Oncology and Translational Medicine
DOI 10.1007/s10330-015-0126-4

June 2016, Vol. 2, No. 3, P104–P109

ORIGINAL ARTICLE

Non-specific histological variant of dysembryoplastic neuroepithelial tumor: a diagnostic challenge

Yanyang Chen[1], Bin Li[1], Boning Luo[2], Xiaoying Tian[3], Zhi Li[1] (✉)

[1] Department of Pathology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
[2] Department of Radiology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China
[3] School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China

Abstract

Objective The accurate diagnosis of the non-specific variant of dysembryoplastic neuroepithelial tumor (DNT) is very difficult because it is characterized by absence of the histological hallmark of the "specific glioneuronal element" in lesions. We herein present two cases of the non-specific form of DNT to analyze the clinical, radiological, and histological features of this unusual subtype of DNT.

Methods A 16-year-old and a 23-year-old patient had been treated for pharmacoresistant epilepsy for several years before undergoing referral to the hospital for further examination and treatment. Magnetic resonance imaging (MRI) revealed that both patients had a small, well-demarcated cystic lesion within the cortex of the brain without obvious contrast enhancement or peritumoral edema. The lesions were totally resected and routinely examined using histological and immunohistochemical analysis.

Results Both lesions exhibited similar histological appearances with cyst formation and mural nodule architecture. The glial nodules were mainly composed of oligodendrocyte-like components, and partly of piloid cells resembling pilocytic astrocytoma. The cortex adjacent to the lesion in both cases was found to have the histological features of focal cortical dysplasia (FCD) Type I. Immunohistochemically, the oligodendrocyte-like components were diffusely positive for Syn and Olig-2, but staining for CD34, p53, and IDH1 R132H was negative. The Ki-67 (MIB-1) labeling index was low, approximately 1%. There was no 1p/19q co-deletion in either lesion by fluorescence in situ hybridization (FISH) assay. Neither patient received postoperative adjuvant treatment, and both underwent regular follow-up for at least 24 months. No signs of recurrence or epileptic attacks were observed during the follow-up period.

Conclusion The non-specific variant of DNT is a diagnostic challenge for pathologists in clinical practice, and differentiation from some low-grade gliomas needs to be considered. The careful inspection of radiologic and histopathologic findings, accompanied by analysis of patients' clinical manifestations, may be helpful in making an accurate diagnosis.

Received: 16 December 2015
Revised: 13 January 2016
Accepted: 25 March 2016

Keywords: brain tumor; dysembryoplastic neuroepithelial tumor; cortical dysplasia; differential diagnosis

Dysembryoplastic neuroepithelial tumor (DNT) is a benign tumor entity that is usually located in the supratentorial cortex and frequently occurs in children or young adults. According to the World Health Organization (WHO) classification in 1993, 2000, and 2007, DNTs belong to the category of "neuronal and mixed neuronal-glial tumors", are characterized by drug-resistant partial seizures, and are often associated with cortical dysplasia [1]. Histologically, three morphological variants have been described, namely, simple, complex, and non-specific forms. The histological hallmark of the DNTs is the "specific glioneuronal element", in which bundles of axons lined by small oligodendroglia-like cells (OLCs) and large floating neurons within mucinous pools may be typically observed in simple and complex variants. Glial nodules, which lend the tumor a characteristic multinodular architecture, are also seen in complex forms with the specific glioneuronal element [2]. However, the concept of non-specific variants of DNT, which were firstly described by Daumas-Duport in 1999, remains controversial, as these

✉ Correspondence to: Zhi Li. Email: lizhi@mail.sysu.edu.cn
© 2016 Huazhong University of Science and Technology

variants lack the specific glioneuronal element and multinodular architecture [3]. In clinical practice, non-specific variants of DNTs often present a diagnostic challenge and may be confused with low-grade gliomas. However, the accurate diagnosis of DNTs is important because patients with DNTs misdiagnosed as gliomas will receive adjuvant radiation and/or chemotherapy inappropriately. We herein report two cases of the non-specific variant of DNT in young patients. The clinical and histological features of this rare histological form, as well as differential diagnosis, are discussed.

Materials and methods

Patients and clinical manifestations

Case 1. A 16-year-old boy presented with a history of at least two complex seizures over the previous three years. According to his parents, he had been treated unsuccessfully with antiepileptic drugs. As a result, the patient was referred to our hospital for further examination and treatment. Magnetic resonance imaging (MRI) revealed a small, well-demarcated cystic lesion within the cortex of the left frontal lobe that was 1.0 × 1.0 × 1.0 cm in size, and a mural nodule could be observed on the cystic wall. The lesion appeared hypointense on T1-weighted images and hyperintense on T2-weighted images. Contrast-enhanced imaging displayed mild heterogeneous enhancement of the lesion. There was no obvious peritumoral edema or mass effect (Fig. 1). A subdural grid recording revealed that the epileptic focus lay in the cortex covering the lesion. The clinical diagnosis was epilepsy-related low-grade glioma or ganglioglioma. The lesion was completely removed surgically. The mass appeared grayish and was covered with normal-looking cortex. No postoperative radiotherapy or chemotherapy was administered. After surgery, the patient underwent regular follow-up for 24 months, and there was no evidence of recurrence in that period.

Case 2. A 23-year-old female patient presented with progressive headache, nausea, and vomiting for five months. She had been diagnosed with focal epilepsy with seizure onset at the age of 10, but no abnormal findings were present in general or on neurological examination. MRI scans revealed a large non-enhanced cystic lesion with a mural nodule, measuring 5.5 × 3.0 × 1.0 cm, in the cortex of the left temporal lobe. The lesion appeared hypointense on T1-weighted images and hyperintense on T2-weighted images, with mild peritumoral edema, but no contrast enhancement was observed (Fig. 2). The lesion was removed via a standard left craniotomy. At surgery, the lesion was observed to be poorly vascularized and the border between the lesion and the normal brain was demarcated. Total resection was achieved. The postoperative course was uneventful and no postoperative radiotherapy or chemotherapy was administered. The patient underwent follow-up for 36 months without any evidence of tumor recurrence. No further epileptic attacks were observed during the follow-up period.

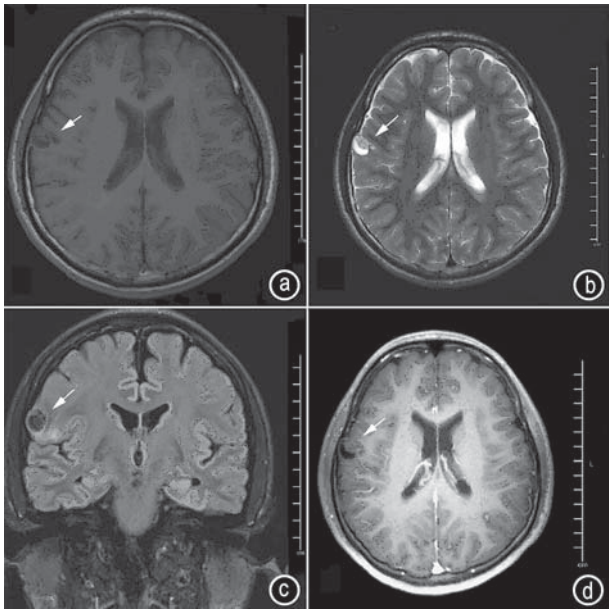

Fig. 1 Pre-operative MRI of the lesion of Case 1. (a) T1-weighted axial MRI demonstrated a hypointense lesion in the left frontal lobe containing a circumscribed cystic component and solid mural nodule (white arrow); (b) T2-weighted axial MRI showed a well-circumscribed lesion was located in the cortex of brain with high intensity of fluid content of the cyst and low intensity of a solid component without obvious peri-tumoral edema (white arrow); (c) On coronal MRI, the lesion was observed to be located in the cortex completely (white arrow), and (d) there was no remarkable contrast enhancement after administration of Gd-DTPA (white arrow)

Pathological examination

Both surgical specimens were fixed with 10% buffered formalin and embedded in paraffin for histological examination. Four-μm-thick sections were stained with hematoxylin and eosin (H&E). Immunohistochemical staining of paraffin sections was performed using the ChemMate Envision/HRP Kit (Dako, Glostrup, Denmark). The primary antibodies used in this study were: GFAP, vimentin, pan-cytokeratin (AE1/AE3), S-100 protein, oligodendrocyte transcription factor 2 (Olig-2), neuronal nuclei (NeuN), synaptophysin (Syn), CD34, IDH1 R132H, p53, and Ki-67.

For cytogenetic analysis, 1p/19q co-deletion in both lesions was detected by fluorescence in situ hybridization (FISH) utilizing the Vysis Dual Color Break Apart Probe (Vysis, Abbott Laboratories Inc., Maidenhead, UK). We detected 1p36 and 19q13 as target probes and 1q25 and 19p13 as control probes in paraffin-embedded sections in accordance with the manufacturer's protocol.

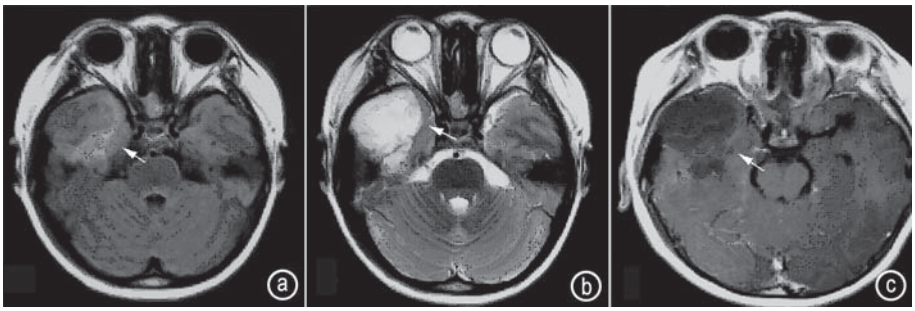

Fig. 2 Pre-operative MRI of the lesion of Case 2. (a) T1-weighted axial MRI exhibited a large hypointense cystic lesion with a mural nodule in the cortex of left temporal lobe (white arrow); (b) But the lesion was hyperintense on T2WI, with mild peri-tumoral edema (white arrow); (c) There was no contrast enhancement was observed in lesion (white arrow)

Results

Histopathological findings

On microscopic examination, both lesions exhibited similar histological appearances. The well-demarcated lesions were located within the cortex and partly extended into the adjacent cortex. They were non-encapsulated and displayed a cystic formation. No specific glioneuronal element with floating neurons within small mucoid lakes was found in either lesion. However, glial nodules, which constituted mural nodules on the cyst walls in both cases, were seen in association with the cystic architecture. The glial nodules were mainly composed of oligodendrocyte-like components, which showed a monomorphic appearance with uniform round nuclei and perinuclear halos. Scattered neuronal cells were observed to be embedded in the oligodendrocyte-like components. However, in contrast to typical oligodendrogliomas, no branching network of capillaries was present (Fig. 3a–c). In some areas of glial nodules, piloid cells with long, hair-like processes, resembling pilocytic astrocytoma, were identified (Fig. 3d). However, there were no Rosenthal fibers or eosinophilic granular bodies in either lesion. In addition, the cortex adjacent to the lesion in both cases was found to have the histological features of focal cortical dysplasia (FCD) Type I. In those areas, blurring of layer boundaries and distinct microcolumnar arrangements, which were composed of more than eight small diameter neurons, could be identified by NeuN immunohistochemistry (Fig. 3e–f, Fig. 4e).

Immunohistochemical and FISH findings

Immunohistochemically, the oligodendrocyte-like component was diffusely positive for Syn and Olig-2 and focally positive for S-100 protein. The scattered neuronal cells were positive for NeuN. The piloid cells in the lesions were positive for GFAP and Olig-2. However, there was no positive signal found for detection of pan-cytokeratin, CD34, P53, or IDH1 R132H. The Ki-67 (MIB-1) labeling index was only 1% focally (Fig. 4a–d). A total of 200 cells were observed for chromosomal abnormalities. We utilized 1p36 and 19q13 as target probes and 1q25 and 19p13 as control probes. Based on a cutoff value of 20%, there was no 1p/19q co-deletion found in either case (Fig. 4f).

On the basis of clinical manifestations, radiological features, and histopathological appearance; cortical location; cystic and mural nodule architecture without specific glioneuronal element; and the presence of FCD in adjacent cortex, a pathological diagnosis of DNT, non-specific variant, WHO grade I, was made.

Discussion

DNTs were first characterized by Daumas-Duport and his colleagues in 1988 to describe a surgically curable tumor found in young patients with intractable partial seizures [4]. Since 1993, the WHO classification of tumors of the central nervous system has accepted DNTs as a unique entity of "neuronal and mixed neuronal-glial tumors" [1]. However, at that time, the histological criteria of DNT were based on the initial description by Daumas-Duport and allowed only for the diagnosis of a morphological variant now referred to as the "complex form". In 2000 and 2007, the "simple form" and "non-specific form" of DNT were additionally described as unique variants of DNTs in later editions of the WHO classification [1, 5].

It has been suggested that DNTs include a large spectrum of tumors that cannot be distinguished histologically from ordinary gliomas, and that the diagnosis of such "non-specific histological forms" requires that clinical presentation and imaging features be taken into consideration. Because the "non-specific form" of DNTs lacks the specific glioneuronal element and multinodular architecture, this variant of DNTs is often histologically indistinguishable from low-grade gliomas, particularly when the cortical topography of the tumor is not apparent on non-representative samples. Therefore, it is important for neuropathologists that the diagnosis of DNT be considered whenever all of the following criteria are present: (I) partial seizures with or without secondary generalization, usually beginning before the age of 20 years; (II) no progressive neurological deficit; (III) predominantly cortical topography of a supratentorial lesion, best demonstrated on MRI; and (IV) no mass effect on computed tomography (CT) or MRI, except if related to a cyst, and no peritumor-

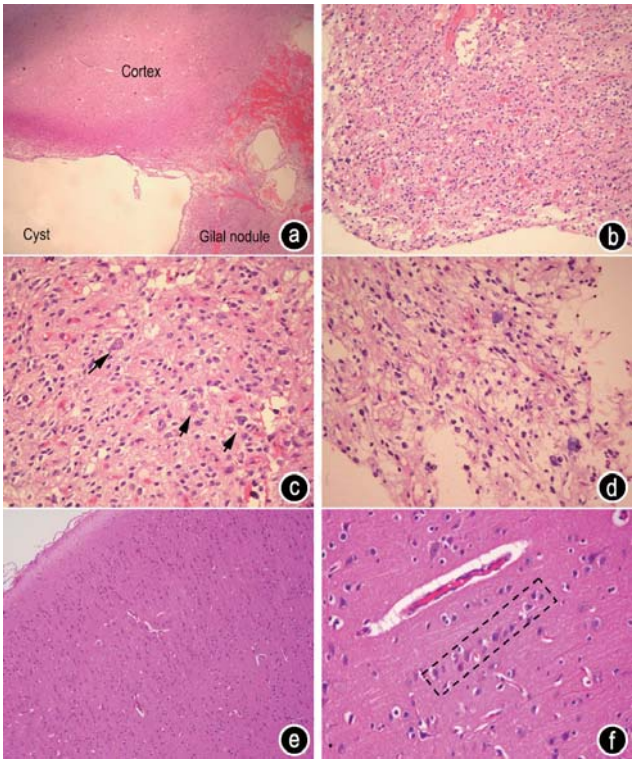

Fig. 3 Histological features of lesions in both cases. (a) At the lower power fields, the lesions could be found to be composed of cyst, cortex and glial nodule; (b) The glial nodule was mainly composed of oligodendrocytic-like cells with uniform round nuclei and perinuclear halos, resembling oligodendroglioma; (c) Scattered neuronal cells (black arrows) were observed to be embedded in the oligodendrocytic-like components; (d) In the some areas of glial nodules, piloid cells with long, hair-like processes, resembling pilocytic astrocytoma were identified, but there were no Rosenthal fibers and eosinophilic granular bodies in lesions; (e) The adjacent cortex of lesions was found to have the histological features of focal cortical dysplasia (FCD) Type I with blurring of layer boundaries and distinct microcolumnar arrangements; (f) At the higher power fields, a microcolumnar arrangement, which were composed of more than eight small diameter neurons could be identified (black dashed box) (a and e, HE staining × 100; b–d, f, HE staining × 400)

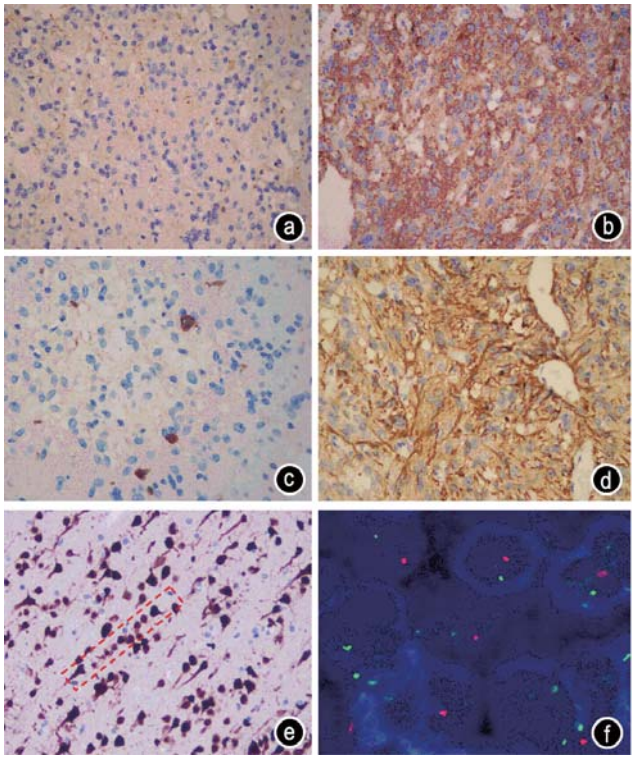

Fig. 4 Immunohistochemical and FISH assay of lesions. (a) The oligodendrocytic-like cells in glial nodule were negative for GFAP, but were diffusely positive for Syn (b); (c) The scattered neuronal cells were observed to have positive signal to Neu N; (d) However, the piloid cells with long, hair-like processes showed GFAP immuno-positivity; (e) NeuN immunohistochemical staining exhibited the microcolumnar arrangement in adjacent cortex with FCD (red dashed box); (f) FISH assay showed that there was no 1p/19q co-deletion in both lesions. The figure only showed FISH assay for 1p, the data of 19q detection was not shown here (a–e, immunohistochemical staining with original magnification × 400; f, FISH assay × 400)

al edema [1, 3]. In our cases, both patients had a supratentorial intracortical lesion with cyst formation, and no peritumoral edema or contrast enhancement was observed . They were young patients without neurological deficits or mass effect on MRI examination. The entire clinical presentation and all radiological features were consistent with the diagnostic criteria for DNTs. Furthermore, as in the complex form of DNTs, foci of cortical dysplasia could be identified in the cortex adjacent to both lesions. Such dysplastic changes in our cases strongly suggested that these tumors belonged to the category of DNTs.

Due to the absence of the specific glioneuronal element, which is characterized by parallel strands of axons, oligodendrocyte-like cells, and floating ganglion cells in microcystic mucopolysaccharide-rich areas [1], the diagnoses in our cases remain controversial. In addition, the histological appearance of oligodendroglioma-like and pilocytic astrocytoma-like areas in the lesions engenders diagnostic confusion with other low-grade infiltrating neoplasms, such as gangliogliomа, oligodendroglioma, and central neurocytoma. It has been documented that DNT has areas composed of astrocytic, oligodendroglial, and neuronal components. Theoretically, overgrowth of any of these may result in an independent tumor [1–4]. However, gangliogliomas, the presence of abnormal neurons, and lymphocytic cuffing were not observed in our cases. It is now well known that oligodendrogliomas are often characterized by 1p/19q co-deletion and mutation in the IDH1 gene [6–7]. In the present tumors, 1p/19q co-deletion and expression of mutant IDH1 were not detectable. The combination of these two negative findings is suggestive of DNT rather than oligodendroglioma. It is important to note that the precise origin of the OLCs in DNTs is still

unknown. Some of these cells express neuronal markers and exhibit synaptophysin, suggesting that the OLCs of DNTs may show an early neuronal differentiation [8–9]. However, recent results with in situ hybridization demonstrated that OLCs transcribe myelin genes and express myelin oligodendrocyte glycoprotein protein, indicating oligodendroglial differentiation [10]. Results from some studies have suggested that DNTs are originally oligodendrogliomas that occur preferentially in the cerebral cortex and have more benign biological behavior, corresponding to WHO grade I [11].

Although DNTs have been subcategorized into simple, complex or non-specific histological forms, we are well aware of the fact that there have been no clinical or therapeutic implications related to the different histological forms. Different histological subtypes of DNT might only reflect varied histological features and remind pathologists to avoid over-diagnosing lesions as low-grade or even high-grade gliomas or gangliogliomas. As there is no specific immunohistochemical marker for recognition of different subtypes of DNTs, we herein emphasize that the diagnosis of DNTs should be confirmed by clinical, radiological, and histological characteristics of patients. If there is absence of the specific morphological features in the lesion, all of the four criteria described above must be present to make an accurate diagnosis. In our experience, the diagnosis of the non-specific form of DNT should be considered particularly in children or young patients in cases in which a glial tumor exhibits an unusual histological appearance without the specific glioneuronal element, but showing a supratentorial intracortical lesion without peritumoral edema and mass effect. If the case presents diagnostic difficulties, close surveillance by imaging might be a better plan to objectively determine the actual behavior of the tumor, because radiotherapy and chemotherapy are contraindicated for DNTs [12–14]. Previously reported DNTs have usually shown no evidence of recurrence following resection. However, some studies have suggested that tumor recurrence after gross total resection or enlargement of the residual tumor with subtotal resection of DNTs may occur. There have even been reports that have documented tumor progression [15–16] or malignant transformation [17–18]. Risk factors for the development of recurrent seizures after operation on long-term follow-up included longer preoperative history of seizures, presence of residual tumor, and presence of cortical dysplasia adjacent to DNT [19–21]. Therefore, we suggest that a long period of follow-up is necessary even if the patient experienced complete relief upon initial surgical treatment.

In conclusion, we report two additional rare cases of the non-specific form of DNT with favorable prognosis occurring in young patients. Both tumors exhibited the conventional clinical manifestations and radiological appearance of DNTs, but lacked the specific histological features. In clinical practice, non-specific variants of DNTs are a diagnostic challenge for pathologists and may be confused with other low-grade gliomas. The careful inspection of radiologic and histopathologic findings may be helpful to make an accurate diagnosis.

References

1. Louis DN, Ohgaki H, Wiestler OD, *et al.* WHO classification of tumours of the central nervous system. Lyon: IARC Press. 2007.
2. Daumas-Duport C. Dysembryoplastic neuroepithelial tumours. Brain Pathol, 1993, 3: 283–295.
3. Daumas-Duport C, Varlet P, Bacha S, *et al*. Dysembryoplastic neuroepithelial tumors: nonspecific histological forms-a study of 40 cases. J Neurooncol, 1999, 41: 267–280.
4. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, *et al*. Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Report of thirty-nine cases. Neurosurgery, 1988, 23: 545–556.
5. Kleihues P, Cavenee WK. WHO classification of tumors of the nervous system. Lyon: IARC Press. 2000.
6. Reifenberger G, Kros JM, Louis DN, *et al*. Oligodendroglioma. In: Louis DN, Ohgaki H, Wiestler OD, *et al*. WHO classification of tumors of the central nervous system, 4th edn. Lyon: IARC Press, 2007. 54–59.
7. Thom M, Blümcke I, Aronica E. Long-term epilepsy associated tumors. Brain Pathol, 2012, 22: 359–379.
8. Wolf HK, Buslei R, Blumcke I, *et al*. Neural antigens in oligodendrogliomas and dysembryoplastic neuroepithelial tumors. Acta Neuropathol, 1997, 94: 436–443.
9. Hirose T, Scheithauer BW, Lopes MB, *et al*. Dysembryoplastic neuroeptihelial tumor (DNT): an immunohistochemical and ultrastructural study. J Neuropathol Exp Neurol, 1994, 53: 184–195.
10. Gyure KA, Sandberg GD, Prayson RA, *et al*. Dysembryoplastic neuroepithelial tumor: an immunohistochemical study with myelin oligodendrocyte glycoprotein. Arch Pathol Lab Med, 2000, 124: 123–126.
11. Takahashi H, Kakita A, Tomikawa M, *et al*. Oligodendroglioma (WHO grade I) in a young epilepsy patient: a specific entity lying within the spectrum of dysembryoplastic neuroepithelial tumor? Neuropathology, 2013, 33: 645–651.
12. Taratuto AL, Pomata H, Sevlever G, *et al*. Dysembryoplastic neuroepithelial tumor: morphological, immunocytochemical and deoxyribonucleic acid analyses in a pediatric series. Neurosurgery, 1995, 36: 474–481.
13. Raymond AA, Fish DR, Sisodiya SM, *et al*. Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumour and dysgenesis of the archicortex in epilepsy. Clinical, EEG and neuroimaging features in 100 adult patients. Brain, 1995, 118: 629–660.
14. Ranger A, Diosy D. Seizures in children with dysembryoplastic neuroepithelial tumors of the brain-A review of surgical outcomes across several studies. Childs Nerv Syst, 2015, 31: 847–855.
15. Sampetrean O, MaeharaT, Arai N, *et al.* Rapidly growing dysembryoplastic neuroepithelial tumor: case report. Neurosurgery, 2006, 59: E1337–1338.
16. Daghistani R, Miller E, Kulkarni AV, *et al.* Atypical characteristics and behavior of dysembryoplastic neuroepithelial tumors. Neuroradiology, 2013, 55: 217–224.

17. Hammond RR, Duggal N, Woulfe JM. Malignant transformation of a dysembryoplastic neuroepithelial tumor. Case report. J Neurosurg, 2000, 92: 722–725.
18. Chae JH, Kim SK, Wang KC. Hemifacial seizure of cerebellar ganglioglioma origin: seizure control by tumor resection. Epilepsia, 2001, 42: 1204–1207.
19. Aronica E, Leenstra S, van Veelen CW, *et al.* Glioneuronal tumors and medically intractable epilepsy: a clinical study with long-term follow-up of seizure outcome after surgery. Epilepsy Res, 2001, 43: 179–191.
20. Sakuta R, Otsubo H, Nolan MA, *et al.* Recurrent intractable seizures in children with cortical dysplasia adjacent to dysembryoplastic neuroepithelial tumor. J Child Neurol, 2005, 20: 377–384.
21. Nolan MA, Sakuta R, Chuang N, *et al*. Dysembryoplastic neuroepithelial tumors in childhood: long-term outcome and prognostic features. Neurology, 2004, 62: 2270–2276.

DOI 10.1007/s10330-015-0126-9
Cite this article as: Chen YY, Li B, Luo BN, *et al*. Non-specific histological variant of dysembryoplastic neuroepithelial tumor: a diagnostic challenge. Oncol Transl Med, 2016, 2: 104–109.