Unusual Occurrence of Multifocal Desmoplastic Infantile Astrocytoma: A Case Report and Review of the Literature

Vinayak Narayan\textsuperscript{a} Amey R. Savardekar\textsuperscript{a} Anita Mahadevan\textsuperscript{b} A. Arivazhagan\textsuperscript{a} Lingegowda Appaji\textsuperscript{c}

Departments of \textsuperscript{a}Neurosurgery and \textsuperscript{b}Neuro-Pathology, NIMHANS, and \textsuperscript{c}Department of Pediatric Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, India

Established Facts

- Desmoplastic infantile gliomas – desmoplastic infantile astrocytomas (DIAs) and desmoplastic infantile gangliogliomas – are WHO grade I tumors, usually presenting as solitary, supratentorial, solid-cystic lesions.
- Surgical extirpation is the treatment of choice for solitary DIAs, and these lesions are noted to have an excellent prognosis following total excision.
- Atypical, aggressive, and multifocal variants of DIA are extremely rare, with only few case reports documenting the diagnostic as well as therapeutic dilemmas posed by this entity.
- Management of patients with multifocal DIAs remains a challenge because of very limited experience worldwide and is an area of focus for future glioma research.

Novel Insights

- The review of the literature shows that the benign nature of DIA invariably turns malignant when it presents with multiple localizations, either as metachronous lesions or through extensive dissemination via CSF, and this portends a poor prognosis for the patient.
- Surgical intervention is limited to excision of symptomatic mass lesions and management of hydrocephalus, while the role of adjuvant treatment using chemotherapeutic drugs or monoclonal antibodies is still unclear and will require further studies.

Keywords

Desmoplastic infantile glioma · Desmoplastic infantile astrocytoma · Infantile brain tumors · Multifocal localization · Pathology · Chemotherapy · Treatment

Abstract

Desmoplastic infantile gliomas are rare, benign tumors of the early infancy period. Two histological subtypes – desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma – have been described. The characteristic features of DIAs are lobar location, glial histology, and excellent prognosis after complete surgical excision. DIAs usually present as solitary, cortical-surfacing, solid-cystic neoplasms; however, atypical, aggressive, and multifocal variants of DIA have been reported in the literature. These rare DIAs presenting with multiple lesions pose a diagnostic as well as a therapeutic dilemma. We report an unusual case of an 8-month-old female infant diagnosed with multifocal (cranial and spinal) DIA and obstructive hydrocephalus and dis-
cuss the radiological and histological features of this rare variant of DIA. The patient underwent ventriculoperitoneal shunt placement to relieve the hydrocephalus, excisional biopsy from a suracing lesion in the right frontal lobe, and multiple cycles of chemotherapy; however, the lesions continued to progress, and the patient is likely to have an unfavorable outcome.

**Introduction**

Desmoplastic infantile astrocytomas (DIAs) are rare, benign, infantile brain tumors representing 15.8% of infantile intracranial tumors and 1.5% of all childhood intracranial tumors [1, 2]. They are most frequently seen in children under 18 months of age and have a predilection for males [3]. The World Health Organization (WHO) classifies DIA as a grade I tumor. Two histological types of desmoplastic infantile gliomas are described in the WHO classification (2016) of the nervous system tumors: DIA and desmoplastic infantile ganglioglioma, the presence of a neuronal component in the latter being the only difference between the two types [3–5]. DIAs typically present as large, solitary, solid-cystic, supratentorial tumors, located on the cortical surface and having a dural attachment; however, aggressive variants with multifocal localizations or leptomeningeal spread have been described, although these are extremely rare [1]. Gross total resection of solitary DIA usually results in a good outcome, but management of patients with multifocal DIAs remains a dilemma because of very limited experience worldwide [1, 6]. In this report, we describe the sixth case of DIA with intracranial and intraspinal lesions and review the pertinent literature (Table 1) [4, 6–8].

**Case Report**

**Clinical Presentation**

An 8-month infant girl, born of a full-term normal vaginal delivery, presented with a progressively increasing head circumference for 5 months, regression of developmental milestones for 2

**Table 1. Summary of the reported cases of multifocal DIA**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical features</th>
<th>Histology and IHC features</th>
<th>Localization</th>
<th>Treatment summary</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setty et al. [7], 1997</td>
<td>4 months</td>
<td>male</td>
<td>macrocephaly, nystagmus</td>
<td>anaplasia present</td>
<td>tumors in the suprasellar region, hypothalamus, posterior fossa, and spinal canal</td>
<td>Biopsy of the suprasellar mass + chemotherapy</td>
<td>alive after 38 months</td>
</tr>
<tr>
<td>Bock et al. [11], 2002</td>
<td>4 months</td>
<td>male</td>
<td>raised intracranial pressure + focal symptoms</td>
<td>anaplasia absent</td>
<td>tumor in the suprasellar region with diffuse leptomeningeal spread</td>
<td>biopsy + chemotherapy</td>
<td>patient expired at 5-month follow-up due to progression</td>
</tr>
<tr>
<td>Darwish et al. [4], 2007</td>
<td>4 months</td>
<td>male</td>
<td>macrocephaly, failure to thrive and irritability; hydrocephalus present</td>
<td>anaplasia absent low Ki-67 index (1–2%)</td>
<td>tumors in the suprasellar region, fourth ventricle</td>
<td>partial resection of suprasellar lesion + ventriculoperitoneal shunt</td>
<td>patient expired 1 week after surgery (hypothalamic dysfunction and respiratory insufficiency)</td>
</tr>
<tr>
<td>Uro-Coste et al. [8], 2010</td>
<td>5 years</td>
<td>male</td>
<td>generalized tonic-clonic seizures</td>
<td>anaplasia absent</td>
<td>tumors in the left temporal area, posterior fossa, and basal cistern</td>
<td>resection of posterior fossa tumor + chemotherapy</td>
<td>alive after 12 months</td>
</tr>
<tr>
<td>Abuharbid et al. [6], 2015</td>
<td>11 months</td>
<td>female</td>
<td>nystagmus</td>
<td>anaplasia absent</td>
<td>tumors in the suprasellar region, posterior fossa, spinal canal</td>
<td>resection of posterior fossa tumor.</td>
<td>alive after 16 months</td>
</tr>
<tr>
<td>Present case, 2016</td>
<td>8 months</td>
<td>female</td>
<td>macrocephaly, regression of milestones</td>
<td>anaplasia absent low Ki-67 index (0.5–1%)</td>
<td>tumors in left thalamus, right cerebellum, right parietal cortex, basal cisterns, tentorium, leptomeninges, spinal cord</td>
<td>excisional biopsy of the right frontal tumor + chemotherapy</td>
<td>alive after 12 months, but with severe mental retardation and lower limb spasticity</td>
</tr>
</tbody>
</table>

GFAP, glial fibrillary acidic protein; IHC, immunohistochemistry.
months, and irritability and projectile vomiting of 2 weeks’ duration. Clinical examination revealed bulging anterior fontanelle and loss of head holding.

Radiological Findings
Magnetic resonance imaging (MRI) of the brain showed multiple, solid-cystic lesions in the left thalamus, left medial temporal region, and left cerebellum, and diffuse leptomeningeal spread in the basal cisterns surrounding the left petrous apex, tentorial edge, and right cerebellum (Fig. 1). Obstructive hydrocephalus was present due to compression at the level of the fourth ventricle. The solid component was isointense on T1-weighted (T1W) sequences and hypointense on T2-weighted (T2W) sequences with intense, homogenous enhancement on contrast administration. The cystic components corresponded to CSF intensity in both T1W and T2W sequences, with enhancement of the cyst wall on contrast injection.

Surgical Intervention
The patient underwent right Frazier’s point ventriculoperitoneal shunt placement for hydrocephalus and a right parietal mini-craniotomy with excisional biopsy of the surfacing frontoparietal cortical lesion (Fig. 1f). At surgery, the tumor was whitish, firm, and avascular arising from the parietal cortex with normal surrounding parenchyma and a loose dural attachment. The CSF obtained at the time of shunt placement, on cytology examination, revealed the presence of tumor cells. Completion MRI of the spine (Fig. 2) was done after the shunt surgery, which revealed an intramedullary solid-cystic lesion in the dorsal spine with similar MRI characteristics to those of the intracranial lesions.

Histopathological Diagnosis
Histological examination of the tumor revealed a spindle cell neoplasm arranged in storiform pattern with tight intersecting fas-

![Fig. 1. Preoperative MRI of the brain: T1W axial (non-enhanced; a), T2W axial (b), T1W axial (contrast-enhanced; c), T2W sagittal (d), T1W sagittal (contrast-enhanced; e), and T1W axial (contrast-enhanced; f) images showing multiple solid-cystic lesions in the left temporal, left cerebellum, and left petrous apex region, with hydrocephalus and perilesional edema. The lesions were hypointense on T1W and T2W images and showed intense homogenous contrast enhancement. Excisional biopsy was taken from the right frontal cortical lesion (shown by arrow in f).]
cicles, closely resembling a fibrous meningioma (Fig. 3a). The tumor cells displayed small nuclei with long tapering processes. There was a rich meshwork of thin reticulin strands enclosing individual tumor cells (Fig. 3b). There was no primitive neuroectodermal component or cortical component included in the biopsy. No necrosis or microvascular proliferation was seen. Immunohistochemistry (IHC) showed strong diffuse labeling of the spindle cells for GFAP confirming its glial nature (Fig. 3c). Epithelial membrane antigen was negative excluding meningioma. Synaptophysin did not detect any ganglionic component (Fig. 3c, inset). MIB-1 labeling index was low (0.5–1%) (Fig. 3d). IHC for BRAF V600E mutation was negative. Based on the histological features and IHC findings, diagnosis of DIA was made.

Postoperative Management and Follow-up
The child improved clinically following the shunt surgery and was seen to be gradually regaining her developmental milestones. She was administered 7 cycles of chemotherapy comprising the regimen of vincristine, cyclophosphamide, etoposide, and cisplatin, through the chest chemoport. Cycle A comprised vincristine (dosage: 1.4 mg/m² i.v.) and cyclophosphamide (1.2 mg/m² i.v.) and was alternated with cycle B comprising carboplatin (600 mg/m² i.v.) and etoposide (150 mg/m² i.v.). The time gap for alternating between cycle A and cycle B was 3 weeks. Radiation treatment was not administered in view of the young age of the patient (<3 years). MRI of the brain and spine performed at the 1-year follow-up (Fig. 4) demonstrated a mixed response in the lesions with mild regression of the solid lesions, progression of the cystic cranial as well as spinal lesions, and the development of new lesions in the right cerebellum. Surgery was offered for the spinal intramedullary lesion but, in view of the gradual progression and multifocal diffuse localization of the pathology, further treatment was declined by the girl’s parents. At the 1-year follow-up (patient age: 2 years), the patient was conscious, alert, and responding to her mother. The anterior fontanelle was sunken and nearing closure. She was able to perform tasks with both hands and sit without support; however, she had bilateral lower limb spasticity and hence could not stand.

Discussion
Desmoplastic infantile gliomas are rare intracranial tumors, typically occurring within the first 18 months of life and having a slight male predominance [3]. Taratuto et al. [9], in 1984, were the first to report the clinical and pathological features of DIA. Vandenberg et al. [10], in 1987, were the first to report desmoplastic infantile ganglioglioma. Presently, both pathological entities are considered to be histological subtypes of desmoplastic infantile gliomas and are classified as benign (WHO grade I) tumors according to the WHO classification (2016) of central nervous system tumors [5]. Despite the fact that DIAs are classified as WHO grade I tumors with favorable prognosis, DIAs with aggressive, clinical, and pathological features have been described, albeit as case reports [1]. DIAs are primarily solitary tumors but have been reported, albeit rarely, to occur as multiple localizations in the central nervous system (Table 1) [4, 6–8, 11, 12].

DIAs are slow-growing tumors, usually present with increased intracranial pressure (ICP) (dysphoria, vomiting), bulging fontanelle, abnormally increasing head circumference, seizures, and sensorimotor deficits [13]. Our patient presented with signs and symptoms of raised ICP.

Fig. 2. Completion MRI of the spine (plain and contrast) done after the shunt surgery, where T2W sagittal (a) and T1W sagittal (contrast-enhanced; b) showed an intramedullary, solid-cystic lesion in the dorsal spine, with similar MR characteristics to the intracranial lesions.
but also had regression of developmental milestones, which may be attributed to the raised ICP or to the diffuse central nervous system involvement (demonstrated on MRI).

Typically, DIAs occur as supratentorial, contrast-enhancing solid mass lesions with loculated cystic components [3]. These tumors tend to be large, with the frontal and parietal lobes being most commonly involved [3]. The solid components are typically superficially located (with focal attachment to the overlying dura), involving the cerebral cortex and leptomeninges [3, 9, 10]. The loculated cystic components appear to be located deep vis-a-vis the solid portion [13, 14]. On MRI, the solid components, bordering the dura, are iso- to hypointense on T1W sequences, predominantly hypointense on T2W sequences, and exhibit intense, homogenous enhancement on contrast administration. The cystic portion corresponds to CSF intensity on MRI, and the cyst walls may or may not show enhancement on contrast [3]. In our case, multiple lesions were noted in the parenchyma as well as in the cisternal spaces. The solid lesions displayed the characteristic findings of DIA on MRI, and the walls of cystic lesions showed contrast enhancement. Unusual findings were diffuse ependymal enhancement (Fig. 1c) and involvement of the basal cisterns (Fig. 1f).

Fig. 3. a Microphotograph of tumor shows spindled tumor cells arranged in a storiform pattern (b) with a reticulin rich stroma. c Immunohistochemistry revealed strong GFAP labeling of tumor cells; there was no ganglionic component detected on synaptophysin stains (inset). d MIB-1 labeling index is very low. H&E (a), reticulin silver stain (b), immunoperoxidase (c, d). Scale bars, 100 μm (a–c), 50 μm (d).
In our patient, the predominant supratentorial tumor (composed of multiple cysts of varying sizes) was in the left temporal lobe extending into the left thalamic region. Extensive solid lesions were noted in the basal cisterns around the left petrous apex and left tentorial edge. Infratentorially, cystic lesions in the left cerebellum led to severe obstructive hydrocephalus. In view of the diffuse involvement and the absence of any single lesion causing significant mass effect, a decision was taken to perform excision biopsy from the surfacing cortical lesion in the right frontal lobe for histopathological diagnosis, with least morbidity to the patient. CSF diversion was performed to relieve the raised ICP in the same sitting. As documented in literature, in these cases, the final diagnosis can only be established on histological and IHC examination. Diagnostic dilemmas may arise due to the multiple localizations, dural attachment, and desmoplastic nature of the pathology, which may be confused with fibrous meningioma/inflammatory pathologies. IHC played a definitive role in confirming the diagnosis in our case.

DIAs with multiple brain and/or spinal canal localizations represent either metachronous or metastatic lesions \cite{7, 12}. It is hypothesized that multiple DIAs are due either to metastatic CSF spread from a single intracranial lesion or to tumors growing independent of each other due to an inherited genetic disorder \cite{6}. The CSF, collected from the ventricles in our case, showed the presence of tumor cells, and it is likely that CSF was the principal route for the extensive dissemination of DIA seen in

**Fig. 4.** MRI of the brain at 1-year follow-up: T1W axial (a), T2W axial (b), T1W axial (contrast-enhanced; c), and T1W sagittal (contrast-enhanced; d). Follow-up MRI revealed a mixed response pattern with regression of solid lesions and progression of cystic lesions.

---

Pediatr Neurosurg
DOI: 10.1159/000455926

Narayan/Savardekar/Mahadevan/
Arivazhagan/Appaji

---
our case. This also explains the diffuse ependymal enhancement observed in the MRI (Fig. 1f). However, the presence of multiple parenchymal cystic lesions and the de novo right cerebellar lesions detected on the follow-up brain MRI hinted towards these lesions developing independent of each other. This highlights the need for a concerted multicenter effort towards a better understanding of the genetic and molecular basis for DIAs.

Solitary DIAs are benign tumors and usually have good prognosis after radical excision of the lesion [10, 13, 15]. In a case of multifocal DIA, surgery for the symptomatic mass lesion and CSF diversion for hydrocephalus may be combined, either with close observation of the remaining lesions or with adjuvant chemotherapy [6].

The relatively rare occurrence of this entity, in addition to the limited chemotherapeutic treatment options available for infants, has restrained efforts towards defining the role of adjuvant chemotherapy in this setting [12]. Some studies have shown positive therapeutic response with chemotherapeutic agents such as carboplatin and vincristine in multifocal DIA; however, consensus has not been reached so far [6, 8]. BRAF V600E mutations have been postulated to play a role in the etiopathogenesis of this rare tumor, and selective BRAF inhibitors like vemurafenib have been considered as chemotherapeutic options, but their use is still debatable [6]. In our case, IHC ascertained that BRAF mutation was absent, and hence BRAF inhibitors were not tried and the patient received a carboplatin- and vincristine-based regimen. The regression of solid lesions in the basal cisterns observed in our case may be attributed to the chemotherapy; however, at the same time, the cystic lesions had progressed, and new lesions had developed in the right cerebellum. The diffuse multifocal nature of this tumor precludes surgery to be the only treatment option, despite being a grade I tumor. Therefore, an effective adjuvant therapy regimen for these patients is needed for disease control, and a better understanding of its pathogenesis is likely to direct our efforts towards achieving this goal [12].

Conclusion

The review of the literature shows that the benign nature of DIA invariably turns malignant when it presents with multiple localizations, either as metachronous lesions or through extensive dissemination via CSF. The final diagnosis in such cases can only be confirmed on histopathological and IHC examination. Surgery, for symptomatic mass lesions and for alleviating raised ICP, is all that may be possible in multifocal localization. The role of adjuvant treatment using chemotherapeutic drugs or monoclonal antibodies is still unclear and will require further studies.

Acknowledgments

The authors would like to acknowledge the assistance of Mr. K. Manjunath and Mrs. U. Hemavathy in preparing the montage of microphotographs and performing IHC, respectively. We also wish to acknowledge the assistance of Dr. Chitra Sarkar, Professor of Neuropathology, All India Institute of Medical Sciences, New Delhi, for carrying out the BRAF V600E mutation analysis for our patient.

Ethics Statement

As the patient’s father gave written informed consent for the publication of this manuscript and the patient’s confidentiality is maintained in the manuscript, ethical approval was not required for this case report.

Disclosure Statement

No financial or other support from any source was received for this study. The authors declare that there is no conflict of interest.

References


