulated its expression morphology in DNT. However, KIAA1549-BRAF fusion gene was identified by fluorescence in situ hybridization (FISH), supporting for the diagnosis of PA.

Diagnoses: DNT-like PA (WHO grade I).

Interventions: The tumor was totally removed via a right temporal-occipital craniotomy.

Outcomes: The patient is free of local recurrence and dissemination eleven months after surgical resection of the lesion.

Lessons: We herein report a rare case of DNT-like PA. For diagnosis, KIAA1549-BRAF fusion gene should be detected under similar situation.

Abbreviations: DNT = dysembryoplastic neuroepithelial tumor, FISH = fluorescence in situ hybridization, GFAP = glial fibrillary acidic protein, GG = ganglioglioma, IDH1 = isocitrate dehydrogenase 1, MRI = magnetic resonance imaging, NF1 = neurofibromatosis type 1, Olig2 = oligodendrocyte transcription factor 2, PA = pilocytic astrocytoma, PXA = pleomorphic xanthoastrocytoma.

Keywords: dysembryoplastic neuroepithelial tumor, fluorescence in situ hybridisation, *KIAA1549–BRAF* fusion gene, pilocytic astrocytoma

1. Introduction

Pilocytic astrocytoma (PA) is a common World Health Organization (WHO) grade I glioma occurring in children and adolescents. Most PAs show benign clinical behavior and favorable prognosis. But in a small subset of patients, they may behave aggressively.[1,2] Under the microscopy, besides classical biphasic architecture, morphological heterogeneity may be found in PAs, which simulates the characteristics of the other low-grade glial neoplasms, such as oligdendroglioma, pleomorphic xanthoastrocytoma (PXA), ependymoma, and diffuse astrocytoma.[3] However, PAs that are histopathologically similar to dysembryoplastic neuroepithelial tumors (DNTs) in both histological morphology and immunophenotype have not been reported before. We herein showed a DNT-like PA case, which expanded the morphological profile of PA.

2. Case report

A 22-year-old male visited local hospital due to a car accident in November 2016. CT scans detected a mass located in the right temporal-occipital lobe. The patient refused to do any treatment because of no clinical symptoms at that time. Two months later, he presented with a focal epilepsy, which was improved after having anti-epileptic drugs. In February 2017, he was referred to our hospital (Southern District of Anhui Provincial Hospital) because of deteriorating symptom. Magnetic resonance imaging (MRI) examination revealed a $1.1 \times 1 \times 1$ cm round homogenous mass, which was hyperintense on T2 (Fig. 1A) and slightly hypointense on T1 weighted images (Fig. 1B) without gadolinium enhancement (Fig. 1C). The patient denied having any family history of neurofibromatosis type 1 (NF1) and no associated symptoms were found during the previous physical examinations. The lesion was totally removed via a right temporal-occipital craniotomy. Intraoperatively, the lesion was well

Editor: N/A.

JML and WW have contributed equally to the article.

The authors have no conflicts of interest to disclose.

[a] Department of Clinical Laboratory, Southern District of Anhui Provincial Hospital, [b] High Magnetic Field Laboratory, Chinese Academy of Sciences, [c] Department of Pathology, Southern District of Anhui Provincial Hospital, Hefei, Anhui, China.

[*] Correspondence: Hai-Bo Wu, Department of Pathology, Southern District of Anhui Provincial Hospital, No. 1 Swan Lake Road, Hefei, Anhui 230036, China (e-mail: bbwuhaibo@sina.com).

Medicine (2018) 97:20(e10755)

Received: 10 February 2018 / Accepted: 25 April 2018

http://dx.doi.org/10.1097/MD.0000000000010755

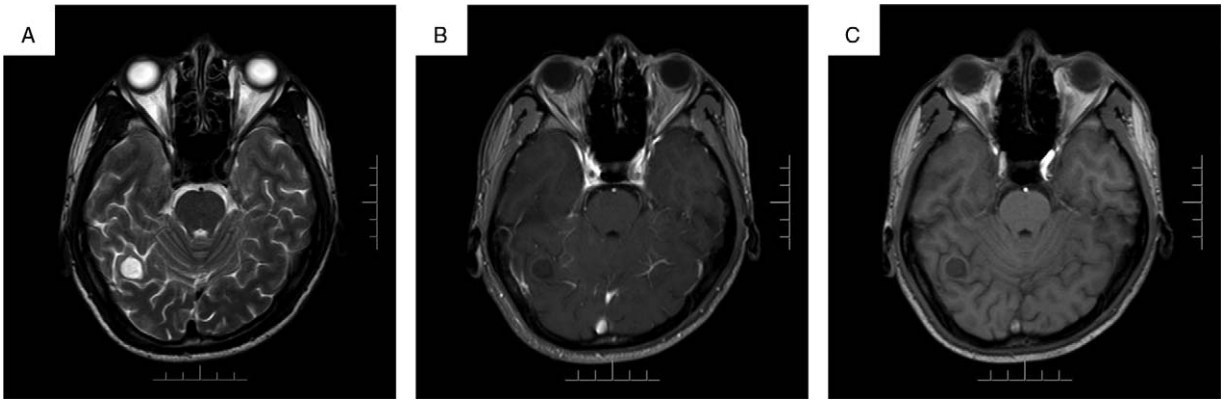

Figure 1. Neuroradiologic features of DNT-like PA. (A) Axial T2-weighted MRI showed a 1.1 × 1 × 1 cm round homogenous hyperintense mass in right temporal-occipital lobe. (B) Axial T1-weighted MRI showed slightly hypointense mass. (C) Contrast-enhanced T1-weighted MRI showed no enhancement of the mass. DNT = dysembryoplastic neuroepithelial tumor, PA = pilocytic astrocytoma.

circumscribed without obvious capsule. The substance within the tumor was jelly like.

The resected tissue was fixed in 10% neutral buffered formalin for pathological study. Histomorphologically, a distinctive microcystic pattern was detected (Fig. 2A). The tumor cells had uniform round to oval nuclei without any observed mitoses. A small amount of hyperchromatic nuclei were scattered distribution within microcystic background. The classical biphasic pattern with a mixture of loose microcystic and compact regions of PAs were not examined. Immunohistochemistry assay revealed that the tumor cells were diffusely positive for GFAP (Fig. 2B) and Olig2 (Fig. 2C). In contrast, IDH1 (Fig. 2D), BRAF V600E, H3K27M, CD34 and p53 staining cells were not detected in the tumor. The Ki67 labeling index was <1% (Fig. 2E). Confusingly, neuronal marker NeuN was expressed in tumor cells scattered in the background which normally found in DNT (Fig. 2F). To confirm the diagnosis, further assay with fluorescence in situ hybridization (FISH) was applied and *KIAA1549–BRAF* fusion gene was found in the tumor (Fig. 3). The final diagnosis was DNT-like PA (WHO grade I).

Ethical approval was not required for this case report as it did not relate to any human trials or the patient's privacies. Informed consent was provided by the patient for the publication of this case report.

3. Discussion

PA is a clinicopathological heterogeneous WHO grade I tumor.[3,4] Clinically, PAs accounts for 20% of brain tumors in the patients under 20 years old.[5] Approximately 5% to 10% PAs are associated with neurofibromatosis type 1 (NF1), especially those cases which arise in the optic/chiasmatic region.[6] PAs mainly involve the neuraxis, such as cerebellum, optic pathway, hypothalamus, brainstem, and spinal cord, while the supratentorial region is also frequently encountered.[3,6] Clinical manifestations of PAs are dependent on the lesion locations. Neuroradiologically, PAs typically show hypo- or iso-intense lesion on T1-weighted images with enhancement and hyperintense on T2-weighted images. Most lesions in the cerebellum are cystic accompanying with a mural enhancing nodule under MRI, while others display as infiltrative masses in the optic pathway.[7] However, just like our case, the imaging findings of the lesions can be atypical in other areas.[7] Instead of typical contrast enhancement under MRI, they showed an atypical solid mass without cystic change and infiltration.

Histologically, PAs typically show biphasic pattern with a mixture of loose microcystic and compact regions. In the loose microcystic parts, esoinopholic granular bodies can be seen. Meanwhile, the bipolar piloid cells compose the compact areas, in which rosenthal fibres are easily detected. Occasionally, PAs exhibited a predominantly or even entirely growth pattern.[3] It is not unusual to find heterogeneous morphological characteristics in PAs, such as oligdendroglioma, PXA, ependymoma, and diffuse astrocytoma.[3] However, PA with NeuN positive cells in entirely microcystic background which mimicked DNT was not reported in the literature before. The exact reason for this is not clear. We inferred that these NeuN positive cells may be entrapped neurons or due to unspecific immunohistochemical reactions.

In addition to clinicopathological heterogeneity, PAs also display molecular heterogeneity. Jones et al[8] firstly found the *KIAA1549–BRAF* fusion gene exhibited in most of the PAs. This fusion gene can activate the mitogen-activated protein kinase pathway and participant in the formation of PAs. Except PAs, *KIAA1549–BRAF* fusion gene can only be detected in diffuse leptomeningeal glioneuronal tumors.[4,9] Therefore, harboring *KIAA1549–BRAF* fusion gene contributes to the diagnosis of PAs. In our case, the detection of *BRAF* fusion gene was the determining factor in the distinguishing between PA and DNT. In addition to *KIAA1549–BRAF*, other *BRAF* fusion partners were also found in PAs, including *FAM131B*, *RNF130*, *CLCN6*, *MKRN1*, *GNAII,* and *GIT2*.[10] Besides, activating point mutation *BRAF V600E* occurs in a small part of PAs, especially in the supratentorial locations,[11] whereas it is the most common finding in papillary craniopharyngiomas, PXA, gangliogliomas (GG) and DNT.[11] Moreover, aberrant DNA methylation has been studied in PAs, which varied according to tumor locations as well.[6]

From a differential diagnosis perspective, our case should be distinguished from DNT. It is well known that DNT is a type of epilepsy-associated low-grade glioneuronal tumor which typically occurs in the cerebral cortex of children and adolescents. After surgery, the recurrence and progression of DNTs are exceptional. Their histological features are multinodular with glioneuronal elements, which contain oligodendrocyte-like cells attached to bundles of axons and neurons with normal cytology floating in a

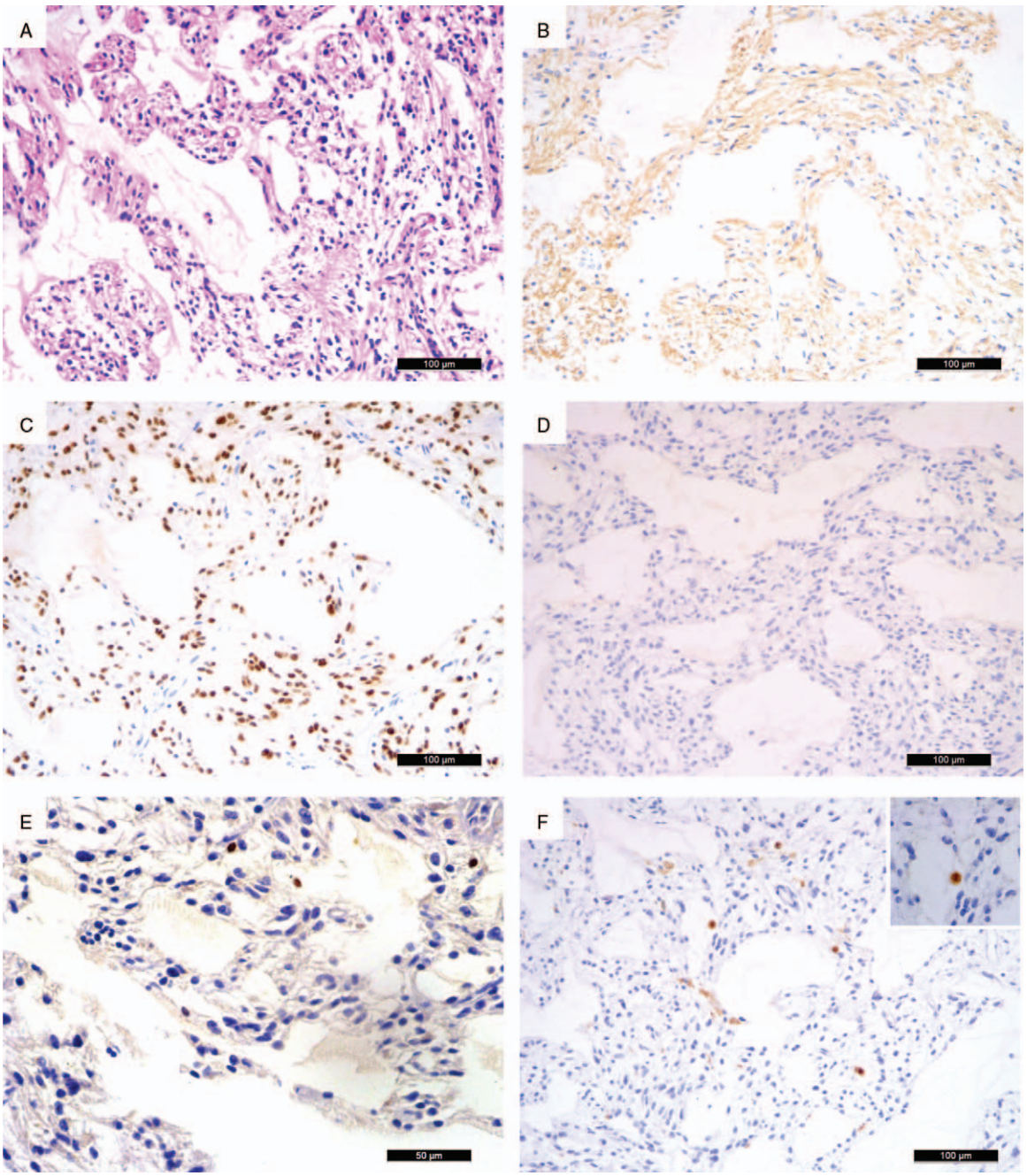

Figure 2. Pathological findings of DNT-like PA. (A) Hematoxylin-eosin section of DNT-like PA showed a distinctive microcystic pattern. Immunochemistry staining revealed diffuse expression of GFAP (B) and Olig2 (C). (D) The tumor cells were negative for IDH1. (E) The Ki67 labeling index was less than 1%. (F) Neuronal marker NeuN was expressed in tumor cells scattered in the background. The image magnification of (A–D, F) is ×200, € is ×400. DNT = dysembryoplastic neuroepithelial tumor, GFAP = glial fibrillary acidic protein, IDH1 = isocitrate dehydrogenase 1, PA = pilocytic astrocytoma.

myxoid interstitial fluid.[12,13] In rare cases, DNTs in the septum pellucidum or the supratentorial midline may be misdiagnosed as glioma,[14,15] while astrocytoma with microcystic change and oligodendrocyte-like cells is hard to distinguish from DNT.[16] In our case, both histological morphology and immunophenotype are similar to DNT, molecular detection was the only way to distinguish between PA and DNT. 30% of DNTs harbor *BRAF V600E* mutation,[17] while *KIAA1549–BRAF* fusion gene has never been detected in DNT. Therefore, the detection of *BRAF* fusion gene supports the diagnosis of PA. However, it is important to note that DNT can coexist with PA,[18] and the recurrent DNT may display the morphology of PA.[19] Besides, our case also needs to differentiate from other histologic mimics, including GG, oligodendroglioma and extraventricular neurocytoma. GG is another type of epilepsy-associated low-grade glioneuronal tumor which contains NeuN positive neuronal and GFAP positive glial cell elements. But loose microcystic regions were not easy to see in GG. *BRAF V600E* mutation occurred in 35% GG.[20] However, there has no *BRAF* fusion been detected in GG. It is not uncommon to see oligodendrocyte-like cells in PAs, resulting in some overlapping features with oligodendroglioma or extraventricular neurocytoma. However, oligodendroglioma frequently demon-

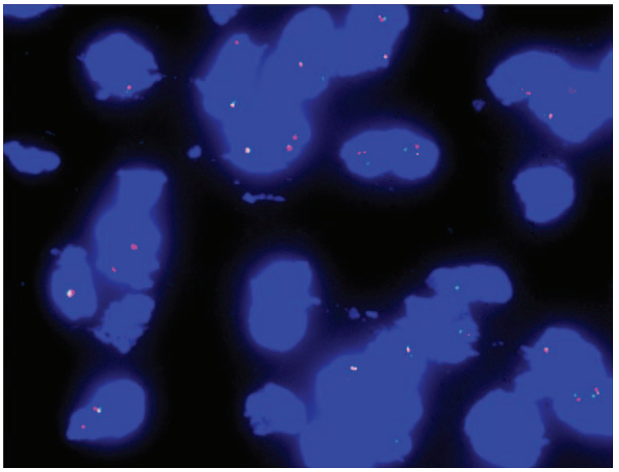

Figure 3. The *KIAA1549–BRAF* fusion gene was positive by fluorescence in situ hybridization (FISH) analysis. FISH = fluorescence in situ hybridization.

strates *IDH* mutation and 1p/19q codeletion,[4] while extraventricular neurocytoma diffuse expresses neuronal marker.[21] Both of them have no *BRAF* fusion.

As a WHO grade I glioma, PAs generally have favorable prognosis. The 10-year survival rate is over 95% after operation.[3] Spontaneous regression may be encountered in PAs, especially in patients with neurofibromatosis type 1.[3,21] A small minority of PAs may recur after surgery or disseminate to the leptomeninnges.[1,2] Surgical resection is the first treatment choice for patients with PAs, and radiotherapy or chemotherapy is applied to patients who are inoperable, subtotally resected, or progressive.[5] Eleven months after the operation, our case showed no local recurrence and dissemination.

PAs are heterogeneous tumors in histological morphology, immunophenotype and molecular characteristics. We report here a case of PA that both histological morphology and immunophenotype are similar to DNT, which expanded the morphological profile of PA. Therefore, we suggest that *KIAA1549–BRAF* fusion gene status should be assessed under similar situation to confirm the diagnosis.

Author contributions

Conceptualization: Hai-bo Wu.
Investigation: Jing Xie.
Writing – original draft: Jia-Ming Liao.
Writing – review & editing: Wei Wang.

References

[1] Yecies D, Fisher PG, Cheshier S, et al. Long-term outcomes of primarily metastatic juvenile pilocytic astrocytoma in children. J Neurosurg Pediatr 2017;10:1–5.
[2] Upadhyaya SA, Ghazwani Y, Wu S, et al. Mortality in children with low-grade glioma or glioneuronal tumors: a single-institution study. Pediatr Blood Cancer 2018;65:e26717.
[3] Matyja E, Grajkowska W, Stępień K, et al. Heterogeneity of histopathological presentation of pilocytic astrocytoma—diagnostic pitfalls. A review. Folia Neuropathol 2016;54:197–211.
[4] Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–20.
[5] Sadighi Z, Slopis J. Pilocytic astrocytoma: a disease with evolving molecular heterogeneity. J Child Neurol 2013;28:625–32.
[6] Sexton-Oates A, Dodgshun A, Hovestadt V, et al. Methylation profiling of paediatric pilocytic astrocytoma reveals variants specifically associated with tumour location and predictive of recurrence. Mol Oncol 2017; Epub ahead of print.
[7] Gaudino S, Martucci M, Russo R, et al. MR imaging of brain pilocytic astrocytoma: beyond the stereotype of benign astrocytoma. Childs Nerv Syst 2017;33:35–54.
[8] Jones DT, Kocialkowski S, Liu L, et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 2008;68:8673–7.
[9] Dodgshun AJ, SantaCruz N, Hwang J, et al. Disseminated glioneuronal tumors occurring in childhood: treatment outcomes and BRAF alterations including V600E mutation. J Neurooncol 2016;128: 293–302.
[10] Helgager J, Lidov HG, Mahadevan NR, et al. A novel GIT2-BRAF fusion in pilocytic astrocytoma. Diagn Pathol 2017;12:82.
[11] Breton Q, Plouhinec H, Prunier-Mirebeau D, et al. BRAF-V600E immunohistochemistry in a large series of glial and glial-neuronal tumors. Brain Behav 2017;7:e00641.
[12] Komori T, Arai N. Dysembryoplastic neuroepithelial tumor, a pure glial tumor? Immunohistochemical and morphometric studies. Neuropathology 2013;33:459–68.
[13] Campos AR, Clusmann H, von Lehe M, et al. Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. Neuroradiology 2009;51:433–43.
[14] Baisden BL, Brat DJ, Melhem ER, et al. Dysembryoplastic neuroepithelial tumor-like neoplasm of the septum pellucidum: a lesion often misdiagnosed as glioma: report of 10 cases. Am J Surg Pathol 2001;25:494–9.
[15] Gessi M, Hattingen E, Dörner E, et al. Dysembryoplastic neuroepithelial tumor of the septum pellucidum and the supratentorial midline: histopathologic, neuroradiologic, and molecular features of 7 cases. Am J Surg Pathol 2016;40:806–11.
[16] Shinohara Y, Kinoshita T, Kinoshita F, et al. F-18 FDG-PET imaging of dysembryoplastic neuroepithelial tumor-like astrocytoma. Clin Nucl Med 2009;34:700–2.
[17] Chappé C, Padovani L, Scavarda D, et al. Dysembryoplastic neuroepithelial tumors share with pleomorphic xanthoastrocytomas and gangliogliomas BRAF (V600E) mutation and expression. Brain Pathol 2013;23:574–83.
[18] Nasit JG, Shah P, Zalawadia H. Coexistent dysembryoplastic neuroepithelial tumour and pilocytic astrocytoma. Asian J Neurosurg 2016;11:451.
[19] Takeuchi Y, Arakawa Y, Mikami Y, et al. Dysembryoplastic neuroepithelial tumor with rapid recurrence of pilocytic astrocytoma component. Brain Tumor Pathol 2014;31:144–8.
[20] Qaddoumi I, Orisme W, Wen J, et al. Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology. Acta Neuropathol 2016;131:833–45.
[21] Sakai K, Miyahara T, Tsutsumi K, et al. Spontaneous regression of multicentric pilocytic astrocytoma with CSF dissemination in an adult. Brain Tumor Pathol 2011;28:151–6.