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CASE REPORT

Desmoplastic infantile astrocytoma: recurrence with malignant transformation into glioblastoma: a case report

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Abstract Desmoplastic infantile astrocytoma (DIA) is an uncommon brain tumor of early infancy. The tumor is characterized by a lobar location, glial histology, and excellent prognosis after surgical removal. DIA and a similar tumor, desmoplastic infantile ganglioglioma (DIG) have been considered to be benign neoplasms, but the prognosis of DIA and DIG is currently under question as atypical and aggressive clinical features of the tumors have been reported. We encountered a patient who was diagnosed with DIA at the age of 22 months and exhibited tumor recurrence 8 years later. Surgical removal of the recurred tumor revealed that the tumor had transformed to overt glioblastoma. This case demonstrates that DIA is not an absolutely benign tumor and that careful clinical surveillance is needed during the follow-up period.

Keywords Desmoplastic infantile astrocytoma · Malignant transformation · Glioblastoma

Introduction

Desmoplastic infantile astrocytoma (DIA) is an uncommon brain tumor affecting young children that usually develops within the first 2 years of life. The tumor is typically a huge cystic tumor in the superficial cerebrum, composed of neoplastic astrocytes and marked desmoplastic stroma. DIA, along with desmoplastic infantile ganglioglioma (DIG), has a relatively favorable prognosis after total surgical resection. Therefore, the tumors are considered benign in most instances and correspond to the World Health Organization (WHO) grade 1. However, the invariably benign nature of these tumors is under question because there are several reports describing DIA and DIG with aggressive clinical and pathological features. Cerebrospinal seeding at presentation [1–6], high proliferation index [7], and possible transition to ganglioglioma [8] have been reported for patients with DIA and DIG. However, overt malignant transformation of these tumors has rarely been reported. We encountered a patient who underwent complete surgical removal of DIA that recurred and progressed to glioblastoma 8 years later. This case clearly demonstrates that DIA is not an absolutely benign tumor and that careful clinical surveillance is needed during the follow-up period.

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Case report

A 7-month-old female baby was referred to Seoul National University Children's Hospital because of syncope and vomiting. Magnetic resonance imaging (MRI) revealed a hemorrhagic lesion in the right frontotemporal lobe. The baby was conservatively treated and discharged without neurological deficits. Follow-up MRI taken after 3 months showed a huge hemorrhagic cyst and a discrete small round mass with strong rim enhancement in the cyst (Fig. 1a). Cerebral angiography revealed no vascular abnormalities. Surgical exploration was recommended, but the parents refused to allow their child to undergo an operation. At the

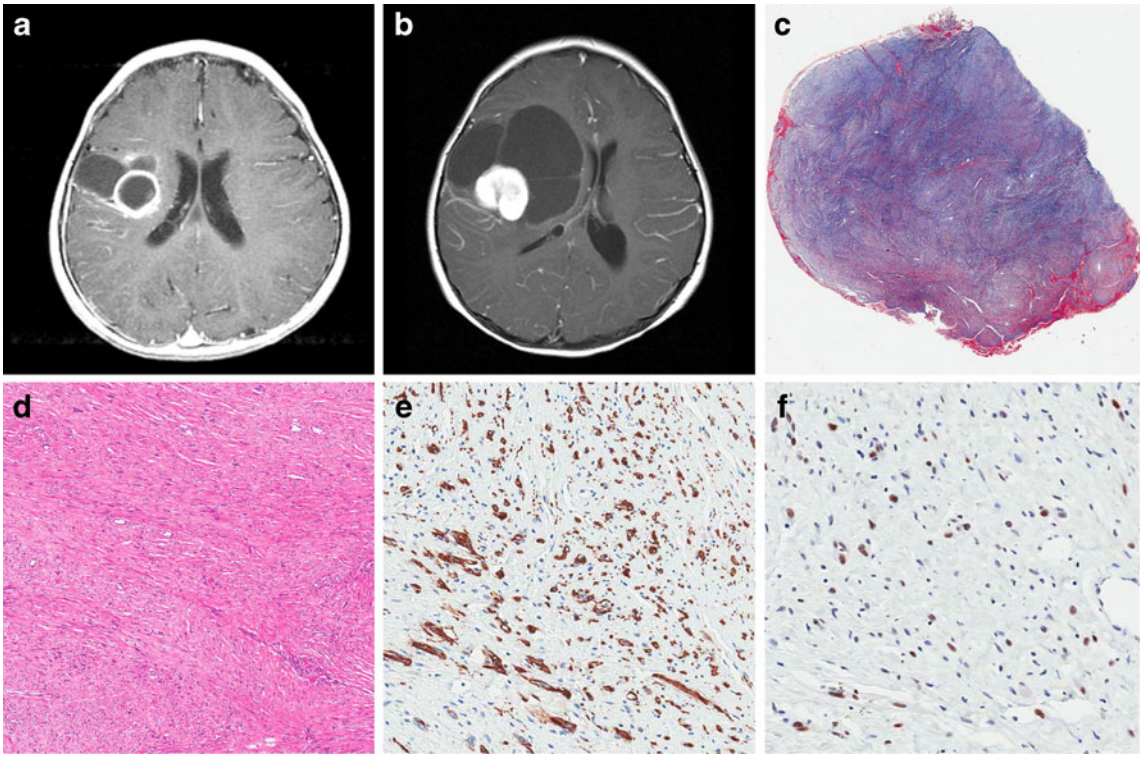

Fig. 1 **a** An axial T1-weighted MR image of the patient 3 months after the initial presentation. There is a resolving hematoma with a rim-enhancing cystic mass at the right frontotemporal lobes. **b** An axial T1-weighted MR image taken 1 year later shows a huge cystic mass with multiple septations and a solid well-enhancing portion. **c** On Masson's trichrome staining, the tumor looks blue due to marked collagen deposits (Masson trichrome, ×1). **d** Hematoxylin and eosin (H & E) staining reveals the characteristic fascicular arrangement of tumor cells (H & E, ×30). **e** The individual tumor cells were robustly positive for GFAP (immunohistochemistry, ×200). **f** P53 was strongly positive in 25–50% of tumor cells (immunohistochemistry, ×200)

age of 22 months, she developed progressive hemiparesis in the left side. At that time, MRI showed a huge cyst with a solid mural nodule in the same area. The cystic wall showed faint enhancement, and several septa were observed within the cyst. The solid portion had dot-like signals on T2-weighted images, which indicated the presence of calcification and showed strong enhancement on T1-weighted images (Fig. 1b). The initial radiological features of this patient were previously reported [9]. Surgical removal of the lesion was attempted. The solid tumor was completely removed after aspiration of the cystic fluid. Pathological examination confirmed the diagnosis of DIA, which was composed of long fascicles of spindle cells embedded in the densely collagenous background. Marked collagen deposition was noted on Masson's trichrome staining (Fig. 1c). The tumor cells showed low cellularity but exhibited nuclear pleomorphism (Fig. 1d). Low mitotic index (<1/10 HPF) with low Ki-67 labeling index (<1%) was noted. There was scattered calcification. The tumor was positive for glial fibrillary acidic protein (GFAP) and P53 (Fig. 1e, f).

After the operation, the patient recovered fully from hemiparesis. Postoperative MRI (1 year after the operation) showed no enhancing lesion. However, 18 months later, a new, small enhancing mass was observed along the medial side of the surgical cavity. Close follow-up was planned, but the patient was lost to follow-up for 7 years thereafter.

At her age of 10 years, the patient visited the outpatient clinic due to the recent development of left arm weakness. MRI revealed a huge cystic lesion with a mural nodule on the medial side of the previous tumor site. Strong rim enhancement was noted in the solid portion of the tumor and along the cystic walls (Fig. 2a, b). The patient underwent gross total removal of the tumor by craniotomy. However, proximity to the right internal capsule prevented the creation of a wide resection margin. Pathological examination showed a highly cellular and GFAP-positive astrocytic tumor. Pleomorphic nuclei, pseudo-palisading necrosis, and vascular endothelial hyperplasia were observed (Fig. 2c, d). Mitoses were frequent (7/10 HPF) and the Ki-67 index was 19.7%. The tumor was diagnosed as glioblastoma. A long fascicular pattern, reminiscent of DIA, was observed in a small portion of the tumor, but marked nuclear pleomorphism and mitoses were also present in that area (Fig. 2e). Neither 1p and 19q chromosomal deletion nor EGFR gene

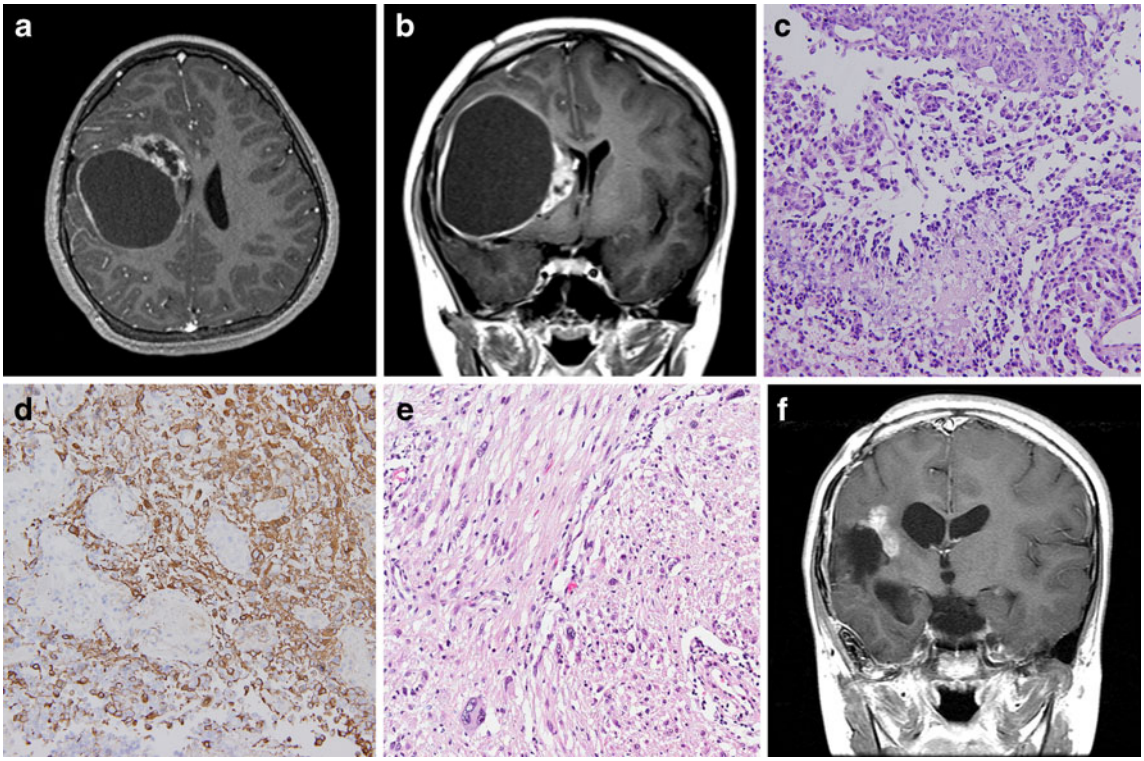

Fig. 2 **a**, **b** Axial and coronal T1-weighted MR images of a recurred tumor in the patient at 10 years of age. A huge cystic mass developed at the same location with an irregularly rim-enhancing solid portion. **c** A typical glioblastoma area shows highly cellular pleomorphic glial cells with geographic pseudo-palisading necrosis and vascular endothelial hyperplasia (H & E, ×200). **d** The tumor cells were positive for GFAP (immunohistochemistry, ×200). **e** The recurred tumor contained an area with a long fascicular pattern, which was reminiscent of DIA, but marked nuclear pleomorphism and mitoses were also observed in that area (H & E, ×120). **f** MRI taken 8 months after the second operation shows new enhancement along the medial side of the surgical defect. The patient underwent a third surgical resection of the tumor

amplification was found by fluorescence in situ hybridization. MGMT methylation was present on methylation-specific PCR. The patient postoperatively developed transient left hemiparesis, but fully recovered from it. She received concurrent radiotherapy (61.2 Gy) with temozolomide (75 mg/day). Maintenance chemotherapy with temozolomide (200 mg/day for 5 days every 4 weeks) was administered. In spite of complete excision and adjuvant therapy, the patient experienced recurrence again 8 months after the second operation (Fig. 2f), and the recurred tumor was completely resected during the third operation. She has been alive with mild left hemiparesis for 14 months after the diagnosis of glioblastoma (6 months after the third operation) and is undergoing adjuvant chemotherapy (Children's Oncology Group A9952 regimen [10] + temozolomide).

Discussion

DIA and DIG are rare brain tumors that occur at infancy. In 1984, Taratuto et al. [11] described the clinical and pathological features of DIA as "superficial cerebral astrocytoma of infancy". Shortly thereafter, Vandenberg et al. [12] reported a similar entity of DIG, which has virtually the same histopathological features as DIA except for the presence of neuronal components. In 1993, DIA and DIG were included in the WHO classification of brain tumors [13]. The prognosis of DIA and DIG is excellent, and these tumors correspond to WHO grade I tumors. Complete surgical resection generally results in long-term remission and survival. Moreover, there are reports on patients who showed spontaneous regression of DIA and DIG [14, 15] or no progression after incomplete resection [16–18].

However, several studies reported atypical clinical and pathological features of DIA and DIG, raising questions about the invariably benign nature of DIA and DIG. Al-Sarraj et al. [19] reported a brain tumor characterized by a superficial location with onset occurring at infancy and glial cells with desmoplasia, which are all characteristics typical of DIA, but the tumor had brisk mitoses and necrosis. The authors described it as "desmoplastic cerebral glioblastoma of infancy" despite the indolent clinical course of the patient. A patient with a potentially malignant DIG with

high mitotic activity, high Ki-67 index, necrosis, and endothelial proliferation was reported [20]. This patient developed rapid progression and metastases after partial resection. Hoving et al. [21] reported a patient with DIG with a recurrence and transformation to a high-grade primitive neoplasm. Several authors also reported seeding of DIA and DIG along the craniospinal axis [1–6]. These anecdotal cases provoked skepticism regarding the invariably benign nature of DIA and DIG (Table 1).

Our patient also had a DIA that progressed to overt glioblastoma 9 years after the initial presentation (8 years after pathological diagnosis of DIA). Initially, the tumor in this patient was typical of DIA in terms of tumor location, age of onset, histology, low mitotic index (<1/10 HPF), and low Ki-67 labeling index (<1%) except for hemorrhagic presentation and calcified dots on neuroimaging. Although hemorrhage is unusual for DIA, many benign tumors often present with hemorrhage. Calcification in the tumor, which was previously considered as unusual for DIA [9], appears to be a common feature of DIA and DIG [22]. After 8 years of a symptom-free state, the tumor in the presented case recurred with malignant transformation. This case report adds to the rare, but important documentation of aggressive clinical behavior exhibited by DIA and DIG.

The origin of DIA and DIG is still obscure. The WHO classification of brain tumors placed DIA and DIG in the category of neuronal and mixed neuronal–glial tumors along with ganglioglioma [13]. Interestingly, regarding DIG, the relevancy between the tumor and classic ganglioglioma has been proposed based on some cases with DIG containing areas suspected as conventional ganglioglioma [8, 23]. Komori et el.[8] suggested that "ganglion-like cells" in the immature component of DIG may progress to mature ganglion cells of ganglioglioma and that DIG may be a variant of ganglioglioma. Ganglioglioma is a potentially malignant neoplasm. Anaplastic features and malignant transformation have been reported, especially after incomplete surgical resection [24, 25]. If DIA and DIG share their histogenesis with ganglioglioma, the pathogenetic link can lead to malignant transformation to high-grade glioma.

In conclusion, the invariably benign nature of DIA and DIG is questionable. Although benign in the overwhelming majority of cases, DIA and DIG can progress to aggressive biological behavior. Therefore, careful observation is necessary after the surgical resection of DIA and DIG, especially after incomplete surgical resection of the tumor.

Table 1 DIA and DIG with histologically or clinically malignant behaviors

Author [reference]	Sex/age	Histology	Malignant features	Prognosis
Al-Sarraj [19]	F/8 months	DIA	Mitoses and pseudo-palisading necroses	Alive after 36 months
Setty [1]	M/4 months	DIA	Tumors in the suprasellar area, hypothalamus, posterior fossa, and spinal canal	Alive after 38 months
De Munnynck [20]	F/2 years	DIG	High Ki-67 index (45%), necrosis, and endothelial proliferation. Tumors in the right hemisphere and hypothalamus with pial enhancement along the brain stem and spinal canal	Dead after 2 months
Taranath [2]	M/3 months	DIG	Tumors in the left hemisphere, basal cisterns, and cervical spine	Alive after 8 months
Taranath [2]	M/4 months	DIG	Tumors in the suprasellar cistern, fourth ventricular outlet, tentorium, and brainstem	Dead after 1 month
Milanaccio [5]	M/22 months	DIG	Diffuse leptomeningeal seeding	Alive after 30 months
Tantbirojn [7]	M/10 months	DIG	High Ki-67 index (30%)	Alive
Lonnrot [6]	M/5 months	DIG	Tumors in the suprasellar cistern, ventricle, prepontine cistern, and optic nerve	Alive after 24 months
Hoving [21]	M/7 months	DIG	(First operation) astrocytic and neuronal elements with desmoplasia and some primitive component, low Ki-67 index (5%); (second operation) highly primitive cells with glial differentiation, high Ki-67 index (30%)	Dead after 9 months
Uro-coste [4]	M/5 years	DIA	Tumors in the left temporal area, posterior fossa, and basal cistern	Alive after 12 months
Present case	F/22 months	DIA	(First operation) long fascicles of spindle cells embedded in the densely collagenous background, low Ki-67 index (<1%); (second operation) highly cellular pleomorphic glial cells with geographic pseudo-palisading necrosis and vascular endothelial hyperplasia, Ki-67 index (19.7%)	Alive after 9 years

DIA desmoplastic infantile astrocytoma, *DIG* desmoplastic infantile ganglioglioma

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