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When Hemorrhage Hides a Fetal Brain Tumor, Importance of Fetal Autopsy

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1 | Introduction

Fetal brain tumors (FBT) are rare, accounting for 10% of fetal tumors [1, 2]. Around 10% are diagnosed antenatally [1]. We present two different types of fetal brain tumors hidden by intra-cerebral hemorrhage. Diagnostic orientation of these two cases was initially erroneous because of the difficulty of specifying the diagnosis in an antenatal context. We show the prenatal images of these two fetal brain tumors and compare them with macroscopic and neuropathological examinations.

2 | Cases History/Examination

2.1 | Case 1

A 30-year-old female, with no medical history was referred at 30 weeks of amenorrhea (WoG) for global and homogeneous hyperechogenicity of the right temporo-occipital region, with respected thin-walled ventricular system (right ventricle measured at 10.5 mm, left ventricle at 8.5 mm). No signs of hydramnios nor associated macrocephaly. Medium cerebral artery (MCA) was measured within the norms. Similar echography was found at 33 WoG (Figure 1A). An initial MRI found a unilateral temporo-occipital edematous lesion (Figure 1B). Feto-maternal platelet incompatibility was first evoked. A second specialized opinion evoked an extensive venous thrombosis of the right sinus and the superior sagittal sinus, with reactive edema of the right hemisphere associated to localized right temporal hemorrhagic venous infarction. A second MRI at 34 WoG with gradient ultrasound and FISTA-type vascular sequences supported the hypothesis of thrombosis of the cerebral venous sinuses with extension of the lesions, increase in parenchymal hemorrhage and appearance of an intraventricular hemorrhage (Figure 1C). The couple was informed of the unfavorable prognosis and the parental request to terminate the pregnancy was accepted. The delivery was carried out at 36+6 WoG. Maternal autoimmune and thrombophilia test was negative. No thrombocytopenia on fetal blood was found. On fetopathological examination, encephal weight was 319 g, cerebral parameters were below the 5th percentile for fetal age (head circumference [HC] 31 cm, BIP 78 mm). The brainstem and cerebellum were macroscopically normal. A large right parieto-occipital tumor lesion invading the midline and leptomeninges, delating gyration was found (4 × 3 × 3 cm) (Figure 2A). Neuropathological examination concluded to an embryonic brain tumor of infantile desmoplastic ganglioglioma type (Figure 2B,C). In view of this rare antenatal presentation, an exome sequencing was performed on the fetus. No pathogenic known variant was found.

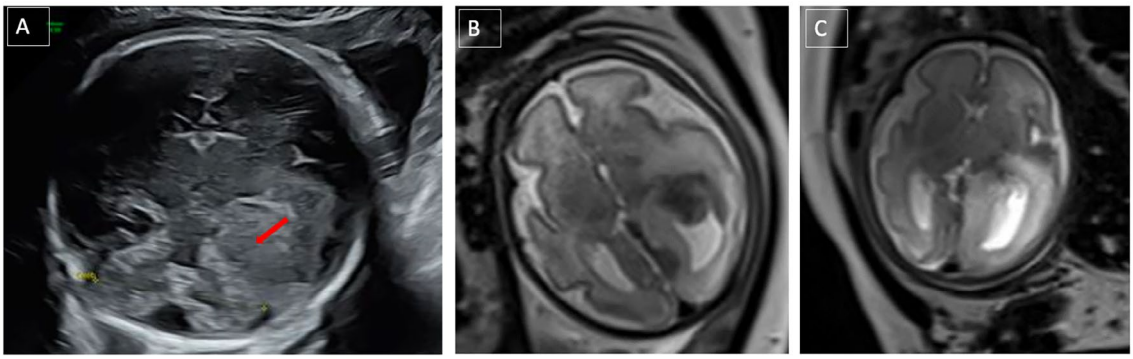

FIGURE 1 | Ultrasound (US) at 30th week of gestation. Hyperechogenicity of the right temporo-occipital region (red arrow), with an erased gyration (A); antenatal Magnetic resonance imaging (T2, axial plane) at 30th WoG. Hyperintense and dedifferentiated aspect of the white-gray substance in temporo-occipital region with obliteration of the furrows at this level (B); Magnetic resonance imaging (T2, axial plane), at 34 WoG. Aggravation of the right hemispheric lesions (C).

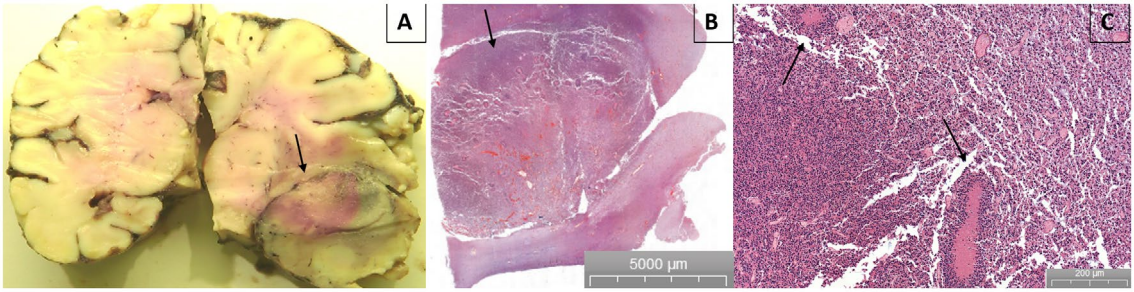

FIGURE 2 | Macroscopic coronal cut (A). Large right parieto-occipital tumor lesion invading the midline and leptomeninges, delating gyration (arrow); Hematoxylin–eosin staining of tumor section (arrow) (B). Biphasic tumor with fusocellular component infiltrating the leptomeninges. At higher magnification (C), we see undifferentiated component and pseudo rosettes (arrows) evocative of an embryonic brain tumor of infantile desmoplastic ganglioglioma.

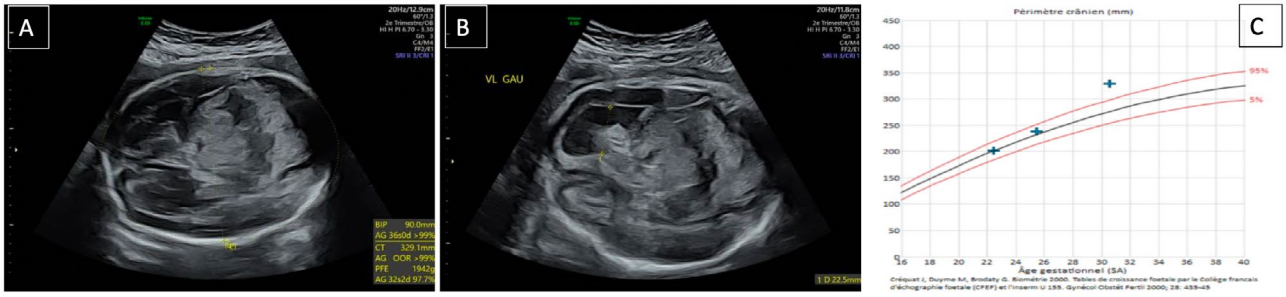

FIGURE 3 | Fetal ultrasonography at 30th week of gestation (A). Macrocephaly with head circumference > 99th percentile; Left ventricle dilation measured at 22.5 mm and right hemisphere deviation (B); Macrocephaly reported on a head circumference growth curve at 30th week of gestation (C).

2.2 | Case 2

A 33-year-old female patient, G4P1, was referred in our unit at 30+4WoG because of the discovery of a major intracerebral hemorrhage in the left hemisphere with ventriculomegaly, macrocephaly and a massive anechoic image with compression of the right hemisphere (Figure 3A–C). The cerebellum was backed up to the foramen magnum and clearing of the great cistern was noted. MCA measurement was not possible. No other hemorrhagic signs and usual extra cerebral morphology were noted, except a single umbilical artery. Amniocentesis showed no unbalanced chromosomal rearrangement on array CGH. Given the severity of the cerebral hemorrhagic signs and hydrocephalus, the parental request to terminate the pregnancy was accepted. The delivery at 31+5 WoG was complicated by a uterine rupture. Fetal autopsy found macrocrania (HC measured at 33 cm). The brain was liquefied, and showed the presence of a major ventricular dilatation with necrosis and hemorrhage of the cerebral parenchyma associated with a median tumor nodular lesion measuring 6×5 cm (Figure 4A). The neuropathological examination concluded to a malignant embryonal tumor, Grade 4 according to the international histopronostic classification (Figure 4B–D).

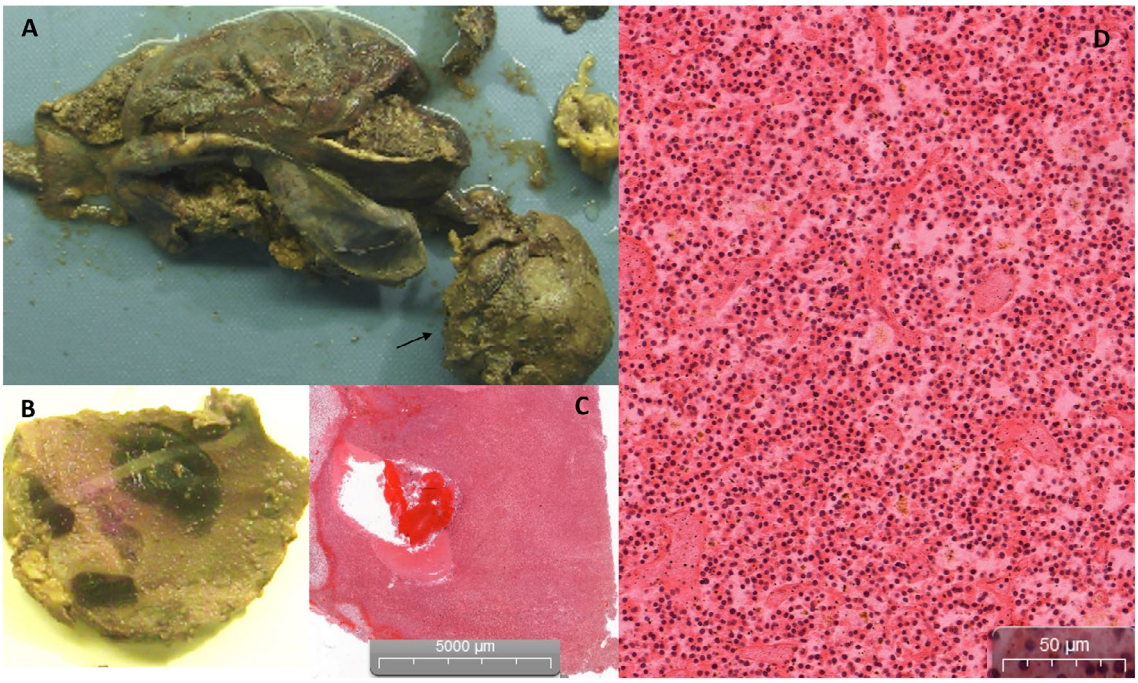

FIGURE 4 | Neuropathology exam: External morphological aspect (A). Hemorrhagic alterations of the brain with significant ventricular dilation and identification of an intra-ventricular nodular mass measuring 6 × 5 cm (arrow). Macroscopic coronal cut of the nodular lesion (B) showing tumoral proliferation with hemorrhagic and necrotic damages also seen on hematoxylin–eosin staining of tumor section (C). At higher magnification, there is a proliferation of monomorphic cells arranged in nests or sheets separated by vessels, corresponding to an undifferentiated tumor named malignant embryonal tumor, Grade 4 according to the international histoprognostic classification (D).

2.3 | Differential Diagnosis

The main presenting sign in both cases was an intracerebral hemorrhage, which concealed the underlying tumoral lesion. Fetal intracerebral hemorrhage can result from various causes, mainly: (i) fetal cause (congenital vascular abnormalities, such as arteriovenous malformations, coagulopathy, which may be inherited or acquired, genetic or developmental abnormalities affecting the brain or blood vessels); or (ii) maternal cause (trauma or abdominal injury during pregnancy, maternal hypertension or preeclampsia, substance abuse, such as alcohol, cocaine or tobacco use during pregnancy, maternal infections that affect the fetus like cytomegalovirus [CMV] or toxoplasmosis) [3, 4].

3 | Conclusion and Results

Unexpectedly, for both cases, autopsy revealed a fetal brain tumor and settled their respective histological profile. Each of these two fetal brain tumors was rare respectively an embryonic brain tumor of infantile desmoplastic ganglioglioma type for Case 1 and a malignant embryonal tumor for Case 2 [5].

4 | Discussion

FBT are rare, accounting for 10% of fetal tumors [1, 2]. Around 10% are diagnosed antenatally [1]. Prognosis depends on age at diagnosis, size and histological type [1, 6]. Prognosis is usually poor, with survival rates ranging from 16% to 28% [1, 2, 7–10], and around 1/3 of fetuses die in utero [2, 6]. Prenatal treatment focuses mainly on alleviating secondary complications caused by tumors [11, 12]. The main antenatal fetal brain tumors are teratoma, astrocytoma, craniopharyngioma, choroid plexus papilloma and embryonal tumors [1, 6, 11, 13]. Glial tumors can be difficult to diagnose, presenting as vascular lesions due to their high vascularity nature. The ultrasound false-positive rate for suspected cerebral lesions is estimated at 7.1% [14]. In fetal life, ultrasound and MRI are considered the most effective diagnostic tools. The MERIDIAN multicenter cohort study demonstrated high confidence in fetal MRI for the diagnosis of cerebral anomalies, providing additional information in 49% of cases, modifying prognostic information and ultimately leading to changes in management in 20% of cases [15]. Antenatal discovery of cerebral lesions, usually occurs at the end of the second or third trimester [1, 7, 11, 13]. In our cases ultrasound lesions were visualized as early as 30 WoG, in line with published studies reporting that gliomas are often diagnosed around 32 WoG, teratomas around 27 WoG, and hamartomas around 21 WoG [1, 9, 13]. These two tumors were supratentorial, which is in agreement with the preferential localization found in the literature, as fetal and neonatal tumors are predominantly supratentorial (around 70%), whereas pediatric tumors are more often infratentorial [1, 7, 9–11, 13]. Ultrasound findings often associate with hydrocephalus (58.3% of cases), macrocephaly (79.2% of cases) and hydramnios (37.5% of cases) [1, 2, 6, 9]. Hydrocephalus is caused either by compression of the ventricular system or intracranial hemorrhage from the tumor [9]. For the two cases reported here, the main presenting sign was intracerebral hemorrhage, manifested by intraparenchymal hyperechogenicity with reactive edema (Case 1), and hemorrhage with macrocephaly and ventricular dilatation (Case 2). Macrocephaly and ventriculomegaly was present in 1/2 cases in accordance with the literature

[1, 2, 6, 10]. This can lead to cephalopelvic/fetal-maternal disproportion, resulting in starter dystocia and delayed delivery. Rarely, spontaneous rupture of the fetal head or uterine rupture during delivery may occur [1, 13], as shown in our Case 2, where the pregnancy termination was complicated by cervical and vaginal uterine rupture. While definitive diagnosis can only be made by neuropathology, the literature shows that only 30%–40% of parents agree to autopsy [1, 16]. In our two cases, autopsy enabled us to rectify the initial antenatal diagnosis and establish the phenotypic profile based on the post mortem histological and immunohistochemical characteristics of each brain tumor as well as ultrastructural study of microvasculature [17]. Molecular analysis is accessible from tumor tissue which helps typing brain tumors sometimes poorly differentiated and offers more personalized genetic counseling [8, 18]. The significant increase in molecular testing of brain tumor samples has led to the discovery that childhood brain tumors have molecular characteristics that differ from those of older children. In our cases, genetic counseling can be reassuring regarding the risk of recurrence due to the probable accidental nature of these lesions.

Author Contributions

Claire Comba: conceptualization, writing – original draft. **Agnès Sartor:** data curation. **Annick Sevely:** data curation. **Magalie Raveneau:** data curation. **Yves Chaix:** data curation. **Annie Laquerriere:** data curation, investigation. **Jessie Ousselin:** data curation. **Jacqueline Aziza:** supervision. **Charlotte Dubucs:** writing – review and editing.

Consent

Patients give their written consent for publication.

Data Availability Statement

The authors have nothing to report.

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