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REVIEW PAPER

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Desmoplastic infantile ganglioglioma – clinicopathological and immunohistochemical study of four cases

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Abstract *Case reports:* Four cases of desmoplastic infantile ganglioglioma (DIG) seen in India are described. These patients presented with large, supratentorial, superficially situated cystic tumours that showed glial and ganglionic differentiation; accompanied by a severe desmoplastic reaction. MIB-1 labelling was rare, despite foci of apparently primitive neuroepithelial cells. There was lacking p53 protein expression by tumour cells in all cases. The prognosis was good following either partial or complete tumour resection. DIGs are a distinct form of developmental neuroepithelial tumour, probably arising from neural progenitor cells in subcortical zone along with mature subpial astrocytes. *Conclusions:* In view of its favourable prognosis, this tumour has to be diagnosed accurately by immunohistochemical techniques using glial and neuronal markers. The absence of p53 protein expression suggests that DIG probably has different molecular genetic pathways from other supratentorial astrocytomas.

Keywords Infantile neuroepithelial tumour · Desmoplasia · Ganglioglioma · Immunohistochemistry

Introduction

Desmoplastic infantile gangliogliomas (DIGs) are rare, large cystic tumours of infants; most occur within the first 2 years of life, involving the superficial cerebral cortex and leptomeninges, and they are often attached to the dura. This tumour entity was first described by VandenBerg et al. in 1987 [25]. It is characterized histologically by a prominent desmoplastic stroma with a variable neuroepithelial component comprising neoplastic astrocytes and ganglion cells [12, 17, 25]. A closely related lesion without detectable ganglion cells, the desmoplastic cerebral astrocytoma of infancy (DAI), had been described earlier by Taratuto et al. in 1984 [19]. CT and MRI typically reveal largely cystic tumours with a solid, contrast enhancing cortical component with moderate surrounding oedema [10]. Aggregates of more primitive neuroepithelial cells may be seen in both tumours. Despite their large size and cellular atypia, the prognosis following surgical resection is quite favourable; hence the importance of recognizing these neoplasms. DIGs have been often misdiagnosed as highly aggressive neoplasms, such as malignant meningiomas, leptomeningeal sarcomas or gliosarcomas. To date more than 60 cases of DAI/DIG have been reported in the literature [5, 7, 13, 16, 18, 21], the largest single series comprising 22 cases of DIG [24]. Occasional cases of DAI have been reported from India [2], but hitherto there have been no reports of DIG from our country.

In this communication, we describe the clinical and histomorphological features of four cases of DIG to extend the reported spectrum. We also provide the immunohistochemical data relating to differentiation, proliferative markers and p53 protein expression in order to further characterize this unusual neuroepithelial tumour and get an insight into the histogenesis and cellular ontogeny of this neoplasm.

Case reports

Case 1

A 2-month-old female infant presented with progressive head enlargement, vomiting and lethargy with irritability since 15 days of age. Her birth history was unremarkable. A CT head scan revealed a large cystic mass with a mural nodule located in the left frontotemporal lobe. The infant underwent craniotomy with gross-total excision of the nodule and decompression of the cyst. She did not receive postoperative radiation or chemotherapy. She was well for 18 months after surgery but was subsequently lost to follow-up.

Case 2

A 6-month-old male infant presented with increasing head size, seizures and unresponsiveness of 1.5 months duration. His birth and postnatal development had been uneventful. A CT head scan revealed a slightly enhancing, partly cystic, partly solid left parietotemporal mass. The patient underwent craniotomy with gross-total removal of a firm tumour, which was superficially located and partially attached to the overlying dura. He did well postoperatively and was not treated with radiation or chemotherapy. At the last follow-up 4 years after surgery, he was developing normally without focal neurological deficits and seizures.

Case 3

A 9-month-old female infant presented with left-sided hemiparesis of 2 weeks duration. A CT scan of head revealed a large cystic lesion superficially located in the right temporoparietal cortex. The lesion had an enhancing nodule. At surgery, this solid nodule appeared ill defined, and it had a firm consistency. The lesion was totally excised. Postoperatively, the hemiparesis improved and after 12 months the child is developing normally with no further treatment.

Case 4

A 6-year-old girl who had been having seizures for over a year had developed features of raised intracranial pressure and right-sided hemiparesis 2.5 months before presentation. A cranial CT scan revealed a left-sided superficially placed frontoparietal mass. The lesion was mostly cystic, with a solid enhancing mural nodule. Subtotal excision proved possible. The child received postoperative radiation therapy. She was doing well at follow-up 9 months after surgery.

Materials and methods

Formalin-fixed, paraffin-processed blocks from all four cases were retrieved. Sections were cut and stained routinely with haematoxylin and eosin, phosphotungstic acid haematoxylin (PTAH) for glial fibres, Masson's trichrome for stromal elements and Gomori's silver stain for reticulin fibres. Paraffin sections 5 μm thick, collected on poly-L-lysine-coated slides, were subjected to immunoperoxidase staining using the following monoclonal antibodies, except for synaptophysin, where the antibody is polyclonal.

1. Glial fibrillary acidic protein (1:100, DAKO)
2. Synaptophysin (1:50, DAKO)
3. MIB-1 antibody (1:50; Immunotech, USA)
4. p53 antibody (DO–7; 1:50; Santacruz, USA)

Peroxidase-conjugated rabbit anti-mouse and goat anti-rabbit immunoglobulin (1:100; Dakopatts, Denmark) were the secondary antibodies, and DAB/H_2O_2 was used as chromogen. Appropriate positive and negative controls were incorporated during staining.

The MIB-1 labelling index was determined by enumerating the percentage of positively stained tumour cell nuclei among 1,000 tumour cell nuclei evaluated.

Results

Gross

In all four cases, the solid part of the excised tumour tissue was homogeneously greyish white, ill defined and 2–4 cm in diameter. The tumour was firm with a rubbery consistency and was hard to cut with a scalpel. Fragments of dura and cerebral tissue were focally adherent to the resected parts.

Microscopy

The cardinal histological feature in all the four cases was the prominent desmoplastic stroma, which appeared whirly and wavy and in places had a distinct storiform pattern, creating an appearance reminiscent of that seen in fibromatosis. However, the bulk of the tumour was moderately cellular, and most of the intervening stromal cells were spindle shaped, resembling fibroblasts (Fig. 1A). In some foci, the cells were plump and oval with bright eosinophilic cytoplasm and eccentric nuclei, resembling gemistocytes (Fig. 1B). A few other cells were larger, polygonal, with a vesicular nucleus and prominent nucleolus representing ganglion cells. Throughout, the cellular elements were embedded in a collagenized meshwork clearly shown up by Masson's trichrome and reticulin stains. These stains also highlighted the vascularity of the tumour, which was prominent in case 4. In cases 2 and 3 there were focal aggregates of poorly differentiated neuroepithelial cells with small, round, deeply basophilic nuclei and minimal surrounding perikaryon. These cells, however, did not reveal mitotic activity.

Immunohistochemistry

In all these cases, the spindle shaped cells and larger cells resembling gemistocytes stained intensely positive for GFAP. Nearly 30–50% of cells dispersed in the stroma were immunoreactive for GFAP (Fig. 2A). Staining for synaptophysin distinctly labelled the larger, pyramidal cells, thus delineating the admixed ganglionic cell component within the tumour (Fig. 2B). The focal aggregates of poorly differentiated cells, seen in cases 2 and 3, did not express GFAP or synaptophysin.

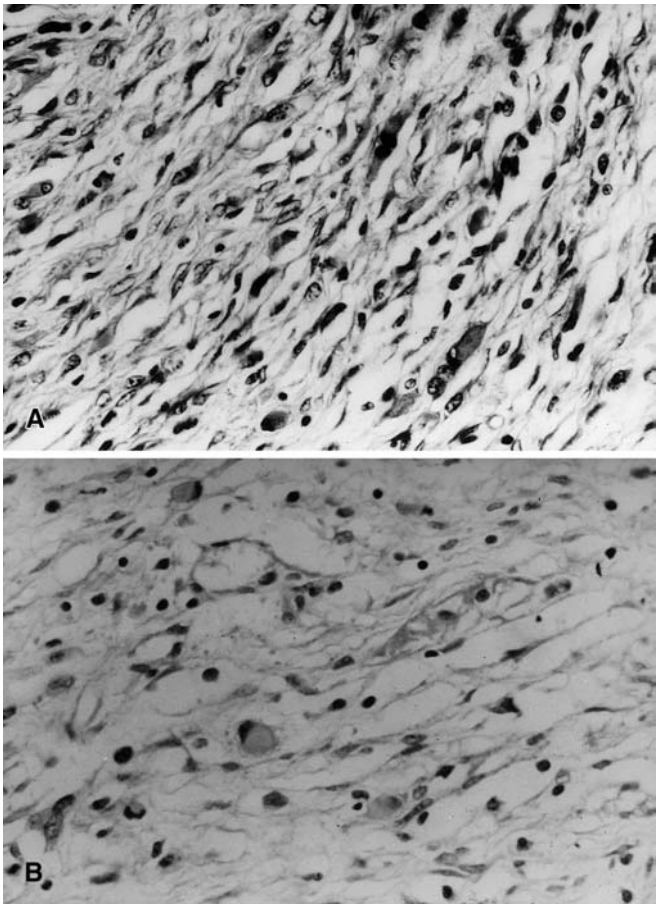

Fig. 1A, B Photomicrographs of desmoplastic infantile ganglioglioma (case 2). **A** shows neoplastic astrocytes and occasional ganglion cells arranged in a linear fashion within a marked desmoplastic stroma. (Haematoxylin-eosin, ×250). **B** another field with fibrillary and gemistocytic astrocytes. (Haematoxylin-eosin, ×250)

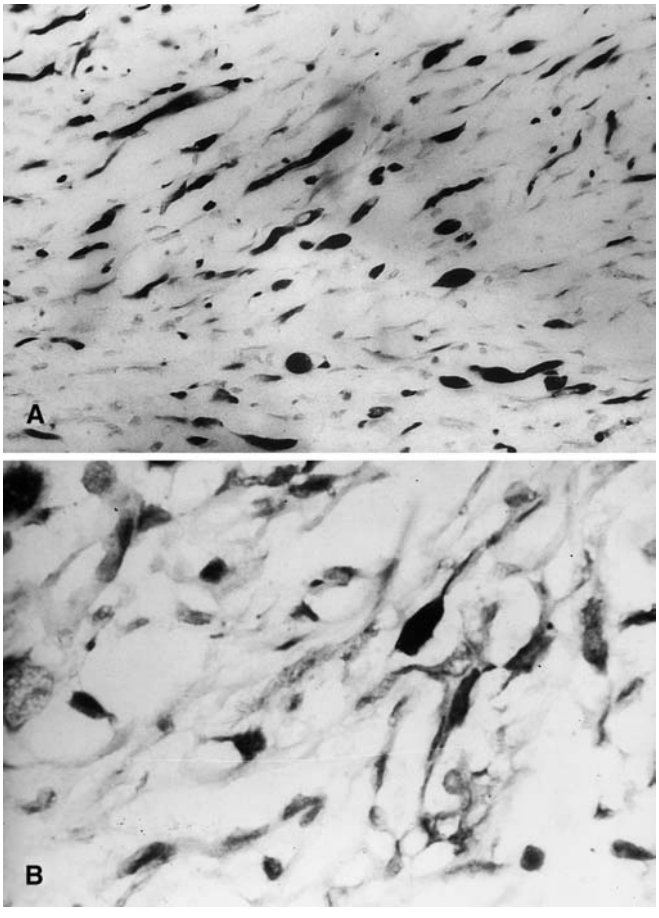

Fig. 2A, B Immunohistochemistry of desmoplastic infantile ganglioglioma (case 2). **A** shows several GFAP-expressing neoplastic astrocytes; the desmoplastic component remains unstained (×400). **B** shows scattered neoplastic ganglion cells expressing synaptophysin (×1000)

MIB-1 labelling indices ranged from 0.5% to3.5%, with a mean of 1.5%, confirming the benign nature of the tumours. p53 immunoreactivity was not evident in any of the tumour cells.

Discussion

Desmoplastic infantile ganglioglioma is an uncommon, relatively recently described, neoplasm [25] This tumour stands out as unique amongst other neuroepithelial tumours because of its superficial, dura-based location in the cerebral hemispheres, its characteristic histological appearance and its occurrence in infancy [5, 10, 19]. Of the 25 reported cases of DIG reviewed by Duffner et al. [5] all but 1 were in children less than 1 year of age. This early age of onset has led to the speculation that DIG's are true prenatal or congenital neoplasms. However, several noninfantile cases, in patients of ages ranging from 5 to 17 years, have recently been reported [2, 6, 26] We also encountered one 6-year-old girl with DIG. Thus, the nosological status of DIG remains unclear. It is possible that DIG could be a variant of the conventional ganglioglioma, differing in the stage of evolution [13]. The points of difference are: the extensive desmoplasia achieved by DIG is usually not attained by conventional ganglion cell tumours, even when they reach the subarachnoid space, and DIGs often contain small foci of primitive neuroepithelial cells, a feature that is not evident in other ganglion cell tumours [24]. Hence, at present, it is felt that DIG must be regarded as a separate entity from conventional ganglion cell tumours unless future evidence establishes a closer link [8].

The superficial desmoplastic astrocytoma of infancy (DAI) is another closely related tumour that resembles DIGs, with intense desmoplasia within which only GFAP positive astrocytes are dispersed [4, 6, 24]. These lesions are also frequently cystic, and they have a simi-

larly favourable prognosis after surgical excision. Whether this tumour is a separate entity or a form of DIG in which neurons have not been detected in the biopsied tissue is not clear. It is important to study larger biopsies to clarify this issue.

DIGs are superficial cerebral hemispheric tumours and at times can be totally extraparenchymal. It is easy to misinterpret DIGs as high-grade malignant lesions because of the focal high cellularity with apparently immature cells, sometimes with mitotic activity. They have often been mistaken for malignant meningeal neoplasms or gliosarcomas [6]. In fact, in small specimens in which desmoplasia is not the main feature, it may be difficult to reach the correct diagnosis [6]. However, mitotic activity is rare, and when present is mostly restricted to the undifferentiated small cells [23, 24]. The mean MIB-1 labelling index in our cases was 1.5%. Other studies have shown Ki-67 labelling indices to range from 0.5% to 5% [20, 22], confirming the benign nature of these neoplasms.

It has been shown that the distinctive feature of neoplastic astroglial cells in DIG is the formation of basal lamina, which is normally associated with subpial astrocytes. Hence severe desmoplasia seen in these tumours could result from extensive proliferation of the basal lamina structures of neoplastic astrocytes along with the reactive leptomeningeal proliferation, a feature also shared by pleomorphic xanthoastrocytoma (PXA), a superficially located astrocytic neoplasm [8]. Further, the neuronal cells seen in DIGs seldom achieve the degree of cytoarchitectural maturation that is seen in ganglion cell tumours. Therefore, it is suggested that the putative progenitor cells of DIG may originate from the neural progenitor cell in the cortical subpial zone proliferating along with mature subpial astrocytes [1]. The components of extensive tumour basal lamina may be elaborated by the tumour cells themselves and may contribute in an autocrine fashion to the slow growth of these lesions [9]. Further, the superficial location of these tumours has also suggested that developmental abnormalities such as glial and/or neuronal ectopias within the subarachnoid space, probably arising as a result of gene mutation, hypoxia, chemical or physical injury to the developing brain could be aetiological factors [3].

Experimental studies in immortalized supratentorial progenitor cells in rats have shown that there are region specific intrinsic factor which are significant determinants for commitment of undifferentiated stem cells towards neuronal/glial lineages [11, 15]. Such studies form a basis for the better understanding of uni- or bipotential differentiation of transformed progenitor or stem cells in a spectrum of tumours ranging from highly mitotic primitive neuroectodermal tumour (PNET) to (low mitotic, benign) DIG.

Earlier studies did not show mutations of the *p53* gene or loss of heterozygosity of chromosomes 10 or 17 in DIGs or DIAs [9, 20]. Our study also confirms this. These findings suggest that the molecular genetic pathways of these neoplasms is probably different from other supratentorial astrocytomas [20].

Follow-up of our cases suggest a good survival after total surgical excision. It has been observed that gross total resection results in long-term survival in both DIA and DIG, despite the primitive appearing cellular aggregates [21]. In one study, 14 patients with DIG survived for 8.7 years (range 1–14.1 years) and no death had resulted from a residual or recurrent tumour [24]. Duffner et al. [5] suggest that infants with DIG should receive as complete a resection as possible. If there is no evidence of gross residual tumour, follow-up without any adjuvant therapy is appropriate. However, in those where definitive surgery is not possible or if there is significant residual tumour after surgery, chemotherapy seems to be a reasonable and effective alternative to irradiating the infant brain [5]. With improved recognition of this tumour entity, further reports would definitely help to identify the efficiency of various treatment options for DIGs.

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