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CASE REPORT

# Desmoplastic non-infantile astrocytic tumor with BRAF V600E mutation

**Pinar Karabagli · Hakan Karabagli · Dogan Kose · Nadir Kocak · Volkan Etus · Yavuz Koksal**

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## Introduction

Desmoplastic infantile astrocytomas (DIA) are rare neoplasms of infancy which are defined by a combination of distinctive clinicopathologic features. DIA was originally defined in 1982 by Taratuto et al. as meningocerebral astrocytoma attached to dura with desmoplastic reaction. In 1993, it was included in the WHO classification under the term 'desmoplastic cerebral astrocytoma of infancy' [1]. DIA accounts for 1.25 % of pediatric brain tumors [2]. The large majority of cases presents within the first 24 months of life [1, 3]. Non-infantile cases are rarely encountered with only eight cases reported before [3–10]. However, in two of these cases, clinical symptoms ensued within the first year of life [4, 5]. Less is known about the molecular etiology of DIA [1, 11]. Recent studies suggest that certain types of mostly low grade and pediatric brain tumors may have higher rates of BRAF alterations. BRAF V600E mutations have been detected in small series of pediatric gangliogliomas, pleomorphic xanthoastrocytomas, desmoplastic infantile gangliogliomas and atypical teratoid/rhabdoid tumors as well as pediatric glioblastomas, anaplastic astrocytomas and diffuse astrocytomas [11–15].

P. Karabagli (✉)
Department of Pathology, Faculty of Medicine, Selcuk University, Candir Mah. Candir Sok. Hazal Sitesi No. 24/C, 42090 Meram, Konya, Turkey
e-mail: pinarkarabagli@yahoo.com

H. Karabagli
Department of Neurosurgery, Faculty of Medicine, Selcuk University, Konya, Turkey

D. Kose · Y. Koksal
Department of Pediatric Oncology, Faculty of Medicine, Selcuk University, Konya, Turkey

N. Kocak
Department of Medical Genetics, Faculty of Medicine, Selcuk University, Konya, Turkey

V. Etus
Department of Neurosurgery, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

## Case report

The patient was a 6-year-old male who presents with headache, nausea and vomiting of 1 year duration. Neurological examination showed no abnormality. Neuroradiological imaging revealed triventricular obstructive hydrocephalus with 45 × 40 mm solid and cystic mass located in the supratentorial and infratentorial region, on the middle line and in the right of middle line as well as cerebral hemisphere (Fig. 1a, b). The mass was hypointense on T1 weighted (W) and hyperintense on T2W, and heterogeneously intensive enhanced with gadolinium (Fig. 1c). The mass located in the neighborhood of the tentorium, falx cerebri, 3rd ventricle, pineal region, and posterior horn of right lateral ventricle was applied significant compression of the mass to surrounding structures (Fig. 1a–c). The patient underwent third ventriculostomy and endoscopic biopsy was taken from the mass. Histopathological examination revealed a low-grade astrocytoma. It was decided to follow the patient.

Four months after the first surgery, radiologically the mass was found to reach to 67 × 50 mm in the same localization. The patient was applied total resection of the tumor. The tumor was rubbery, lobulated, yellowish-grey in color, and harboring cystic components filled with xanthochromic fluid (Fig. 2a, b). Microscopically, the most

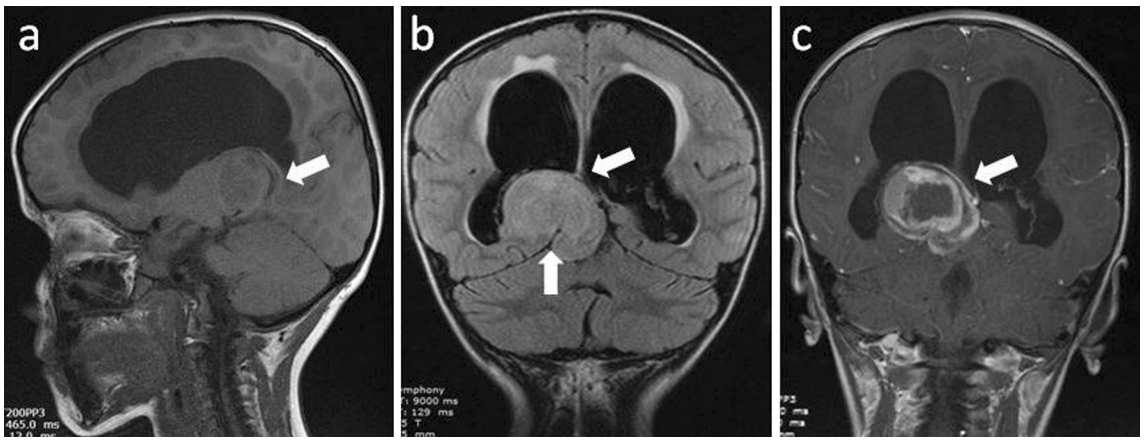


**Fig. 1** MRI on admission and obstructive hydrocephalia with 45 × 40 mm solid and cystic mass located in the supratentorial and infratentorial region, **a** sagittal view of a T1W image (*T1WI*), **b** Coronal view of a T1WI, **c** Coronal view of a contrast-enhanced T1WI. *Arrows* indicate the mass of the neighborhood with tentorium and falx

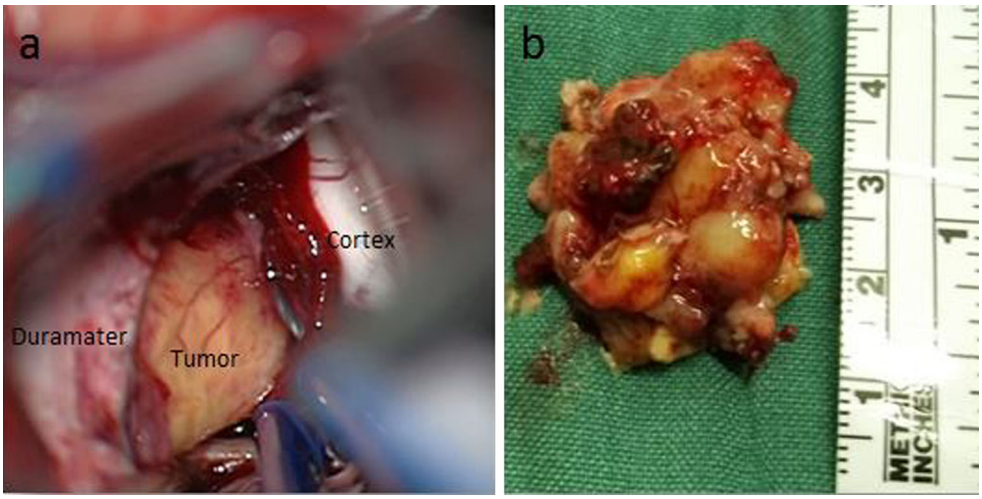


**Fig. 2** **a** Intraoperative view of the tumor, the mass localized between tentorium and cortex. **b** Macroscopic appearance of resected mass

striking feature of the present case was the tumor cells. The spindle or oval nuclei and fine fibrillary cytoplasm were arranged in groups of fascicles (Fig. 3a). Reticulin stain disclosed the rich reticulin network that entrapped the groups of the tumor cells (Fig. 3b). However, there are some reticulin-poor areas in the tumor section (Fig. 3c, d.). Microcalcification and angiomatoid vessels were seen focally (Fig. 4a). Indeed, there were no neurons or apparent neuronal differentiations seen in the examined tumor area. Vascular endothelial proliferation, but no mitosis and necrosis was seen (Fig. 4b). The tumor cells were diffuse positive for glial fibrillary acidic protein (GFAP), vimentin, S-100 and Olig 2 (Fig. 4c, d). Although rare synaptophysin immunopositive cells were seen, still there was also no stainings with neuroflament protein (Fig. 4e). MIB-1 labeling index of the tumor was 3 % in the most marked areas (Fig. 4f). p53 expression in 15 % of tumor cells was detected. Overall features were suggestive of grade I (WHO 2007) desmoplastic astrocytoma.

Tumoral tissue was evaluated in terms of genetic issues. We used the DNA Sample Preparation Kit (Roche Molecular Systems, South in Branchburg, USA) to isolate DNA from paraffin tissue. BRAF V600E mutation analysis from isolated DNA was made through the Light Cycler 480 Real-Time PCR (Roche, Laval, QUE, Canada). To do this, BRAF Mutation Analysis Kit was used (EntroGen, Thessaloniki, Greece) and PCR conditions held in accordance with the instructions. Evaluating the amplification and melting curve, we tried to figure out if it was BRAF V600E mutation. As a result of analysis, the BRAF V600E mutation was found in our case.BRAF V600E mutation is a dominant-acting mutation. Since we carry out the experiment on the parafin block, we present the data in the form of presence/absence.

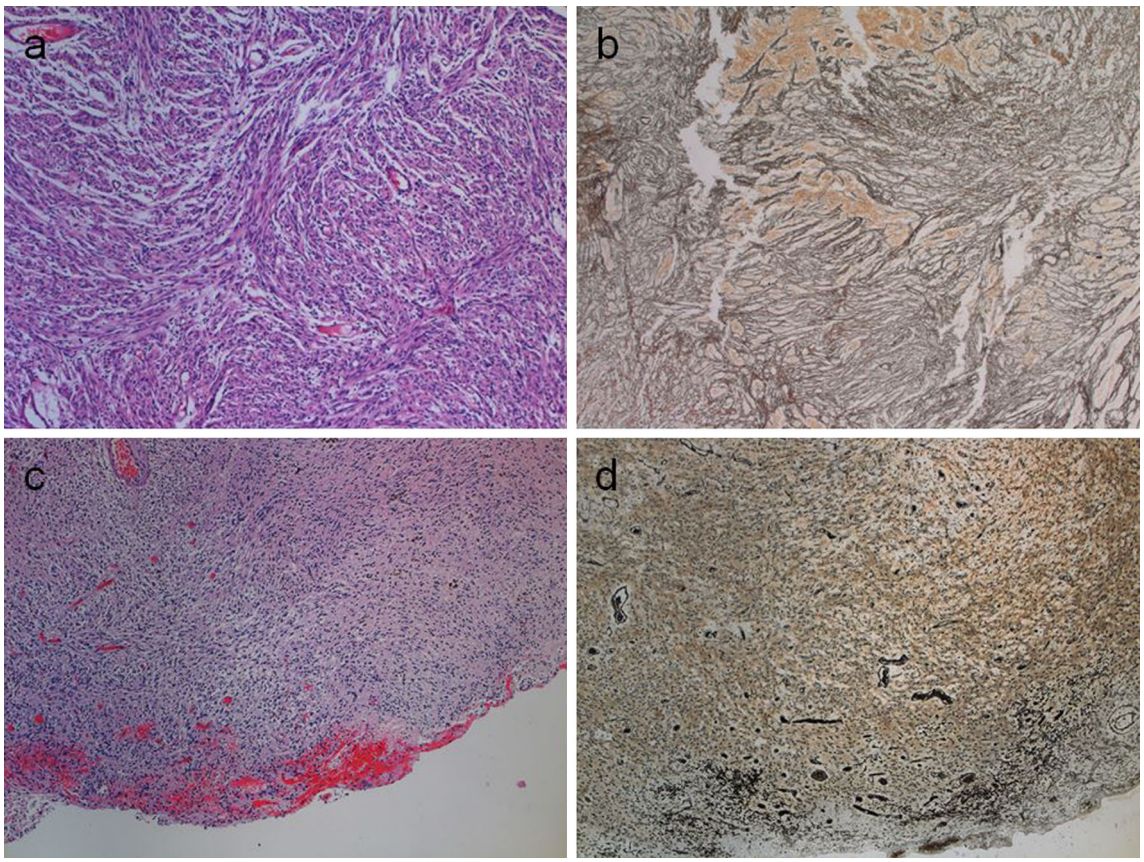


**Fig. 3** **a–b** Histopathologic features of the desmoplastic component of the tumor. **a** The tumor composed of spindle-shaped tumoral cells (HE stain; ×100), **b** reticulin-rich desmoplastic stroma (Gomori reticulin stain; ×100); **c–d** histopathologic features of the cortical, non-desmoplastic component of the tumor. **c** Spindle-shaped tumoral cells in the non-desmoplastic stroma (HE stain; ×100), **d** the reticulin-poor stroma of the tumor (Gomori reticulin stain; ×100)

It was decided to follow the patient, because of the total tumor resection, and diagnosis of the tumor. Nine months after the cranial MRI revealed a 60 × 76 mm cystic and solid mass compress to right lateral ventricle with heterogenous contrast enhancement. The tumor was totally removed (Fig. 5a). The histopathologic features were suggestive of desmoplastic astrocytoma as before (Fig. 5b). However, mitotic figure was 3/10 high power field (Fig. 5c). MIB-1 labeling index was 3 %. Microcalcification was seen. The postoperative period was uneventful. Radiotherapy and chemotherapy (vincristine, cisplatin and etoposide) implementation was planned. Total 5400 cGy radiotherapy was applied in 30 fractions. Chemotherapy implementation continues. At 7th month follow-up, the patient was free of any signs or symptoms.

## Discussion

DIA has distinct clinical and pathological features; these features include occurrence in infancy, a superficial location in the cerebral hemisphere, well demarcated, often partially cystic and a firm mass consisting of an astrocytes and collagen fibers [1, 5].There are 8 non-infantile cases reported to the literature with ages varying between 3.5 and 18 and having similar histopathologic and clinical characteristics [3–10]. The demographic features of the previously reported cases are summarized in Table 1. Four of these cases were male and 3 of these cases were female [3–5, 7–10]. Gender was not reported for one of the cases [6]. Since our case is male, male dominance can be argued for desmoplastic infantile astrocytoma; however, number of the cases is not sufficient to make an accurate statement.

DIA's invariably arise in the supratentorial region and commonly involve more than one lobe massive [1]. Meningeal attachment was reported for two of the published non-infantile cases [3, 7]. In addition to this, more than one lobe involvement was found for three of the cases [3, 4, 9]. One of the case is located in spinal cord [10]. In our case, tumor tissue was located in parieto-occipital lobes both in supratentorial and infratentorial regions. Although the tumor was located in the neighborhood of the tentorium and falx cerebri, there was no apparent dural attachment found.

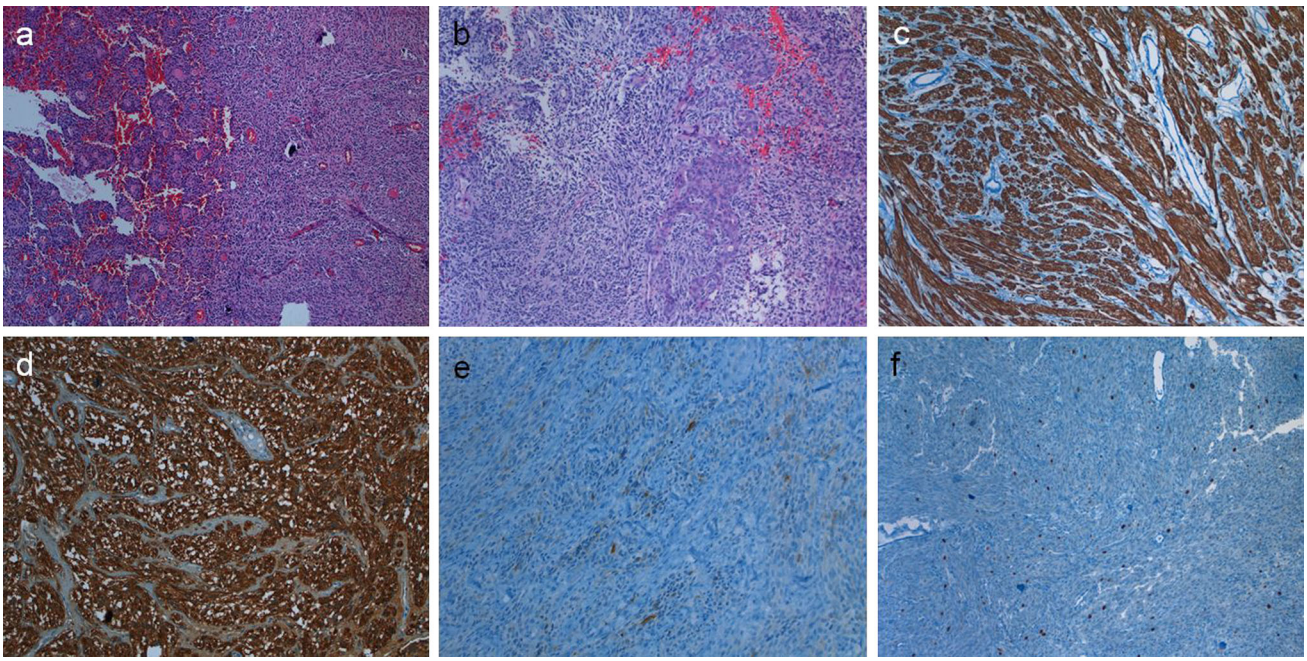


**Fig. 4** **a–f** Histopathologic and immunohistochemical features of the tumor. **a** Calcification and angiomatoid vessels in the tumor (HE stain; ×100), **b** vascular endothelial proliferation was seen (HE stain; ×100), **c** immunohistochemically, tumor cells were diffuse positive for GFAP (×100), **d** diffuse immunopositivity for S-100 (×200), **e** rarely distributed synaptophysin immunopositive cells (×200), **f** MIB-1 index of the tumor was 3 % (×100)

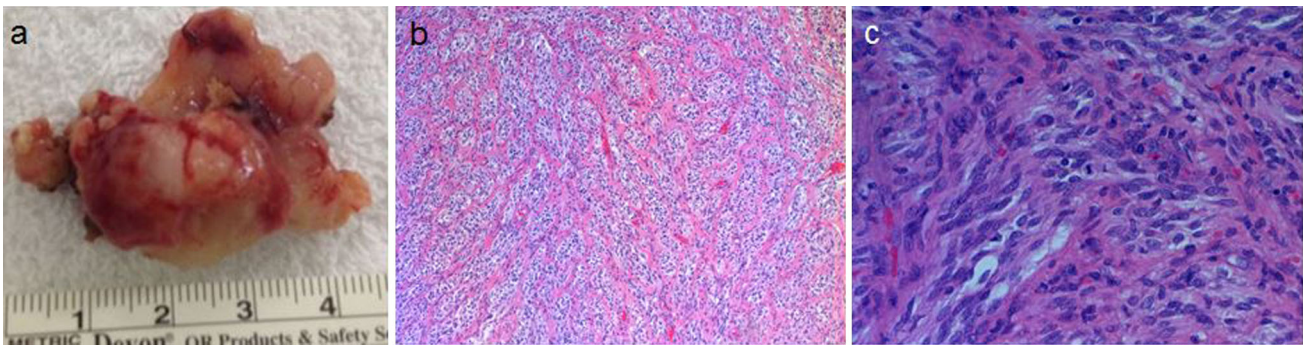


**Fig. 5** **a** Macroscopic appearance of relapsed mass, **b** histopathologic features of the tumor (HE stain; ×100), **c** mitosis was seen in the tumor (HE stain; ×400)

Radiologically, DIA is seen as a cystic mass having a solid peripheral component [1]. The solid component is generally localized in the peripheral of the tumor and attached to the dura and isointense on T1 and T2 [1, 3]. Cystic component is hypointense on T1 and hyperintense on T2 in MRI. Calcification can be seen [1]. Cystic component was not seen only in one of the above mentioned cases [9]. Both cystic component and microscopic level calcification are seen in our case.

Less is known about the molecular etiology of DIA [1, 11]. Alterations in BRAF have been discovered in most pediatric low-grade gliomas [11, 14, 15, 16, 17]. However, knowledge about genetic alterations in desmoplastic infantile astrocytoma/ganglioglioma (DIA/DIG) is limited. Schindler et al. [15] analyzed exon 15 of BRAF spanning the V600 locus by direct sequencing in 1,320 adult and pediatric tumors of the nervous system, BRAF V600E mutation was not detected in none of four DIA/DIGs. Recently, BRAF V600E mutations have been detected in small series of DIA/DIGs, but only one case of them was DIA [11, 17].

The limited number of cases in both studies did not allow any conclusion about mutation frequency of BRAF in this tumor entity. We identified a BRAF V600E mutation in a non-infantile desmoplastic astrocytoma, suggesting that the MAPK pathway may be activated in the present tumor.

**Table 1** The demographic features of the previously reported cases

| References | Age/ sex | Complaint, duration | Physical examination | Neuroradiologic imaging | Histopathology | Location | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|
| Chacko et al. [4] | 7/F | Seizure, 6, 5 years | Hemianopia, facial paralysis | CT: cystic mass | Collagen fibers. Tricrom (+), vimentin (+), GFAP (+), S-100 (−), KP-1 (−) | L fronto-temporo-parietal | Marsupialization + biopsy | 24 months, No recurrence |
| Kurose et al. [5] | 9/M | Seizure, 8, 5 years | Mental retardation | CT: cystic mass Meningeal involvement (−) | GFAP (+), vimentin (+), S-100 (+), synapthophysin (+), calcification (+), MIB-1 LI % 1–2.9, no necrosis and endothelial proliferation (−) | R temporal | Total excision | 6 months, No recurrence |
| Mallucci et al. [6] | 3, 5/NM | Hemiparesis, 16 months | Swelling in the bone | MRI: cystic mass Meningeal involvement (−) | GFAP (+), mitosis (+) | NM | NM | NM, No recurrence |
| Kato et al. [7] | 9/M | Motor and sensorial disturbance, 2 days | NM | MRI: cystic mass Meningeal involvement (+) | Desmoplastic stroma. GFAP (+), vimentin (+), NFP (−), class III beta-tubulin (−), MIB-1 LI 1 % | L sensorio-motor | Total excision | 12 months, No recurrence |
| Ulu et al. [3] | 4/F | Headache, attention deficit, limitation of movement of the left hand, 7 days | Drowsiness, mild hemiparesis | MRI: cystic mass Meningeal involvement (+) | Desmoplastic stroma. GFAP (+), vimentin (+), S-100 (+), MIB-1 LI low. fokal necrosis (+) | R parieto-occipital | Total excision | 11 months, No recurrence |
| Santhosh et al. [8] | 11/M | Stiffness of limbs, visual obscuration, 1 month | Thenar and hypothenar muscle loss | MRI: solid component hypointense in T1W, hyperintense in T2W; cystic component hyperintense in T2W. Meningeal and cervico-thoracic cysts. Calcification (+) | Reticulin(+), GFAP (+), no ganglion cells | L anterior frontal, spinal cord | Ventriculo-peritoneal shunt | 8 months, Recurrence in 8 months |
| Uro-Coste et al. [9] | 5/M | Seizure, 2–3 years | Midriazis | MRI: the mass is isointense in T1 W and T2 W. Multiple leptomeningeal involvement (+). Calcification (+) | Desmoplastic stroma. GFAP (+), NCAM (+), synaptophysin (weakly +), NFP (−), EMA (−), MIB-1 LI 3 %, no mitosis and necrosis | R temporal, cisterna magna, L cerebellar hemisphere | Excision + chemotherapy | 6 months, No recurrence |
| Rasalkar et al. [10] | 18/F | Weakness and stiffness in the legs, 2 years | Spastic paraparesis, (+) plantar reflex | MRI: solid component isointense in T1W and T2W; cystic component iso-hypointense in T1W, hyperintense in T2W. Meningeal involvement (−) | Collagenous stroma. GFAP (+), MIB-1 LI 3 %, no necrosis and neuronal cell | Spinal cord (Thoracal 7–8) | Subtotal excision | 48 months, No recurrence |

**Table 1** continued

| References | Age/sex | Complaint, duration | Physical examination | Neuroradiologic imaging | Histopathology | Location | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|
| Our case (2013) | 6/M | Headache, seizure, 1, 5 years | Normal | MRI: cystic and solid component hipointense in T1W, hyperintense in T2W. Meningeal involvement (−) | Reticulin-rich desmoplastic stroma. GFAP (+), vimentin (+) and Olig 2 (+), P53 (+) in 15 % of cells. Vascular endotelial proliferation (+), microcalcification (+), necrosis (−). Mitosis 3/10 BB in recurrence, MIB-1 LI 3 %. | R parieto-occipital | Total excision + radiotherapy + chemotherapy | 20 months, Recurrence in ninth month |

*F* female, *M* male, *CT* computed tomography, *MRI* magnetic resonance imaging, *T1W* T1 Weighted, *T2W* T2 Weighted, *NM* not mentioned, *LI* labeling index, *R* right, *L* left

Since 1993, DIA has been included in the category of mixed neuronal glial neoplasms under the WHO classification. DIA are voluminous, show intense desmoplasia and astrocytic differentiation. Microscopically, tumor exhibits three distinctive components: the main desmoplastic leptomeningeal component, the poorly differentiated neuroepithelial component, and the cortical component. The desmoplastic component consists of spindle-shaped tumoral cells, embedded in a reticulin-rich desmoplastic stroma [1]. The poorly differentiated neuroepithelial component often present in variable amounts in DIA, is reported to stain with synaptophysin or other neuronal markers [1, 9]. The cortical component devoid of desmoplasia may also be observed, and this neoplastic component is often multinodular. There is a sharp demarcation between the cortical surface and desmoplastic tumor. Calcifications are common. Mitotic activity and necrosis are uncommon [1].

In our case, histopathological examination of the mass showed a tumor without marked atypia and necrosis. There are few mitotic figures but low MIB-1 immunoreactivity in the relapsed tumor. In the large areas of the tumor, spindle and oval shaped tumoral cells stained with GFAP are embedded in a reticulin-rich dense stroma. However, there are reticulin-poor non-desmoplastic areas present in the tumor. Although there are no neurons or neuronal differentiation, still some rare synapthophysin immunopositive primitive neuroepithelial cells were seen. Fragments of the tumor tissue under consideration were free of meninges or cortex.

DIA shares a number of clinicopathologic features with the DIG, including presentation in infancy, supratentorial cerebral location, and desmoplastic stroma. However, their main histopathological difference resides in the absence of neuronal differentiation in the DCAs, as its neuroepithelial component is restricted to neoplastic astrocytes, embedded in a dense fibrous stroma, with no mitotic figures or micronecrosis [1]. Pleomorphic xanthoastrocytoma (PXA) is an astrocytic tumor. PXAs have superficial localization involving the meninges and cerebrum, cystics components and good prognosis. Microscopically, PXAs are differentiated from DIAs by the presence of prominent pleomorphism and xanthomatous change of tumor cells. Moreover, PXAs usually occur in adolescents or young adults [3, 18].

Follow-up studies indicate that gross total resection results in long-term survival case of DIA. Thus, surgery alone with total removal appears to offer local tumor control in DIA despite the presence of primitive-appearing cellular aggregates with mitotic activity or foci of necrosis. In cases of subtotal resection or biopsy, most tumors are stable or regrow slowly [1].A recurrence was reported only in one of the cases [8].

Cases developing metastases and requiring adjuvant treatments such as chemotherapy and/or radiotherapy were

reported in the literature [19]. For partial resection, recurrence not suitable for another operation or progressive residual tumors, chemotherapy is recommended and for the patients for whom chemotherapy turns out to be unsuccessful and above 5 year old, radiotherapy is recommended [20]. In the current case, despite the benign histologic characteristics, a recurrence was seen 9 months after total excision. For this reason, patient received radiotherapy and chemotherapy and then no recurrence was seen in the following 8 months.

## Conclusion

Although it has been generally accepted that the DIA is an tumor of infants, it can also be seen in older patients. We present the first non-infantile desmoplastic astrocytoma case for which a BRAF V600E was identified.

**Conflict of interest** There is no conflict of interest.

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