Case report

Congenital glioblastoma coexisting with vascular developmental anomaly

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Abstract

Congenital central nervous tumours form a unique group of neoplasms. They are different from other tumour groups not only due to the onset time but also to their histopathology, anatomic location, and biologic behaviour. Congenital glioblastoma is one of the rarest types of congenital brain tumours and is uncommon in the prenatal period. We report a rare case of congenital glioblastoma detected prenatally by ultrasound examination and magnetic resonance imaging at 26 gestational weeks. Based on MRI findings and consultation of a team of specialists, pregnancy was terminated at 28 weeks. The newborn presented hydrops foetal. The child died shortly after birth due to cardiorespiratory insufficiency. At autopsy a large tumour with a spongy-like appearance was found. The tumour involved nearly the whole right cerebral hemisphere and led to marked hydrocephalus. In the histological and immunohistochemical examination, the tumour presented features of glioblastoma. Neoplastic cells were immunopositive for GFAP, S-100 protein and negative for neuronal markers. Frequent mitoses and high MIB-1 labelling index were seen in the tumour areas. The coexistence of tumour and vascular developmental anomaly was stated. The conglomerates of numerous, distended, thin-walled foetal-like blood vessels were located beside the tumour tissue, which presented disturbance in differentiation and maturation of the vascular net. Such coexistence of malignant glioma with vascular developmental anomaly is unique.

Key words: congenital brain tumour, congenital glioblastoma, vascular developmental anomaly, persistent foetal-like vessels.

Introduction

Congenital central nervous tumours form a unique group of neoplasms [14,15,26]. They are different from other tumour groups not only due to the onset time but also to their histopathology, anatomic location, and biologic behaviour. Congenital brain tumours account for less than 2% of all paediatric tumours. Congenital glioblastoma (cGBM) is one of the rarest types of congenital brain tumour, with less than 50 cases reported in the literature [13] and is uncommon in the prenatal period.
Screening methods have improved significantly prenatal detection of tumours [28]. Gliomas are the most common primary brain tumours and they are characterized by different molecular pathways and biological behaviour in children and adults [19,29,35]. Molecular alterations in adult GBM include abnormalities associated with the epidermal growth factor receptor [1,21], platelet-derived growth factor receptor, phosphatase and tensin homologue, INK4a/ARF, isocitrate dehydrogenase and TP53 [6,16,19].

Congenital glioblastomas are genetically distinct from adult and TP53 pathway dysregulation is important in their tumorigenesis [7]. Unique molecular features of cGBM include also overexpression of multiple genes involved in glucose metabolism and tissue hypoxia [25].

We present a rare case of congenital glioblastoma, detected prenatally, coexisting with vascular developmental anomaly.

Case report

A 34-year-old woman, gravida 4, para 2, 2 spontaneous abortions. The family history was unremarkable. Routine foetal ultrasonography was done at 24 weeks of gestation. Ultrasonography of the foetus revealed a large mass of rapidly growing brain tumour with hydrocephalus. Examination of the intracranial structures revealed the hypervascular mass measuring 71.0 × 68.0 mm with irregular outlines, occupying the entire right cerebral hemisphere. Asymmetrical ventricular enlargement was stated. Magnetic resonance imaging (MRI) of the foetus was performed at the gestational age of 26 weeks. It revealed a pathological mass in the right cerebral hemisphere. It was heterogeneous, mostly solid but with areas of necrosis and haemorrhage (calcifications within the mass seemed less probable) (Fig. 1A). It measured approximately 66 (anterior-posterior) × 61 (right-left) × 56 (cranio-caudal) mm. There was a shift of the midline structures to the left by 14 mm and hydrocephalus. There was only a very narrow band of the preserved brain tissue around the enlarged left lateral ventricle, mainly in the frontal region. On the right, the cranium was filled with a large mass lesion and only a part of the frontal lobe was preserved around the widened frontal horn. The MRI diagnosis of brain tumour was suggested. The lesion was accompanied by the widened dural sinuses, internal jugular veins, superior vena cava and cardiomegaly (Fig. 1B).

**Fig. 1. Foetal MRI. A)** Heterogeneous mass in the right hemisphere with midline shift and hydrocephalus. FIESTA/2D sequence, axial plane. **B)** Tumour mass, widened superior vena cava and cardiomegaly. SSFSE/T2-weighted image, coronal plane.
vena cava and enlarged heart (Fig. 1B) which showed significant hemodynamic instability.

Based on the MR findings and consultation with obstetricians, paediatric neurosurgeons and neonatal intensive care unit team, the decision to terminate pregnancy was made because of rapidly growing and devastating brain tumour that was suspected to be malignant.

At 28 weeks of pregnancy, a female newborn was delivered by caesarean section. The newborn measured 43 cm and weighed 2680 g (> 95th percentile) and presented foetal hydrops. The head circumference was 40 cm (> 97th percentile), chest circumference 34 cm. Apgar score was 1 (heart rate below 100/min). The child died after 90 minutes.

Material and methods

A post-mortem examination was done. The brain was fixed in 10% formalin. Specimens from the cerebral hemispheres, brain stem and cerebellum were taken, embedded in paraffin and routinely stained with haematoxylin-eosin and cresyl violet. Immunohistochemical studies were performed on paraffin-embedded specimens using the standard avidin-biotin-peroxidase complex method with antibodies against glial fibrillary acidic protein (GFAP), S-100 protein, synaptophysin, CD31, CD34, SMA, p53 and Ki67 (all reagents from Dako).

Neuropathological examination

Macroscopic evaluation showed a large tumour with a sponge-like appearance which involved nearly the whole right cerebral hemisphere, passed across the median line structures and led to marked hydrocephalus by secondary aqueductal stenosis. The tumour was poorly demarcated from the surrounding tissue, infiltrating almost totally the white matter of the frontal, parietal, and temporal lobes. The tumour was soft, spongy, gray-black with haemorrhages and highly vascular areas.

Microscopically, the tumour involved cerebral lobes of the right hemisphere and presented an infiltrative growth pattern in the white matter adjacent to the lateral and third ventricles. The interface between the tumour and adjacent brain parenchyma demonstrated a diffusely infiltrative border. Focal perivascular cuffings of neoplastic cells were seen in the surrounding tissue. The widespread infiltration was seen through the germinal matrix nests and cerebral cortex. In some areas, the mixture of germinal and tumour cells with small necrotic foci and haemorrhages was evident (Fig. 2). The other parts of the cerebral cortex was properly formed and demonstrated widespread neuronal damage.

The main highly cellular tumour mass was predominantly composed of small monomorphic cells with round or ovoid nuclei and minimal discernable cytoplasm (Figs. 3A-B). Some neoplastic cells displayed the prominent eosinophilic cytoplasm or gemistocytic features with mild nuclear hyperchromasia. The tumour was mitotically active and Ki 67 labelling index was high (Figs. 3C-D). Tumour cells exhibited glial fibrillary acidic protein (GFAP)-positivity (Fig. 3E), immunoreactions for S-100 protein. This part of densely cellular tumour was highly vascular (Figs. 3A, 3F) and demonstrated numerous small foci of necrosis surrounded by radially-oriented neoplastic cells forming "pseudopalisading" (Fig. 3G). The capillaries exhibited prominent endothelial proliferation (Fig. 4A). The predominant form of vascular proliferation was presented as glomeruloid structures or ramified new vessels. The multilayered endothelial cells seen around the lumen of vessels exhibited CD31 positivity (Fig. 4B). The αSMA positive pericytes of irregular shape and evident cytoplasmic processes were arranged circumferentially (Figs. 4C-D).

Moreover, the conglomerates of distended, thin-walled foetal-like blood vessels were found within the neoplastic tissue (Fig. 5) or outside the main tumour mass (Fig. 4E). Immature blood vessels lined by a single layer of flat endothelium formed a net of

![Fig. 2. Mixture of germinal and tumour cells in the periventricular germinal nests. Cresyl violet. Orig. magn. ×40.](image)
CD31-positive hemorrhagic vascular channels (Fig. 4F). The SMA positive pericytes located around the vessels were flattened and devoid of processes (Fig. 4G).

The final diagnosis of congenital glioblastoma with vascular developmental anomaly was established.

**Discussion**

The histopathological diagnosis of congenital glioblastoma was based on its typical morphology and immunohistochemical findings. The morphological picture of tumour fulfilled the World Health Organization criteria for diagnosis of GBM, based on the presence of necrosis, pseudopalisading, mitotic figures and microvascular proliferation [24]. A monomorphic cell population characterized predominantly by small, round to slightly elongated, densely-packed cells with mildly hyperchromatic nuclei, high nuclear/cytoplasmic ratios suggests a particular type of GBM called small cell glioblastoma [24].

The tumour was detected prenatally by ultrasonography. The foetal MRI is used to confirm, verify or complete prenatal sonographic diagnosis of CNS abnormalities. In the present case, MR images suggested the malignant brain tumour. So far there have been four congenital brain tumours established in the material of the Department of Diagnostic Imaging of the Institute of Mother and Child: teratoma, desmoplastic infantile astrocytoma (DIA), choroid plexus carcinoma (CPC) and craniopharyngioma [5]. The CPC images had been quite similar to the MRI images of the presented case. The diagnosis of GBM was not taken into account prenatally because of its rarity.

The development of foetal MRI allows to establish the early diagnosis of congenital tumours. To
our knowledge, the described case is the youngest reported so far in the literature. In the majority of reported cases, the gestational age at diagnosis of the tumour was more than 32 weeks [13,23,31,32,37]. In this case, the tumour was detected at 24 week of pregnancy but its growth had begun earlier. The progression of tumour growth occurred very rapidly. During normal brain development the neuronal cells migrate from the germinal matrix, which is a highly vascular source of neuronal glial precursor cells, through the white matter to the cerebral cortex. Migration to the neocortex starts at the end of the second month of gestation. Two great consecutive waves of cells migration from the germinal matrix to the cortex appear during the third and fourth month of gestation. Then, the activity of migration diminishes and is nearly completed by the middle of the seventh gestational month. The affected course of normal neuronal migration resulted in cortical malformations or heterotopias [8,22]. In the present case, the tumour most probably grew after the period of intense neuronal migration because there were no cortical anomalies and arrest of neurons in the white matter.

Fig. 4. Blood vessels in the tumour tissue and in the vascular anomaly. A) Tumoural microvascular hyperplasia. B) CD31-positive proliferating endothelial cells forming multiple layers. Orig. magn. ×200. C-D) Irregularly shaped αSMA protein positive pericytes with prominent cytoplasmic processes. Orig. magn. ×400. E) Numerous, distended, thin-walled foetal-like vessels of the vascular anomaly. Orig. magn. ×200. F) Vessel anomaly-single layer of flat, CD31 positive endothelial cells. G) Small, flattened, devoid of processes αSMA positive pericytes in the vascular anomaly. Orig. magn. ×400.

Fig. 5. The conglomerates of numerous, distended thin-walled vessels accompanying the neoplastic tissue. Haematoxylin eosin. Orig. magn. ×40.
In the presented case, the main tumour mass was accompanied by the rich network of vascular channels embedded in scarce, loose tissue. This abundant plexus of vessels was similar to the thin-walled, non-differentiated foetal-like vessels observed in the early embryonic stages of development. During normal development of vascularisation, the primitive endothelial cells constitute the primary primitive vascular plexus. The primary plexus subsequently develops into a complex organized vascular network due to endothelial proliferation (angiogenesis). In the final process of vascular development, the mesenchymal cells differentiate into pericytes, which surround blood vessels and make them mature and stable. Pericytes are engaged in different stages of normal angiogenesis including initiation, sprout extension, migration and maturation of vessels [3,17]. Some vessels regress and the rest differentiate and matures to a genetically-coded pattern of brain vascularisation. If regression is not complete, the persistent vessels, often not fully differentiated, occur as angiomas [30]. Neonatal angiomas are composed of numerous thin-walled vessels, lined by a single layer of flat endothelium and separated by variable amounts of loose connective tissue [9]. Despite the congenital origin of angiomas, they rarely occur in the neonatal and prenatal period. Only a few such cases have been reported in the literature [12,20,38]. Udayakumaran and co-workers found 21 cases of cavernous angioma in the neonatal and prenatal period described in the English literature [36]. In the presented case, the conglomerates of vessels in the vicinity of tumour may represent the preserved angioma, however it is also possible that the vascular anomaly corresponds to the preserved primitive foetal vessels. Persistent foetal primitive vascular plexus consists of abundant sinusoid capillaries forming a dense plexus in the leptomeninges covering nervous tissue. The foetal pattern of vessels normally persists beyond the period of primary plexus formation [9]. Thus, the primitive foetal-like vessels could be included into the infiltrating neoplastic tissue.

In adults, the primary brain tumours may be accompanied by vascular malformations [27] and such rare coincidence involves mostly gliomas and meningiomas [10,11]. The pathogenetic suggestions consider such angiogliomatic lesions as a result of reactive astroglial neoplastic proliferation secondary to the pre-existing vascular malformation. Only a few cases concerning coexistence of tumour and aneurysm have been reported in infantile cases [2,4]. The coexistence of vascular anomaly and congenital glioblastoma is unique and up to our knowledge has not been reported.

References

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