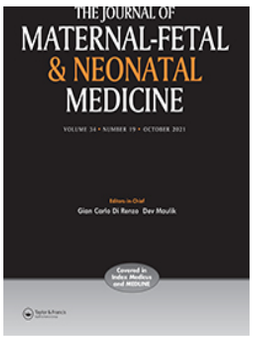

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REVIEW ARTICLE

Case report and literature review: antenatal diagnosis of a fetal anaplastic astrocytoma

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ABSTRACT

Objectives: To describe the ultrasonographic appearance of congenital anaplastic astrocytoma, so as to provide diagnostic clues for it. An updated review of the literature was also carried out.

Results: There was a case of fetal anaplastic astrocytoma detected by ultrasound at 37 + 1 weeks of gestation. It showed that a hypoechoic mass was located in the left hemisphere with a relatively clear margin and subtle color flows. Prenatal magnetic resonance imaging (MRI) which was taken subsequently confirmed the result of ultrasound. Intratumoral hemorrhage was observed in later follow-up and further confirmed by histological examination. The fetus was delivered vaginally at 39 + 6 weeks. The infant died 2 h after delivery due to respiration failure. The histological examination confirmed an anaplastic astrocytoma.

Conclusions: Congenital anaplastic astrocytoma commonly detected by ultrasound has a relatively better perinatal prognosis, especially compared with glioblastoma. Prenatal ultrasonography diagnosis accurately is of critical importance. The anaplastic astrocytoma should be considered in cases in which fetal images reveal a heterogeneous echogenic mass in the brain, especially in the presence of intratumoral hemorrhage, subtle color flow, and relatively clear margin.

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Fetus; intracranial neoplasms; fetal anaplastic astrocytoma; prenatal imaging; ultrasonography

Introduction

Astrocytoma is the foremost neuroglial tumor. High-grade astrocytomas including graded III (e.g. anaplastic astrocytoma) and IV (e.g. glioblastoma) account for approximately 7–11% of pediatric tumors [1]. However, the prevalence may be underestimated, as many cases of stillborn or aborted may not be reported [2–4]. Recently, more and more fetal anomalies can be detected in the prenatal period, which is probably due to the generalization of antenatal ultrasound imaging and the improvement of imaging technology. However, there has been little discussion about the prenatal diagnosis of congenital intracranial astrocytoma, especially the anaplastic astrocytoma until recently. Fetuses with anaplastic astrocytoma have a better outcome [1], but the imaging findings of various congenital intracranial tumors still widely overlap, and the final diagnosis still depends on pathological examination. Although it is hard to make a definitive diagnosis of the histological type by ultrasound alone, routine prenatal sonograms are clinically important to provide physicians and parents with information regarding the prognosis and to discuss the management of pregnancy [5,6]. Thus, this report described a case of congenital anaplastic astrocytoma that has been detected prenatally by ultrasound in the third trimester of pregnancy. The main prenatal magnetic resonance imaging (MRI), as well as perinatal outcomes, is also presented. We also discuss relevant literature. This study adds our experience to the existing literature on anaplastic astrocytoma.

Case report

A 26-year-old gravida 0 para 0 woman was referred to our department at 37 + 1 weeks of pregnancy after an

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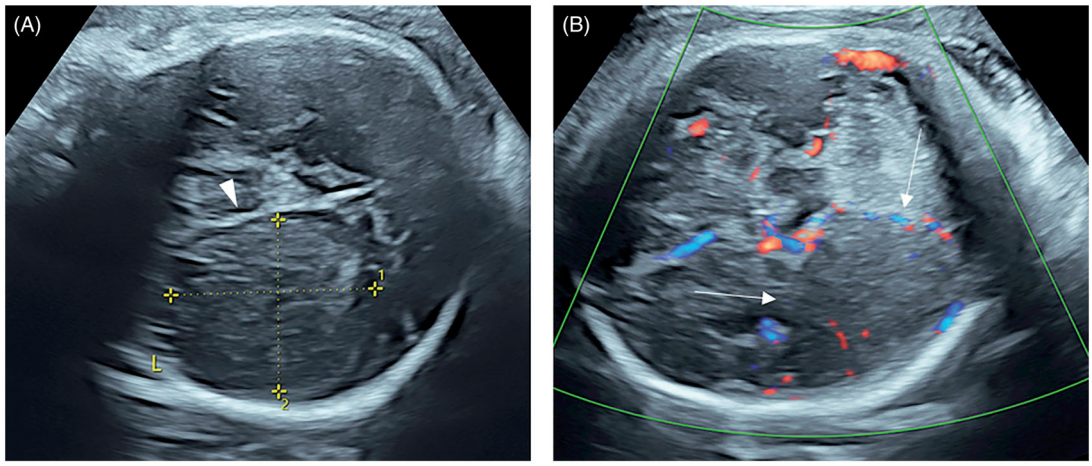

Figure 1. Ultrasonography (US) findings of 37 weeks gestation. (A) A huge solid mass with regular shape and hazy margin is replacing and compressing the cerebral hemispheres. The adjacent midline structure (arrowhead) is slightly deviated to right side. (B) Power Doppler Flow Imaging shows Subtle blood flows in the mass (arrows).

ultrasound examination undergone at another center which had revealed a fetal intracranial hypoechoic lesion with a size of $5.3 \times 4.3 \times 4.0\,cm^3$. There is nothing special about pregnancy with the mother of the fetus. The father of the fetus was healthy but has a family history of cancer, including lung cancer, stomach cancer, and bladder cancer. The mother took levofloxacin for acute appendicitis in early pregnancy and stopped taking it after two days. It had not been revealed of any abnormal findings by ultrasonography examinations performed at 24 and 32 weeks, particularly in the cerebral structures.

There was a hypoechoic lesion with a regular shape and relatively clear margin, located in the left hemisphere (Figure 1). The tumor measured $4.6 \times 4.0 \times 4.7\,cm^3$. The adjacent brain structures were noted to be compressed. The adjacent midline structure and the left lateral ventricle were slightly deviated to the right side. Subtle color flows were present inside the tumor. The evaluation of the fetal Middle Cerebral Artery (MCA) and the umbilical artery was normal. The amniotic fluid was normal, and no other associated malformations were detected.

Fetal magnetic resonance imaging (MRI) performed the day after the ultrasonography study revealed a large intracranial mass with a clear border that showed a hypointense signal on T1-weighed images and heterogeneously iso- or hyper-intense signals on T2-weighted images. Higher T2 intensity areas in the mass indicate intratumoral hemorrhage. Diffusion-weighted imaging showed hypointensity (Figure 2). It was indicated that it may be the teratoma and a diagnosis of the atypical astrocytoma may not be ruled out prenatally.

A second ultrasound examination at $38 + 2$ weeks showed a heterogeneous echogenic mass with a displacement of normal brain tissue (Figure 3(A)). The enlarged tumor was mainly hypoechoic, with an irregular internal hyperechogenic area (the maximal axial area is $2.2 \times 1.3\,cm^2$), which was suggestive of a tumor with a possible presence of an underlying intratumoral bleed.

Subsequently, ultrasound examinations were performed at 39 weeks and $39 + 2$ weeks respectively, which indicated that the tumor and the hyperechoic area (the maximal axial area is $3.2 \times 1.8\,cm^2$) were both further enlarged while causing a slight midline shift (Figure 3(B,C)).

The fetus was delivered vaginally at $39 + 6$ weeks. The infant died 2 h after delivery due to respiration failure.

The sections of tumor tissue and the brain obtained at autopsy. Neuropathological examination found a mass ($4.6 \times 4.0 \times 4.7\,cm^3$) arising from the left temporal lobe and protruding into the left lateral ventricle. The tumor had cystic and hemorrhagic components. Histology showed the diffuse proliferation of atypical glial cells with necrosis and vascular proliferation (Figure 4(A)). These cells were characterized by an increased nuclear to cytoplasmic ratio, and the nuclei were round and oval with mitotic activity to a degree. Immunohistochemical investigations showed that the tumor cells were low positive for GFAP (Figure 4(B)). The Ki-67 labeling index was higher than 15%. ATRX and Olig-2 staining were positive. No other abnormality was found extracranially at autopsy. These findings were felt to be most consistent with a congenital astrocytoma (the WHO grade III) with hemorrhage, necrosis, and cystic degeneration.

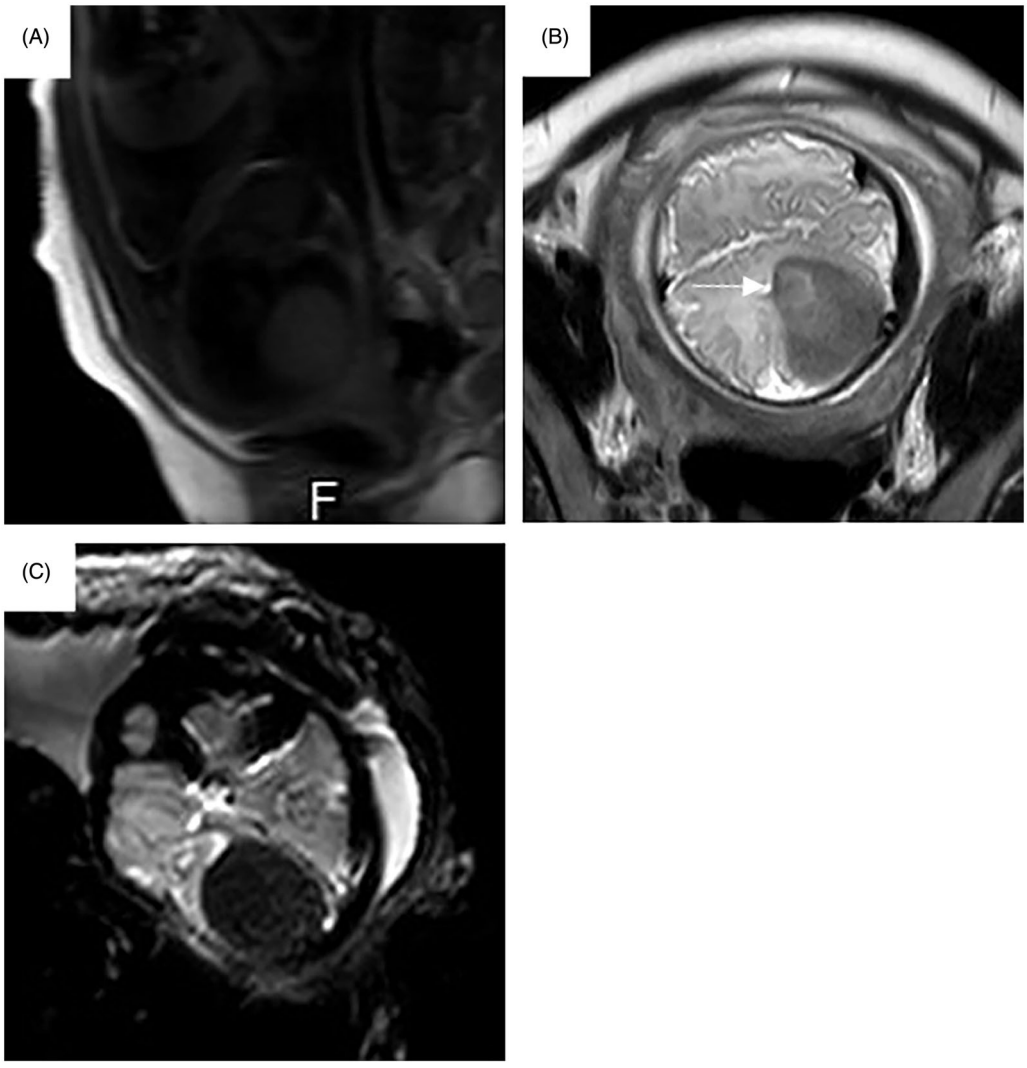

Figure 2. Magnetic resonance imaging. (A) Sagittal T1-weighted image shows a large hypointense signal mass in left temporal lobe. (B) Axial T2-weighted image shows the heterogeneous mass replacing normal brain tissue and resulting in a midline shift and higher T2 intensity areas (arrow) can be seen in the mass. (C) Diffusion weighted imaging shows hypointensity.

The whole-exome sequencing (WES) was performed by fetal tissue samplings and no abnormal changes were found.

Discussion

In this report, we present a case of anaplastic astrocytoma diagnosed prenatally detected by two-dimensional ultrasound in the third trimester of pregnancy. The most striking prenatal ultrasound feature was the incidental detection of the hypoechoic lesion with a regular shape and relatively clear margin, located in the left hemisphere. Once detected, the adjunctive use of color Doppler imaging was used to detect the vascular supply to the tumor. In addition to this, a fetal MRI was also used as a diagnostic technique in this case. Fetal MRI can help in the identification of the tumor anatomical extension. This included determining its exact anatomic relations with surrounding brain parenchyma and skull [7,8]. As seen in our case, it revealed that a mass without invasion of surrounding anatomical structures in ultrasound examination, and further confirmed by fetal MRI, which may indicate that the tumor is less aggressive. We also found that in the ultrasound later follow-up, the hyperechoic area was further enlarged and the boundaries of the tumor became clearer. This illusion may be due to tumor expansion caused by intratumoral hemorrhage which was confirmed by histological examination.

In a case reported by Chuang et al. [9] proposed the contiguous extension and margins of the tumors may represent tumor malignant degree and a poor prognostic indicator. Thus, defining anatomical extension and the margins of the tumors are important. In recent years, fetal MRI has become increasingly available to evaluate fetal malformations, especially in the

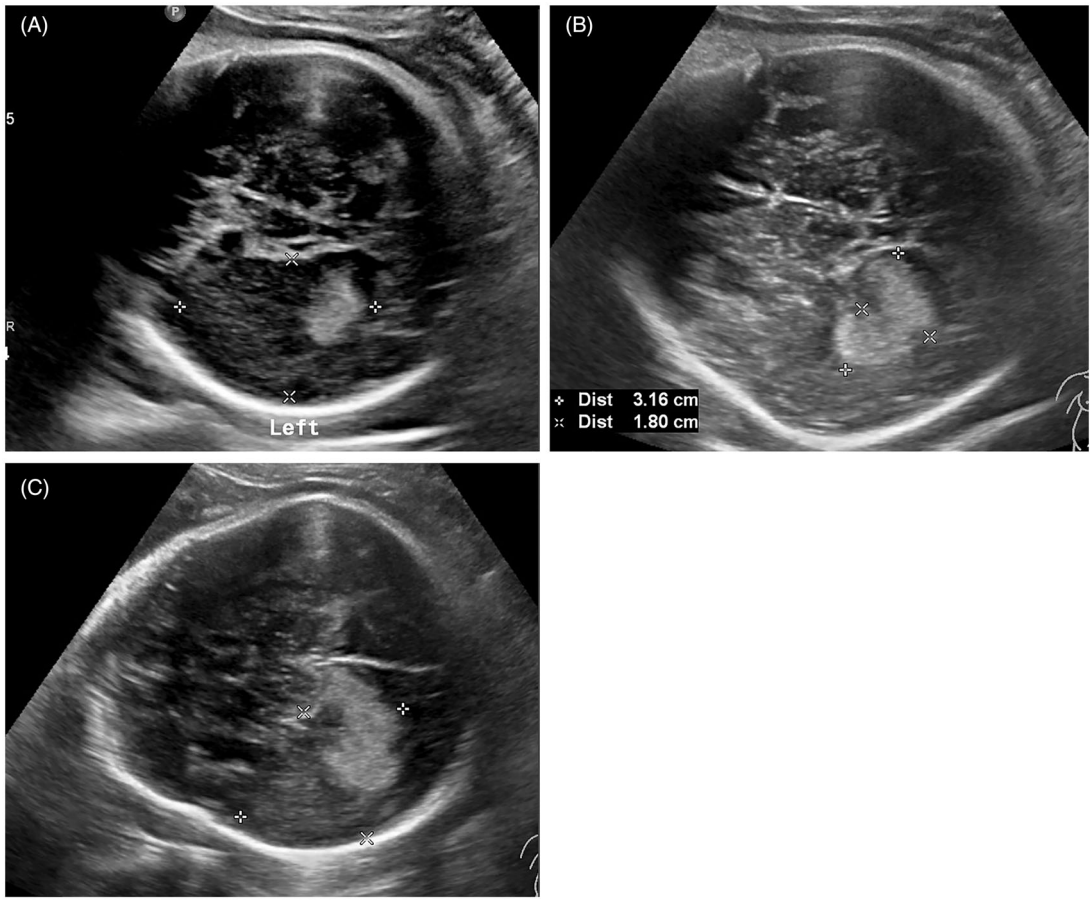

Figure 3. Ultrasonography (US) findings at 38 + 2 (A), 39 (B), and 39 + 2 (C) weeks, showing a slight midline shift. (A) the axial US image of fetal brain reveals an echogenic area in the tumor. (B, C) sonograms showing large bleeding area.

morphological of the developing brain and fetal brain abnormalities, while radiologists have become more and more experienced with the technique [10]. As demonstrated by our case and previously reported clinical experiences, anaplastic astrocytoma usually shows a hypointense signal on T1-weighed images and heterogeneously iso- or hyper-intense signals on T2-weighted images in the presence of intratumoral hemorrhage. Using fetal MRI, it may help in determining the remaining brain structures and the exact localization of the tumor. It is worth noting that the prenatal diagnosis of fetal anaplastic astrocytoma in our case was initially made as an isolated finding in apparently asymptomatic low-risk pregnancy attending for a routine third-trimester scan. Moreover, none of the accompanying complications was developed prenatally, that is, there were no signs of hydrocephaly, polyhydramnios, distortion of the cranium, and bony defects [11].

Our case is unusual, with hypoechoic mass in the early stage of the disease and hyperechoic area appeared in the second ultrasound. The hyperechoic area within the mass was further enlarged in the third and fourth scans. Hemorrhage and necrosis within the tumor may have contributed to its hyperechoic region. Similarly, a slightly higher T2 signal in the tumor seen on fetal MRI may also indicate bleeding. As noted, fetal prenatal ultrasound imaging of three prior reports of anaplastic astrocytoma showed hemorrhage in the tumor [12–14]. The observed enlargement of the tumor in our case could also be attributed to intratumoral hemorrhage. In addition, Color Doppler Flow Imaging (CDFI) is helpful for understanding the pathophysiology of fetal tumors and the accompanying neovascularization. This would be the only way to differentiate between a tumor and brain hemorrhage on ultrasound: it displays blood flow within the mass in the case of a tumor, and conversely demonstrates the lack of color flow signals in the hematoma. However, MRI would be more conclusive [15]. In our case, hemorrhage, subtle color flow, and relatively clear margin were present inside the tumor which may be a diagnostic clue for anaplastic astrocytoma. The follow-up sonographic examination could provide effective information in the process of prenatal diagnosis and neonatal management for fetal tumors.

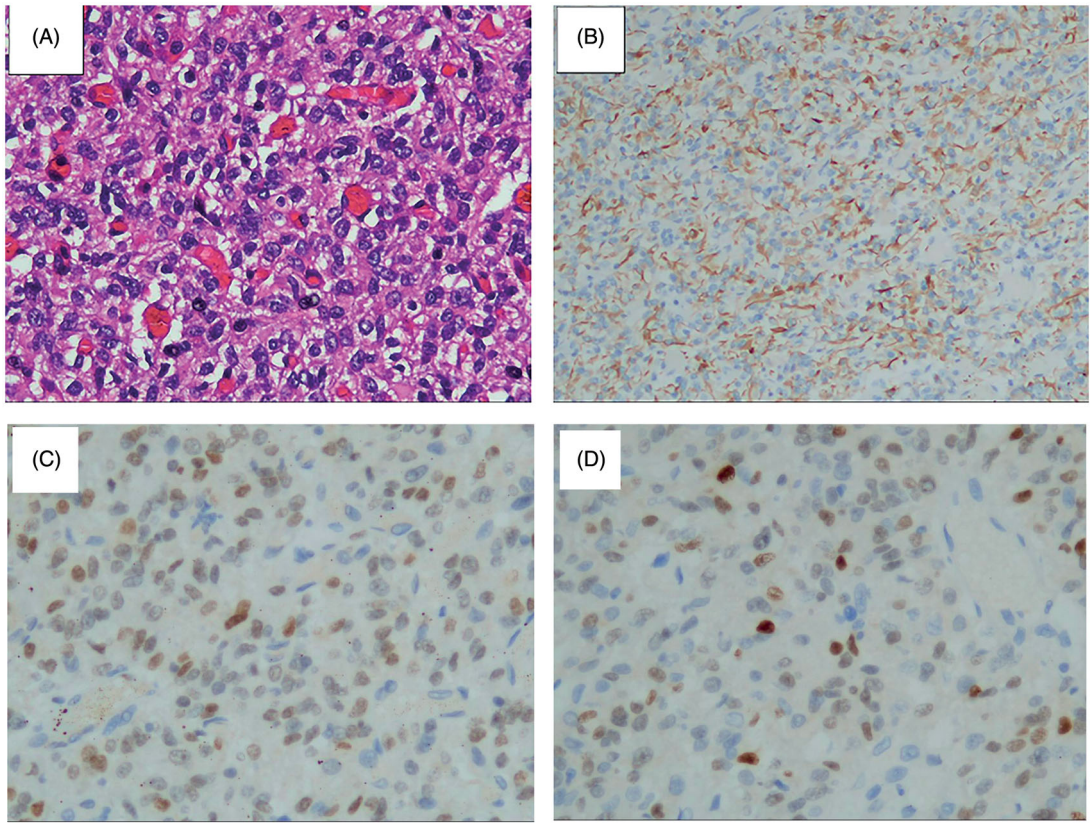

Figure 4. Histological examination. (A) H & E, original magnification ×200 reveals nuclear atypia and some mitoses focal necrosis. (B–D) GFAP, ATRX, and Olig-2 staining are positive as a sign of glial tumor.

Up to now, no more than 11 cases have been reported, nine of which were diagnosed prenatally. We have reviewed the literature for prenatal information about fetal anaplastic astrocytoma which mainly includes single case reports published (Table 1). Almost all the reported cases diagnosed prenatally were found by ultrasound. The prior reports of sonographic appearance of anaplastic astrocytoma *in utero* were that of an echogenic lesion with a midline shift, hydrocephalus, and macrocephaly [12–14,16–19]. 7 of the 9 reported cases have included the information of gestational age at diagnosis [12–14,18–20]. The gestational age at the time of diagnosis prior to delivery ranged from 31 to 42 weeks (mean 35.9 weeks). Normal ultrasound examination in the second trimester does not rule out the probability of a brain tumor developing later in pregnancy. The present case further supports this clinical finding. This may be due to the fact that they may grow very rapidly [5], they are of similar echogenicity as the surrounding structures, or to changes in echogenicity occurring during pregnancy.

Microscopically, Isaacs [1] described that most of the anaplastic astrocytomas lack pseudopalisading necrosis or vascular proliferation, unlike glioblastoma multiforme. However, histological examination was specifically described in detail in six cases and three of them developed intratumoral necrosis or vascular proliferation, along with pleomorphism, hypercellularity, and mitotic activity [12,16,17]. Of interest, focal necrosis and microvascular proliferation were also found in our case. Given the moderate cellular atypia, pathologists classified the case as anaplastic astrocytoma (WHO grade 3). It may be that the classification of fetal gliomas is different from that of adults.

Among the 9 cases of fetal anaplastic astrocytoma, 6 cases were treated [13,16–20]. No matter what kind of treatment, clinicians can offer a better prognosis for a fetus with the kind of brain tumor [1]. Three patients were untreated [12,14], and only one survived but had a mental and motor handicap. In our case, the baby survived only two hours after vaginal delivery, which may be due to the brainstem compressed caused by fetal intracranial tumor during vaginal delivery. Therefore, we are convinced that a cesarean section should be performed if anaplastic astrocytoma was detected in the prenatal period. This is especially important that postnatal intervention should be considered.

In conclusion, a fetal anaplastic astrocytoma is a quite rare pediatric tumor, however, it has a relatively

Table 1. Features of reported cases of anaplastic astrocytoma in the literature.

Authors & Year	Gestional age (weeks)	Pathology	Location	Sonographic features	Theraphy	Survival
Roosen et al. (1988) [17]	—	AA	Right occipitoparietal region	An echogenic mass with macrocephalus and hydrocephalus	Surgical resection	A, 3 years
Heckel et al. (1995) [12]	31	AA	Right hemisphere.	A strongly echogenic mass with macrocephalus, and displacement of flax cerebri to the left		TOP, 32 weeks
Cavalheiro et al. (2003) [13]	35	AA	Occipitoparietal region	—	Surgery	A, 6 years
Das, Simmons, and Danielpour (2005) [16]	The middle of the third trimester	AA	Left hemisphere	Complex mass with hydrocephalus, hemorrhage, and displacement of the midline to the right hemisphere	Surgery + chemotherapy	A, 28 months
Carstensen et al. (2006) [14]	37	AA	Right hemisphere	—	Palliative care	D, 18 days
	42	AA	Bilateral frontal lobe	—	Palliative care	A, 4 years, mental and motor handicap
Stark et al. (2007) [18]	30	AA	Diffuse infiltration of the ventricular wall	Hydrocephalus	Surgery + chemotherapy	A, 12 weeks
Yamashita et al. (2012) [19]	36	AA	Right hemisphere	Macrocephalus and a huge mass	Surgery + chemotherapy	A, 12 months
Shin, Hyun Jung et al. (2013) [20]	38	AA	occipital lobe	A huge mass	Surgery followed by chemotherapy and irradiation	A, 53 months
Present case (2020)	38	AA	Left hemisphere	Hypoechoic mass with displacement of the midline to the right and hemorrhage eappeared in the second ultrasound		D, 2 h

AA: anaplastic astrocytoma; A: alive; D: died; TOP: termination of pregnancy; —: not provided.

better perinatal prognosis, especially compared with glioblastoma. Fetal ultrasound and MRI are of critical importance and help to evaluate intracranial tumors, especially by follow-up sonographic examinations. Ultrasonography is the main method used to establish a correct diagnosis and neonatal management. The diagnosis of congenital anaplastic astrocytoma should be considered in cases in which fetal images reveal a heterogeneous echogenic mass in the brain, especially in the presence of intratumoral hemorrhage, subtle color flow and relatively clear margin. However, the precise histologic type of the tumor was still dependent on pathological examination.

Ethical approval

The authors have no ethical conflicts to disclose. The patient and his family gave their informed consent to publish details and images of the case. This report was approved by our Institutional Review Board.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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Data availability statement

All the clinical, ultrasonographic, and radiological information pertinent to the patient described in this research are fully available in the description of the cases in the Case Reports section of the article.

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