Fetus-in-fetu in the cranium of a 4-month-old boy: histopathology and short tandem repeat polymorphism–based genotyping

Case report

JIN WOOK KIM, M.D., SUNG-HYE PARK, M.D., PH.D., SUNG-SUP PARK, M.D., PH.D., KYU-CHANG WANG, M.D., PH.D., BYUNG-KYU CHO, M.D., PH.D., SO YEOON KIM, M.D., CHAE-YONG KIM, M.D., PH.D., and SEUNG-KI KIM, M.D., PH.D.

1Division of Pediatric Neurosurgery and 2Department of Pathology, Seoul National University Children’s Hospital; 3Department of Laboratory Medicine, Seoul National University Hospital, Seoul; and 4Department of Neurosurgery, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea

Fetus-in-fetu is a very rare condition in which one fetus is contained within another. About 100 cases have been reported, and in most of these the fetus was located in the retroperitoneum. The authors describe an extremely rare case of an intracranial fetus-in-fetu in an extraaxial location. This is the eighth intracranial fetus-in-fetu to be reported, the first intracranial extraaxial case, and involves the oldest documented patient with this condition.

Histopathological analysis of the mass revealed a degenerated amnionic membranelike tissue, well-differentiated extremities (including fingerlike structures), skin, matured lungs, well-formed intestines, cerebellar and cerebral tissue, and a notochord with ganglion cells. DNA analysis using short tandem repeat polymorphisms confirmed that the fetus-in-fetu mass and the host infant had heterozygous alleles and were of identical sex and genotype.

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KEY WORDS • fetus-in-fetu • genotyping • intracranial mass • parasitic twin

In Greek mythology, Athena emerged fully formed from the forehead of Zeus. In the medical field, Meckel reported the first case of fetus-in-fetu in the 18th century. Since then, fewer than 100 cases have been reported. About 80% of these cases presented as retroperitoneal masses, and in the remaining cases, the masses were present in the sacrum, scrotum, mouth, liver, and cranium. Intracranial fetus-in-fetu is extremely rare and, to the best of our knowledge, only 7 cases have been reported previously (Table 1). In this study, we describe a unique case of an extraaxial intracranial fetus-in-fetu. Deoxyribonucleic acid analysis using STR polymorphisms was performed to compare the genotypic identity of the host infant with that of the fetus-in-fetu.

Case Report

History and Examination. This 4-month-old boy was referred to our institution because of a setting-sun sign of the eyes, which had been observed since the 3rd month after birth. Physical examinations revealed a larger head circumference than normal (> 97th percentile) and a bulging anterior fontanelle. Except for the setting-sun sign, he had no neurological abnormalities and his development was appropriate for his age. The level of serum alpha-fetoprotein was 57 ng/ml (normal for his age) and that of human chorionic gonadotropin was within the normal range. No abnormalities had been detected on ultrasonography performed at the 22nd and 29th gestational weeks at a local hospital.

Magnetic resonance images and CT scans revealed a large heterogeneous mass above the tentorium, which occupied the anterior half of the intracranial space (Fig. 1). The mass was ~ 12 cm in diameter and appeared as a large cystic and solid mass mixed with internal fat, calcified components, and some enhancing solid portions. The mass caused posterior displacement of adjacent structures such as the corpus callosum, optic chiasm, and brainstem. Fluorodeoxyglucose and C-methionine positron emission tomography images showed that a hypometabolic lesion was present in the anterior half of the cranium. The lesion was initially diagnosed as a congenital teratoma on the basis of these findings.
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Operation and Postoperative Course. A right frontotemporal craniotomy was performed. The mass was covered with a whitish-yellow membrane and located extraaxially. The mass was easily detached from the surrounding tissues of the brain and removed completely. In the process of debulking, 2 limblike structures were observed (Fig. 2). Postoperatively, the patient was neurologically stable with no additional deficits. Postoperative MR imaging demonstrated that no residual mass was present, but a substantial amount of subdural fluid was observed. Despite serial tapping (cerebrospinal fluid opening pressure of 20 cm), the accumulation of subdural fluid did not diminish, and bulging of the anterior fontanelle persisted. A subduroperitoneal shunt was therefore inserted 10 days after the mass was removed. At the 12-month follow-up consultation, the patient was free of neurological abnormalities and his development was appropriate for his age.

Histopathological Findings. On gross examination, the specimen was composed of capsules, cysts, and limblike appendages. Histological findings were sufficient to render the diagnosis of fetus-in-fetu; present were degenerated amniotic membranelike tissue, well-differentiated extremities with fingerlike structures, skin, matured lungs, well-formed intestines, cerebellar and cerebral tissue, and a notochord with ganglion cells (Fig. 3).

Table 1: Summary of the published reports of intracranial fetus-in-fetu

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Patient Age, Sex</th>
<th>Symptom</th>
<th>Lesion Location</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimmel et al., 1950</td>
<td>1 day, F</td>
<td>hydrocephalus</td>
<td>intraventricular</td>
<td>in good health at 18-mo FU</td>
</tr>
<tr>
<td>Afshar et al., 1982</td>
<td>6 wks, F</td>
<td>hydrocephalus</td>
<td>Lt lat ventricle</td>
<td>ND</td>
</tr>
<tr>
<td>Yang &amp; Leow, 1992</td>
<td>ND</td>
<td>hydrocephalus</td>
<td>Lt lat ventricle</td>
<td>ND</td>
</tr>
<tr>
<td>Hung &amp; Lam, 1993</td>
<td>2 mos, F</td>
<td>hydrocephalus</td>
<td>Lt lat &amp; 3rd ventricle</td>
<td>ND</td>
</tr>
<tr>
<td>Tsai et al., 1993</td>
<td>2 mos, F</td>
<td>hydrocephalus</td>
<td>Lt &amp; 3rd ventricle</td>
<td>died of ICH</td>
</tr>
<tr>
<td>Goldstein et al., 1996</td>
<td>fetus, unknown</td>
<td>macrocephalus</td>
<td>intracranial</td>
<td>died</td>
</tr>
<tr>
<td>Miura et al., 2006</td>
<td>fetus, M</td>
<td>macrocephalus</td>
<td>intracranial &amp; extraaxial</td>
<td>in good health at 12-mo FU</td>
</tr>
<tr>
<td>present case</td>
<td>4 mos, M</td>
<td>setting-sun sign</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FU = follow-up; ICH = intracranial hypertension; ND = not described.

Fig. 1. Preoperative CT scans and MR images of the well-demarcated large cystic and solid mass mixed with internal fat and calcified components, occupying half of the total intracranial space and severely compressing the brain parenchyma. A: Unenhanced CT scan. B: Axial T1-weighted image. C: Axial T1-weighted image with Gd enhancement. D: Axial T2-weighted image. E: Sagittal T1-weighted image with Gd enhancement. F: Coronal T1-weighted image with Gd enhancement.
After the mass had been pathologically confirmed to be a fetus-in-fetu, we performed STR polymorphism–based genotyping to assess the genotypic similarity of the host infant and the fetus-in-fetu mass. Genomic DNA was extracted from whole blood samples obtained from the host infant and his parents using a QIAamp blood Mini Kit (Qiagen), and from the tissue of the fetus-in-fetu using a QIAamp DNA Mini Kit (Qiagen) according to the manufacturer’s protocols. Genetic marker loci, including tandem repeat regions, were tested using an AmpFlSTR profiler plus polymerase chain reaction amplification kit (Applied Biosystems), as previously described.13 The 10 marker loci, representing 11 chromosomes, are listed in Table 2. Analysis was carried out using GeneMapper ID 3.2 software (Applied Biosystems).

The host infant’s genotypes included 1 paternal and 1 maternal allele at each locus. Genetic profiles for the 10 STR loci of the fetus-in-fetu were completely identical to those of the host infant (Table 2).

**Discussion**

This case is unique in that the intracranial fetus-in-fetu was located extraaxially. Only 7 cases of intracranial fetus-in-fetu have been reported.8 Five of these cases involved intraventricular masses, and the authors of the other 2 reports did not supply information about the lesion’s location.1,6,8,11,12,14,16,18 To the best of our knowledge, this is the first report of an extraaxial intracranial fetus-in-fetu. An extraaxial mass may take longer to produce symptoms of increased
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Summary of genotypic information obtained in the host infant, his parents, and the fetus-in-fetu at 10 marker loci

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chromosomal Location</th>
<th>Father</th>
<th>Mother</th>
<th>Host Infant</th>
<th>Fetus-in-Fetu</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3S1358</td>
<td>3p</td>
<td>15/16</td>
<td>14/15</td>
<td>15/16</td>
<td>15/16</td>
</tr>
<tr>
<td>FGA</td>
<td>q428</td>
<td>23/23</td>
<td>21/15</td>
<td>21/23</td>
<td>21/23</td>
</tr>
<tr>
<td>D5S818</td>
<td>5q21-31</td>
<td>10/11</td>
<td>10/13</td>
<td>10/11</td>
<td>10/11</td>
</tr>
<tr>
<td>D7S820</td>
<td>7q11.21-22</td>
<td>10/11</td>
<td>11/12</td>
<td>10/12</td>
<td>10/12</td>
</tr>
<tr>
<td>D8S1179</td>
<td>8</td>
<td>13/13</td>
<td>14/16</td>
<td>13/16</td>
<td>13/16</td>
</tr>
<tr>
<td>vWA</td>
<td>12p12-pter</td>
<td>14/14</td>
<td>18/18</td>
<td>14/18</td>
<td>14/18</td>
</tr>
<tr>
<td>D13S317</td>
<td>13q22-31</td>
<td>8/10</td>
<td>8/11</td>
<td>8/10</td>
<td>8/10</td>
</tr>
<tr>
<td>D18S51</td>
<td>18q21.3</td>
<td>14/14</td>
<td>14/17</td>
<td>14/17</td>
<td>14/17</td>
</tr>
<tr>
<td>D21S11</td>
<td>21</td>
<td>29/30</td>
<td>32.2/33.2</td>
<td>30/32.2</td>
<td>30/32.2</td>
</tr>
<tr>
<td>amelogenin</td>
<td>Xp22.1-22.3</td>
<td>X/Y</td>
<td>X/X</td>
<td>X/Y</td>
<td>X/Y</td>
</tr>
<tr>
<td>&amp; Yp11.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The alleles of all loci were named according to the number of repeat units present as recommended by the DNA Commission of the International Society of Forensic Haemogenetics.

Intracranial extraaxial fetus-in-fetu

Intracranial pressure than an intraventricular lesion because symptoms would be caused by the volume of the mass itself, not by hydrocephalus. This may explain why our patient is the oldest host of an intracranial fetus-in-fetu mass ever reported.

As radiological techniques have advanced, fetus-in-fetu masses have been diagnosed at an earlier host age than previously.\cite{Goldstein1993, Coolen1996} Goldstein and colleagues\cite{Goldstein1993} described a case that was diagnosed during prenatal ultrasonography, and Coolen et al.\cite{Coolen1996} described a case that was detected during prenatal MR imaging. Although the mother of our patient stated that she had undergone fetal ultrasonography as recommended by the local clinic, the lesion was not detected at that stage. Therefore, the ability of routine ultrasonography to detect a fetus-in-fetu prenatally may be limited depending on the technique, equipment, and timing of ultrasonography.

The term “fetus-in-fetu” implies a condition in which a malformed parasitic fetus is found inside the body of its twin partner. Controversy and ambiguity exist regarding the definition of this condition. This is partly attributable to the scarcity of cases, the incidence of which is estimated to be 1/500,000 live births.\cite{Bär1982} Some authors believe that this condition is nothing more than a well-differentiated teratoma, whereas others consider it to be a type of parasitic twin caused by abnormal embryogenesis in a monozygotic diamniotic pregnancy.\cite{Brand1997} Recently, the latter concept has gained credence because an axial skeleton, which is thought to be a sign of individual and separate development of the fetuses, is present in most cases. The presence of a spinal structure implies that the fetus probably progressed to the primitive streak stage, resulting in greater structural organization than that typical of a teratoma.\cite{Chua2004} Notochord and ganglion cells, which are evidence of the presence of an axial skeleton, were present in our case. The whitish-yellow membrane that covered the surface of the mass was confirmed to be amniotic. The existence of an amniotic membrane in the fetus-in-fetu mass suggests that unequal division of the inner cell mass occurred at a fetal age of 3–9 days.\cite{Hing2007} The presence of an axial skeleton and an amniotic membrane suggests that the mass was a monozygotic diamniotic twin rather than a teratoma. Miura et al.\cite{Miura1996} reinforced the concept of monozygotic origin of fetus-in-fetu by analysis of the methylation status, demonstrating different methylation patterns in a host infant and fetiform mass.

In all reports of karyotype analysis, the karyotype of the fetus-in-fetu was identical to that of the host fetus or infant.\cite{Goldstein1993, Coolen1996} We performed molecular genetic analysis using 10 STR markers and showed that the genotypes of the fetus-in-fetu mass and the host infant were heterozygous and identical. This finding confirmed that the fetus-in-fetu originated from a premeiotic stem cell. However, evidence of identical genotype does not distinguish between a parasitic twin and a well-differentiated teratoma because the latter may also have a genotype identical to that of the host if it is of premeiotic stem cell origin.\cite{Hong2000}

In our patient, the mass was removed completely and there were no signs of recurrence during 12 months of follow-up. Based on the benign clinical course in our patient and others, it appears that surgical removal of such masses may be curative. There is 1 report of a recurrent case after resection of an intraabdominal fetus-in-fetu.\cite{Müller1996} The recurrent mass consisted of a mixed germ tumor composed of an immature teratoma and a yolk-cell tumor. Therefore, close postoperative surveillance with imaging studies and serum alpha-fetoprotein examinations would also be warranted, particularly in cases of incomplete removal of the amniotic membrane.

Conclusions

The extraaxial location of the fetus-in-fetu and the age of our patient are unique among reports of this condition. Our diagnosis of a fetus-in-fetu was confirmed by the presence of an axial skeleton and an amniotic membrane, and DNA analysis demonstrated that the genotypes of fetus-in-fetu mass and the host infant were heterozygous and identical, indicating that the origin of the fetus-in-fetu was a premeiotic stem cell.

References


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Address correspondence to: Seung-Ki Kim, M.D., Ph.D., Division of Pediatric Neurosurgery, Seoul National University Children’s Hospital, 103 Daehangno, Jongno-gu, Seoul 110-799, Republic of Korea. email: nstomas@snu.ac.kr.