CASE REPORT

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Body stalk anomaly in a monochorionic-diamniotic twin pregnancy – case report and review of the literature

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Abstract

Body stalk anomaly (BSA) is a rare abdominal defect, generally considered to be lethal. Reported prevalence ranges from 0.4 to 3.2 per 100 000 live births. An early prenatal diagnosis offers the possibility of parental counseling and the termination of pregnancy. Also called limb–body wall complex, the anomaly is characterized by finding the intrathoracic and abdominal organs outside the cavity comprised by amnio-peritoneal membrane attached directly to the placenta and the umbilical cord short or absent. We report a case of BSA in a monochorionic-diamniotic twin pregnancy, diagnosed antenatal by the massive midline thoraco-abdominal wall defect, severe scoliosis and absent umbilical cord, presented at fetal ultrasound first trimester examination; portions of the heart, kidney and lung were contained into the placenta. The second fetus was echographically normal. At 18 weeks of gestation, a recommended amniocentesis exam was performed, an abnormal karyotype being excluded through this method. At 33 weeks of gestation, the patient presented with spontaneous preterm rupture of membranes. Delivery occurred by emergency Caesarean section for acute fetal distress; extracted first live fetus was admitted in the neonatal intensive care; the second live fetus with a severe thoraco-abdominal wall defect, fragments of organs included into the placental mass and severe reduction defect of the inferior right limb, deceased at 30 minutes from delivery. The fetus together with the placenta has been sent for histopathological exam. Clinical examination confirmed the diagnosis suspected by ultrasound examination. There are only a few reports in the literature about BSA in multiple gestations, and fewer about twin pregnancies in which only one fetus was affected by this condition.

Keywords: multiple pregnancy, fetal abnormality, morphology, ultrasound, karyotype.

Introduction

Body stalk anomaly (BSA) or limb–body wall complex (LBWC) is a term used to describe a complex congenital and generally lethal anomaly, in which the abdominal organs develop outside of the abdominal cavity and remain attached directly to the placenta. Martinez-Frías, in 1997, demonstrated the presence of wall defects with evisceration of thoracic and abdominal organs and other congenital abnormalities with or without limb defects and suggested the term body wall complex [1]. This condition involves an abdominal and/or thoracic wall defect covered by amnion a short or absent umbilical cord, with the placenta almost attached to the anterior fetal wall, along with intestinal malrotation, kyphoscoliosis, and lower extremity anomalies. This anomaly may occur in conjunction with defects of the neural tube, genitourinary malformations, intestinal atresia and various anomalies of the chest wall and craniofacial defects, which led to the creation of a confusing range of terms for this disorder [2–5]. Many cases with abnormal facial cleft do not meet the requirements for the true complex. Some reported cases associate absent gallbladder and polysplenia, traits that are not included in the complex. In a 25 series of cases, cranial defects such as exencephaly/encephalocele with facial clefts were present as diagnostic criteria [6]. Generally, BSA is not associated with chromosomal abnormalities [7].

Aim

We describe a case of BSA with exencephaly and palate cleft in a monochorionic-diamniotic twin pregnancy, in an attempt to contribute to a complete image diagnostic association of anomalies and to explain its etiology.

Case presentation

We report the case of a 31-year-old primiparous woman, with no significant history of health issues, no history of drug abuse and no infectious diseases, but with a poor compliance to prenatal visits. She had her first prenatal ultrasound scan performed at 14 weeks of gestation. The ultrasound examination revealed a 14 weeks and two days monochorionic-diamniotic twin gestation, with a healthy

and normally developed fetus and a second, malformed, fetus. An incompatibility in the ABO system with no signs of immunization was detected and investigated throughout the pregnancy. The 14 weeks prenatal diagnosis of malformed fetus included exencephalia, ectopia cordis, large omphalocele with evisceration of bowel and liver, urinary bladder exstrophy, missing limbs, absence of thoracic cage, and partially visible spine with the absence of lumbosacral region, suggesting a caudal regression syndrome (Figure 1). The umbilical cord of the abnormal fetus had two blood vessels, being inserted at less than 2 cm away from the margin of the placenta (which was located on the posterior wall). A decreased volume of amniotic fluid was detected in the amniotic sac of the malformed twin. The conclusion was 14 weeks mono-chorionic-diamniotic twin pregnancy.

Four weeks later, the patient has performed another ultrasound scan for a second opinion, revealing 18 weeks monochorionic-diamniotic twin pregnancy with one healthy fetus and one abnormal fetus with BSA, described as having a large abdominal wall defect and a renal structure floating in the amniotic cavity.

Amniocentesis and karyotype were recommended and performed, revealing no cytogenetic chromosomal abnormality.

At 22 weeks of gestation, a cervical cerclage was performed. At 30 weeks and four days of pregnancy, the patient was admitted in the Department of Obstetrics and Gynecology, University Emergency Hospital, Bucharest, Romania, for premature rupture of membranes, and one week later, the fetuses were extracted by Caesarean section for acute fetal distress. A preterm, 1500 g healthy female newborn was extracted from a cephalic presentation, receiving an Apgar score of 7. A second fetus was then extracted with the single placenta, having a very short marginally inserted cord (Figure 2). The malformed fetus and placenta were sent to the Department of Pathology, University Emergency Hospital, Bucharest, in order to be macroscopically and microscopically analyzed. The mother and healthy baby were released from hospital 40 days later, with no further significant complications, after the premature baby was cared for mild preterm related pathology.

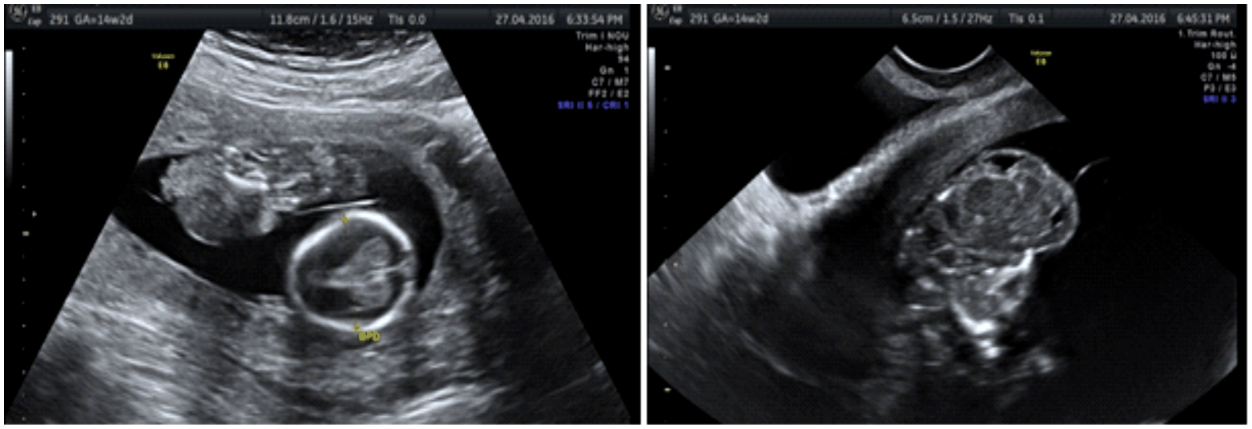

Figure 1 – ***Ultrasound examination at 14 weeks and two days: note monochorionic–diamniotic twin gestation with one normal fetus and one with BSA criteria. BSA: Body stalk anomaly.***

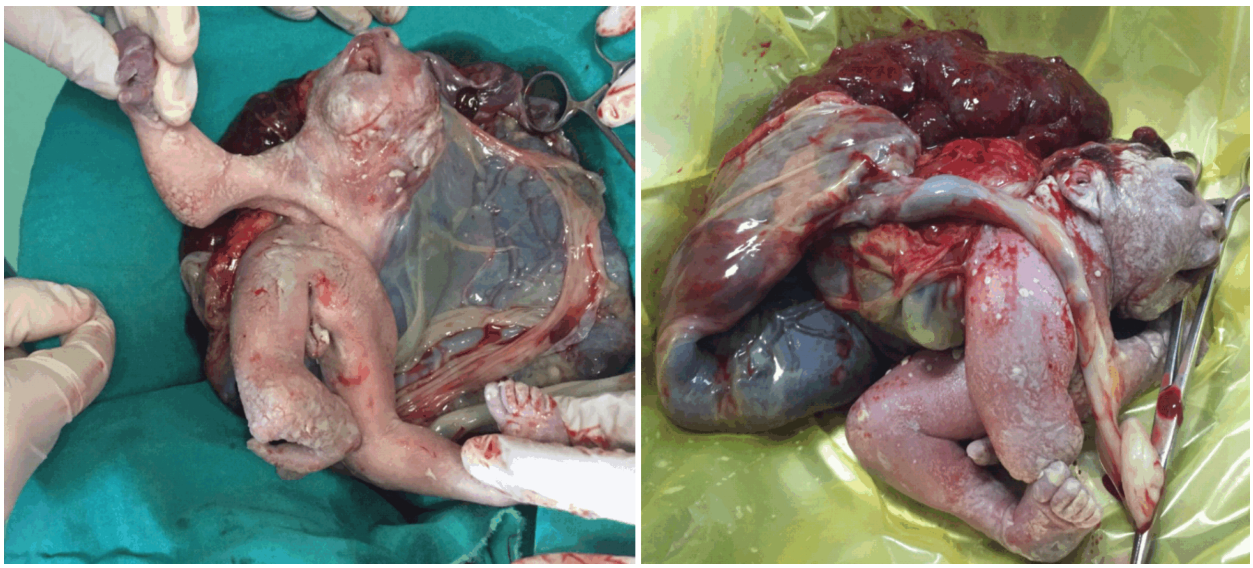

Figure 2 – ***Intraoperative macroscopic examination of the fetus with BSA and the fetal annexes: note the presence of a exencephaly, cleft palate and the large anterior abdomen wall defect with the viscera outside the abdominal cavity. Also, observe the marginal insertion of a very short umbilical cord. BSA: Body stalk anomaly.***

Pathological findings

Gross examination of the fetus and the fetal annexes confirmed the findings seen in ultrasonography (Figure 3). The fetus with ambiguous external genitalia had multiple malformations, some of which have not been seen on ultrasound. We noted extreme malformation of the cephalic region: a large encephalocele was seen over the head of the fetus in the occipital region, the remaining cerebral mass was protected by a thick, dura mater-like membrane and portions of the scalp and calvaria were absent (exencephaly). When the membrane was removed, two asymmetrical cerebral hemispheres were seen. The cerebral cortex gyri were flattened and the sulci were shallower and highly vascular. Cut sections of the brain showed a single large ventricular cavity, a vague corpus callosum like white area and a misplaced hippocampal structure similar to those found in rodent brains. A cleft palate and bulging eyeballs were also noted. Prominent skeletal deformities were observed: amelia of the left upper limb, a severely kyphoscoliotic spine and malrotation of the lower limbs. The limbs were pushed to the right side by the protruding abdominal organs, changing the body axis. A large anterior abdomen wall defect was noted. The entire liver, stomach, small and large intestines, kidneys, a rudimentary sacciform heart and large portion of the hypoplastic lungs were outside the body. The viscera were partially free in the amniotic cavity and partially covered by a membrane. The discoid placenta weighed 400 g and had a very short umbilical cord.

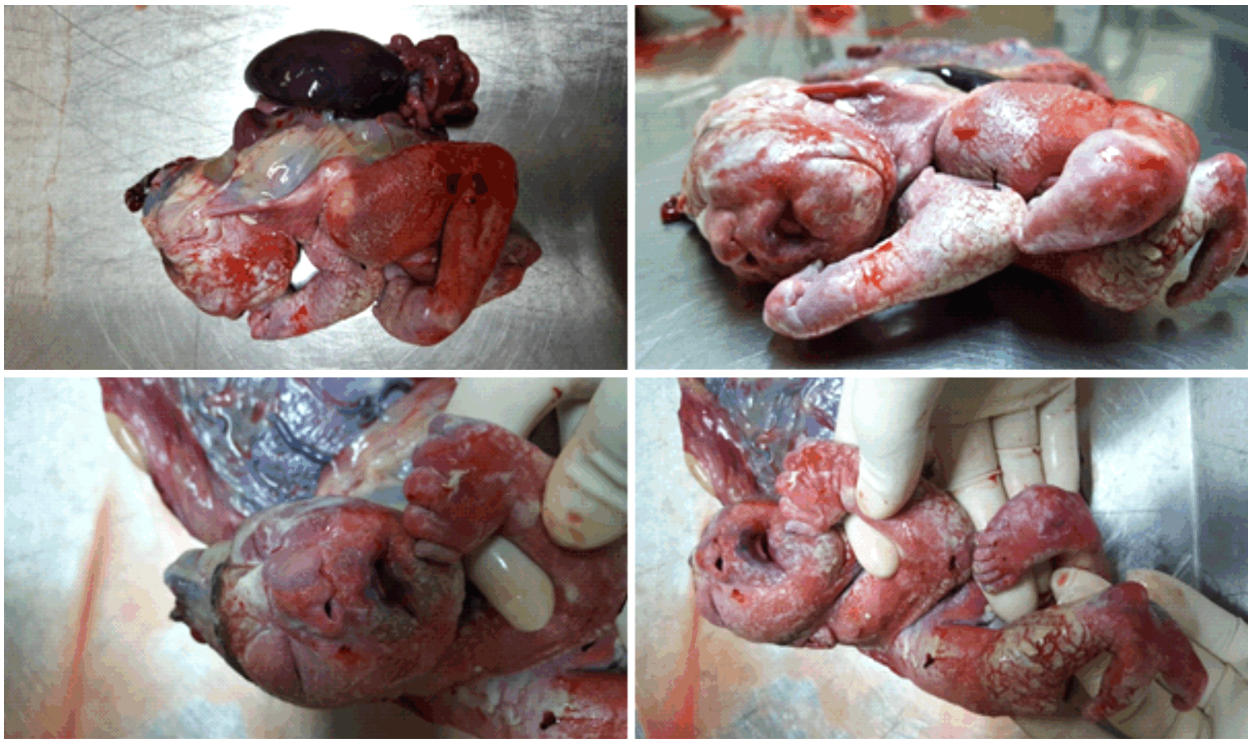

Figure 3 – ***Macroscopic examination of the fetus with BSA in the Pathology Department – note the presence of a large omphalocele, exencephaly, amelia of the left upper limb, a severely kyphoscoliotic spine and malrotation of the lower limbs, the large anterior abdomen wall defect with the viscera outside the abdominal cavity. BSA: Body stalk anomaly.***

Materials and Methods

The microscopic study has been carried out using biological materials previously fixed in neutral formalin solution, at ambient temperature, later included to paraffin by the histopathological protocol. Further, we sectioned the biological materials using the HM350 microtome, equipped with a water section transfer system (STS, microM). For the histological study, we shaped sections with a thickness of 4 μm and stained them with Hematoxylin–Eosin (HE). In order to perform the immunohistochemical (IHC) study, the histological sections were applied to poly-L-lysine slides and kept to thermostat at 37°C for 24 hours. Further on, we used the classic protocol for sections: dewaxing, dehydration, rehydration. For antigens, the slides were boiled in sodium citrate solution, pH 6, for 21 minutes (seven cycles × 3 minutes) in the microwave oven. After boiling and cooling, the slides were washed for 15 minutes in distilled water. In order to block endogenous peroxidase, the slides were introduced for 30 minutes in 2% hydrogen peroxide, at ambient temperature, then washed in distilled water for 10 minutes and in phosphate-buffered saline (PBS) for 5 minutes. The sections were incubated for 18 hours overnight, in the refrigerator, at 4°C, after previously blocking non-specific sites using 2% skim milk for 30 minutes. The next day, the sections have been washed in PBS for 15 minutes, we applied biotinylated secondary antibody for one hour, at ambient temperature. Further on, we washed the slides in PBS 3×5 minutes. The signal was detected using 3,3'-Diaminobenzidine (DAB) (Dako), and the reaction was stopped in PBS. Finally, the contrast has been obtained with Mayer's Hematoxylin, we dehydrated in alcohol 70%, 90%, 96%, 100%, clarified in xylene and assembled the slides using DPX (Fluka).

The IHC study was performed using the following antibodies:

- Anti-CD3 for highlighting T-lymphocytes (polyclonal rabbit anti-human CD3, sodium citrate, pH 6, 1:50 dilution, Dako);
- Anti-CD20 for highlighting B-lymphocytes (clone L26, sodium citrate, pH 6, 1:50 dilution, Dako);
- Anti-CD68 to highlight macrophages (clone KP1, sodium citrate, 1:100 dilution, Dako);
- Anti-neuronal nuclear antigen (NeuN) to highlight neurons (monoclonal, ab177487, sodium citrate, Abcam);
- Anti-oligodendrocyte transcription factor (Olig-2) to highlight oligodendroglia (purified rabbit sera, sodium citrate, 1:500 dilution, Novus);
- Anti-glial fibrillary acidic protein (GFAP) to highlight macroglia (polyclonal rabbit, sodium citrate, 1:150 dilution).

Results

On microscopic examination, we observed highly congested lungs, kidneys and liver (Figure 4). The immature hypoplasic lungs exhibit thick alveolar walls and a prominent alveolar lining of plump epithelial cells.

The rudimentary heart showed important subendocardial fibroelastosis and vascular myocardial congestion (Figure 5).

The cerebral tissue contained scattered neurons, neuroblasts and glial elements with a thinned out layer of cortical tissue.

We also found disorganized, anarchic outgrowth of nervous tissue with polymicrogyria and nodules of heterotopias.

In these areas, we have noted a particular cerebral perivascular lymphocytic infiltration (Figures 6–8). The umbilical cord had only two blood vessels (one artery and one vein). In these areas, the intervillous space was obliterated due to increased fibrin deposition and villous agglutination. The collapsed villi showed a "ghost"-like appearance due to loss of nuclear basophilia, we found microhemorrhage zones with numerous macrophages and macrophagic conglomerates (Figures 9 and 10), the cerebral white matter contains numerous activated microglia (Figure 11), cerebral cortex is under development, the molecular layer is revealed, many apolar neurons in the rest of the layers (Figure 12), oligodendroglia is present in the white matter (Figure 13) and in the cerebral gray matter (Figure 14), macroglia in the cerebral white matter, with well expressed extensions (Figure 15). Numerous foci of placental infarction were observed (Figure 16; Table 1).

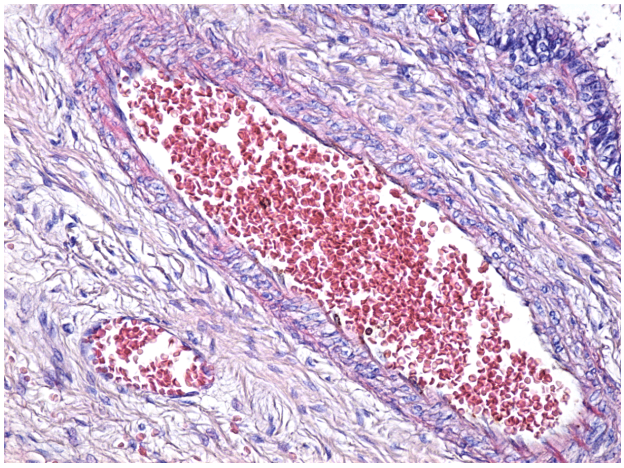

Figure 4 – ***Highly congested lungs (HE staining, ×200).***

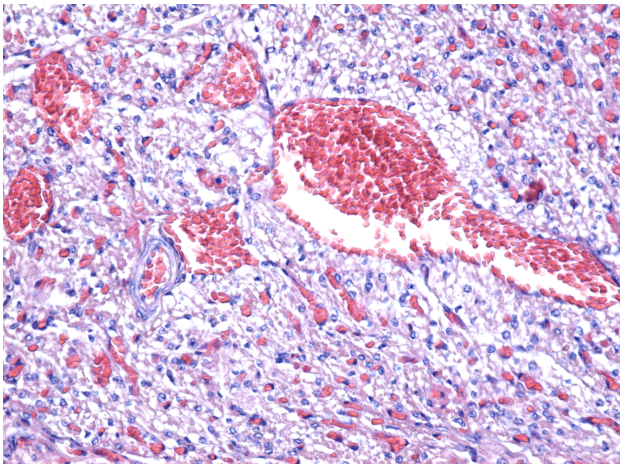

Figure 5 – ***The rudimentary heart showed important subendocardial fibroelastosis and vascular myocardial congestion (HE staining, ×200).***

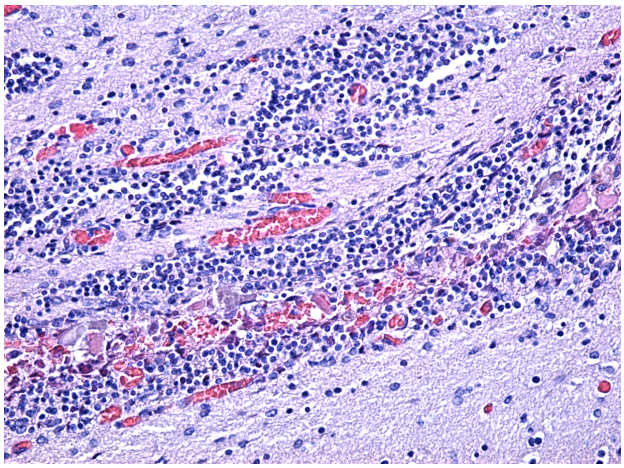

Figure 6 – ***Brain image demonstrating abundant perivascular lymphocytic infiltration (HE staining, ×200).***

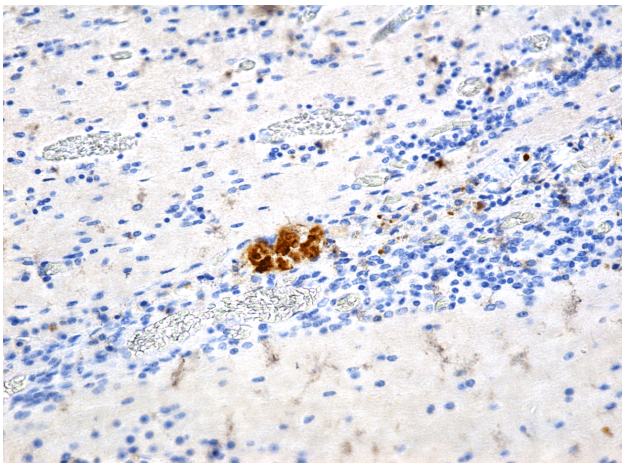

Figure 7 – ***Rare lymphocytic T-cells in the cerebral perivascular inflammatory infiltrate (Immunostaining with anti-CD3 antibody, ×200).***

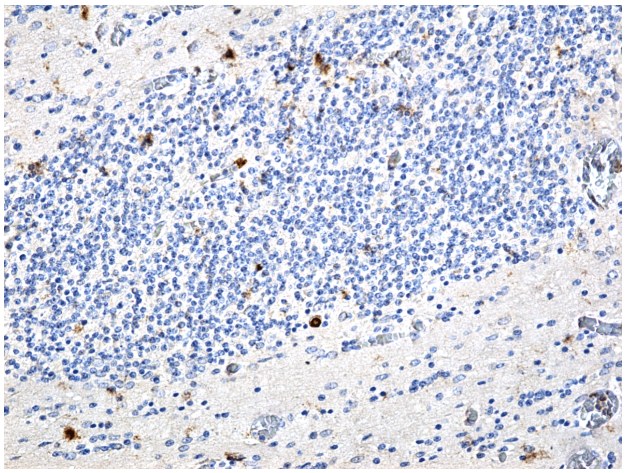

Figure 8 – ***Rare lymphocytic T-cells in the cerebral perivascular inflammatory infiltrate (Immunostaining with anti-CD20 antibody, ×200).***

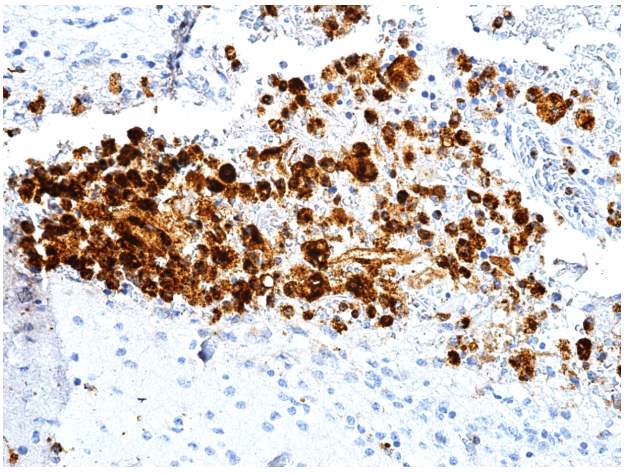

Figure 9 – ***Cerebral microhemorrhagic area with numerous macrophages present in the spot (Immunostaining with anti-CD68 antibody, ×200).***

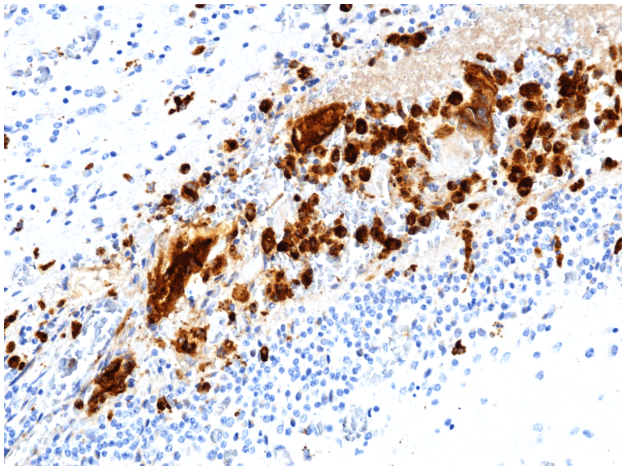

Figure 10 – ***Microhemorrhagic spot with meningeal macrophage conglomerates (Immunostaining with anti-CD68 antibody, ×200).***

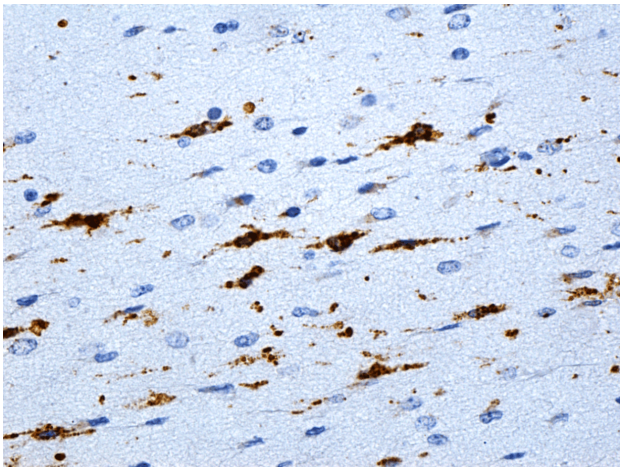

Figure 11 – ***The cerebral white matter contains numerous activated microglia (Immunostaining with anti-GFAP antibody, ×400). GFAP: Glial fibrillary acidic protein.***

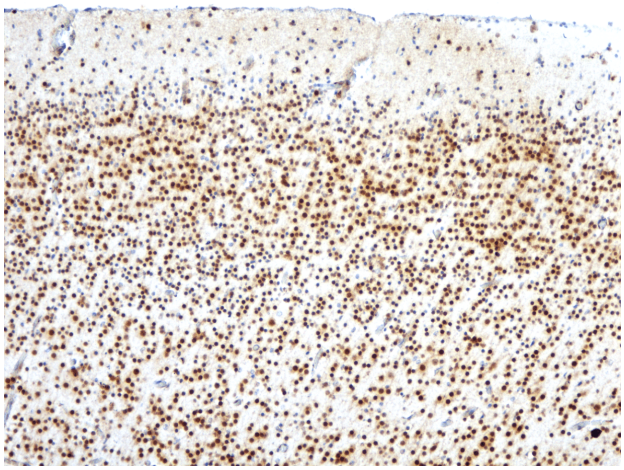

Figure 12 – ***The cerebral cortex in formation, containing a large number of apolar neurons. The molecular layer is well differentiated, but the rest of the layers are not highlighted (Immunostaining with anti-NeuN antibody, ×100). NeuN: Neuronal nuclear antigen.***

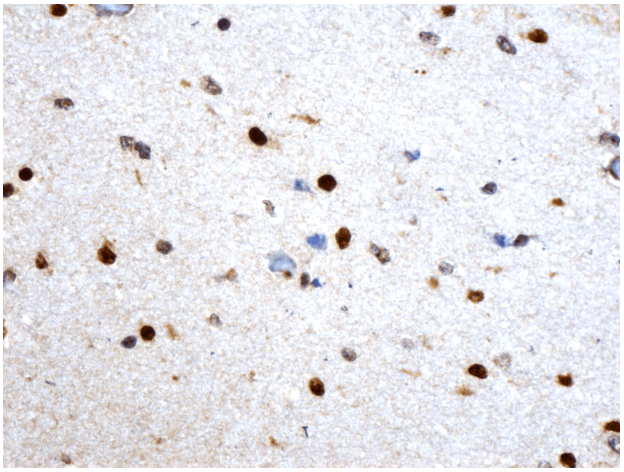

Figure 13 – ***Oligodendroglia is present in the cerebral white matter (Immunostaining with anti-Olig-2 antibody, ×400). Olig-2: Oligodendrocyte transcription factor.***

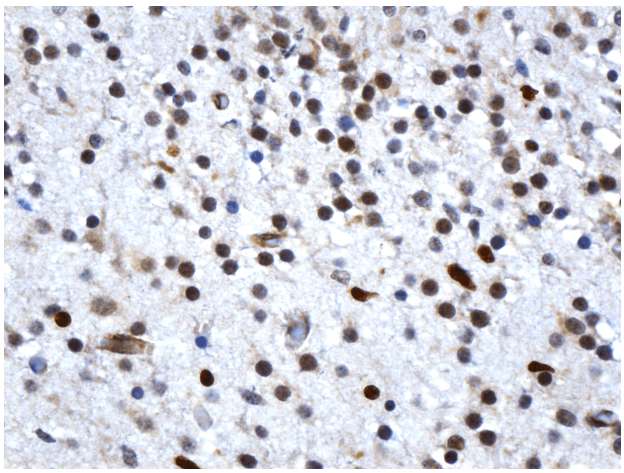

Figure 14 – ***Oligodendroglia is present in the cerebral gray matter (Immunostaining with anti-Olig-2 antibody, ×400). Olig-2: Oligodendrocyte transcription factor.***

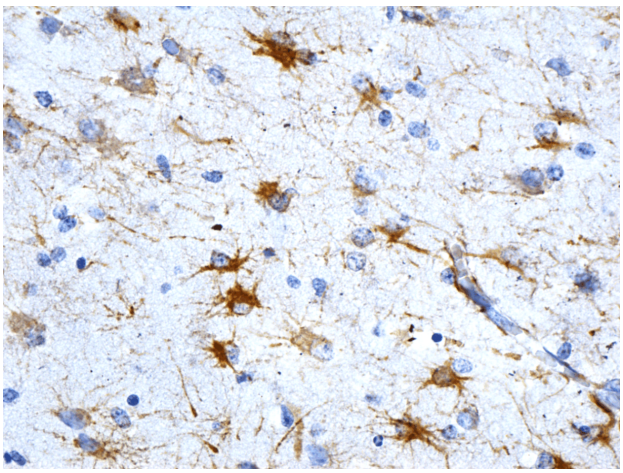

Figure 15 – ***Macroglia in the cerebral white matter, with well-expressed extensions (Immunostaining with anti-GFAP antibody, ×400). GFAP: Glial fibrillary acidic protein.***

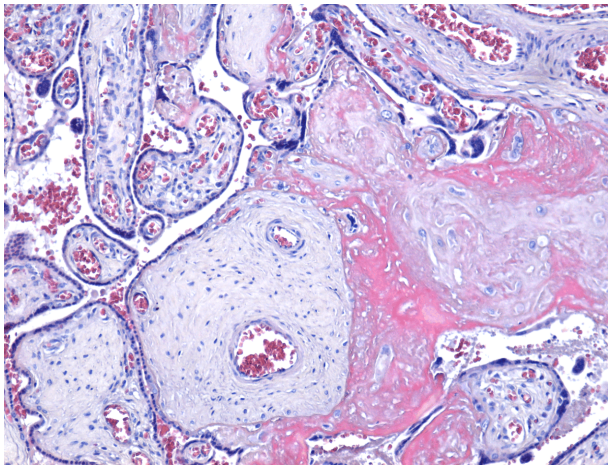

Figure 16 – ***Numerous foci of placental infarction were observed; in these areas, the intervillous space was obliterated due to increased fibrin deposition and villous agglutination. The collapsed villi showed a "ghost"-like appearance due to loss of nuclear basophilia (HE staining, ×100).***

Table 1 – ***Ultrasound, pathology and outcome***

Ultrasound findings	▪ MC–DA twin gestation → one normal fetus → one with BSA criteria
Macroscopic examination *BSA fetus*	Extreme malformation of the cephalic region: ▪ large encephalocoele; ▪ exencephaly; ▪ two asymmetrical cerebral hemispheres; ▪ single large ventricular cavity; ▪ vague corpus callosum; ▪ misplaced hippocampal; ▪ cleft palate; ▪ bulging eyeballs; ▪ amelia of the left upper limb; ▪ severely kyphoscoliotic spine; ▪ malrotation of the lower limbs; ▪ liver, stomach, small and large intestines, kidneys, a rudimentary sacciform heart and large portion of the hypoplastic lungs → outside the body.
Microscopic examination *BSA fetus*	▪ lungs, kidneys and liver → highly congested; ▪ alveolar walls and a prominent alveolar lining of plump epithelial cells; ▪ rudimentary heart → subendocardial fibroelastosis;
Microscopic examination *BSA fetus*	▪ cerebral tissue → scattered neurons, neuroblasts, glial elements → thinned out layer of cortical tissue, oligodendroglia, macroglial cells, microglial cells; ▪ nervous tissue → polymicrogyria, nodules of heterotopias, peculiar perivascular lymphocytic infiltration; ▪ umbilical cord → two blood vessels (one artery + one vein); ▪ placenta → numerous foci of placental infarction, increased fibrin deposition, villous agglutination, loss of nuclear basophilia; ▪ inflammation→ T- and B-lymphocytes, macrophages.
Outcome *Surviving twin*	▪ cervical cerclage → 22 gw; ▪ premature rupture of membranes → 30 (+4) gw; ▪ Caesarean section → 31 (+4) gw; ▪ surviving twin → F, 1500 g, preterm, AS 7; ▪ hospital discharge → 40 days later.

MC: Monochorionic; DA: Diamniotic; BSA: Body stalk anomaly; gw: Gestational weeks; F: Female; AS: Apgar score.

Discussion

Kermauner first described BSA, in 1906, as an abdominal wall defect consisting of an amniotic sac, which contains viscera and is directly attached to the placenta, in the absence of an umbilical cord [8]. BSA is not associated with chromosomal defects [9], however, rare cases of placental trisomy 16 and maternal uniparental disomy 16 have been reported, suggesting premature embryonic disturbance because of placental insufficiency [10]. Such genetic changes show that embryogenesis may play a role in the occurrence of BSA [11]. The exact pathophysiology of BSA has not been established yet, but there are three main theories trying to explain the association of malformations in this complex: premature rupture of amniotic membranes, embryonic circulatory insufficiency and embryonic dysgenesis [12]. Van Allen *et al.* affirm a vascular disruption during the weeks 4 to 6 of gestation as an etiology for LBWC; the disruption and loss of existing tissues, persistence of embryonic structures and extraembryonic coelom may lead to the typical amniotic tags, ring constrictions, adhesions, and secondary malformations [6]. Several authors have

described vascular "interruption" as the result of vascular hypoplasia in the affected area, and therefore, the embryonic dysgenesis to be the cause of this aberrant process [13, 14]. The second theory regarding BSA pathogenesis belongs to Lockwood *et al.* (1986) [15] and is supported by Giacoia (1992) [16], based on the improper histogenesis mechanism proposed by Streeter (1930) [7]; the abnormality in the folding process of the three-layered germinal disk is responsible for failure in separation of the intraembryonic coelom (future peritoneal cavity) from the extraembryonic coelom, formation of the body stalk, and development of the umbilical cord [7, 15, 16]. Thus, any disruption in this transformation process can generate anomalies [16, 17]. In the absence of the umbilical cord, the fetus is directly attached to the placental chorionic plate, through an amnio-peritoneal, membranous sac, resulting in malformations of the fetal extremities (cephalic, the two lateral and caudal) [16, 18]. The early amnion rupture before obliteration of the coelomic cavity is the most plausible theory, formulated by Daskalakis *et al.* (1997) [5]. It is believed that amniotic adhesions can lead to binding and tension of developing tissues and may lead to multiple malformations [19–21]. Gajzer *et al.* sustain, in a 2015 published article, the genetic etiology of this severe malformation, abnormal genes [*HOX*, *bFGF*, transforming growth factor-beta (*TGF-β*)/activins/*BMP4*, *WNT 1-8*, and *SHH*] being involved in laterality and caudal development anomalies [11]. Prevalence is hard to establish. Some specialists state that it is one in 4000 fetuses [22] or one in 7500 fetuses, at 14 weeks [5], or ranging from 0.4 to 3.2 per 100 000 live births [23, 24]. Others report an incidence ranging from one per 14 000 to one per 31 000 pregnancies in various epidemiological studies [25–27]. Daskalakis *et al.* reported a prevalence of 14 to 106 207 pregnancies assessed during the first trimester (approximately 1:7500), suggesting a significant number of fetal demises during the second trimester, in the context of this anomaly [5]. BSA is an abnormal, rare, sporadic and fatal condition, present in monochorionic or dichorionic twin pregnancies and also in singleton ones [13, 28]. BSA seems to be more common in twin pregnancies. There are few documented cases reported on dizygotic twins discordant for this anomaly, but the rarest cases described in the literature are those identified in monozygotic twins [29]. Monozygotic twins seem to be more affected by this anomaly, with an incidence of 12.5% [30], but BSA is rarely encountered in monochorionic twin pregnancies [31]. There are several case reports of BSA associated with diamniotic fetuses in triplet pregnancy [23]. The rate of idiopathic or sporadic cases is inconsequential [9, 14, 32]. Diagnosis of BSA and distinction from other forms of non-lethal dysplasias is usually made by ultrasound scan in the second trimester [5, 24]. Since most abnormalities are diagnosed ultrasonographically during the prenatal period, pregnancy can be interrupted [33]. Ultrasound diagnosis of this abnormality is demonstrated by extra-abdominal eviscerated or herniated viscera through a major abdominal wall defect. The cases with BSA have been differentiated from other abdominal wall defects, such as omphalocele, gastroschisis and bladder exstrophy. Differential diagnosis may include several syndromes presenting body wall defects, such as pentalogy of Cantrell, Beckwith–Wiedemann syndrome, OEIS (omphalocele, extrophy of the cloaca, imperforate anus and spinal defect or amniotic band syndrome) complex [34]. However, an increasing number of cases are being diagnosed from the first trimester due to the high performance acquired by ultrasound (US) scanning technology and awareness of physicians. Moreover, BSA can now be easily diagnosed from 11 weeks' gestation by examining the amniotic membrane continuity, content of the amniotic sac and coelomic cavity, as well as the presence of a short umbilical cord, midline thoraco-abdominal wall defect and skeletal anomalies, especially severe scoliosis or lordosis [6, 24]. Urogenital organs and limbs are commonly affected. Anomalies of the lower limb include clubfoot, polydactyly, syndactyly, oligodactyly, brachydactyly and amelia. An essential element of diagnosis is the insertion of the umbilical cord at less than 2 cm away from the margin of the placenta; the umbilical cord has usually two vessels [15, 30]. All these specific features have been encountered in the case reported by us. The second trimester α-fetoprotein level in maternal serum is elevated in all cases [27]. Almost all cases are karyotypically normal, and the condition is considered sporadic [35]. There are two main phenotypes of BSA described in the literature [36, 37], both being the consequence of various pathogenic mechanisms: the placental-cranial type and the placental-abdominal type [38]. The placental-cranial type associates craniofacial defects, such as encephalocele or exencephaly and amniotic bands between them and the placenta [38]. The placental-abdominal type does not involve any craniofacial defects but associates urogenital anomalies, anal atresia, lumbosacral meningocele, short umbilical cord, persistence of extra embryonic coelom and intact amnion [38]. Our case presented features from both types. The presence of BSA in monozygotic twins is an extremely unusual condition. Our diagnose is supported by the short length of the umbilical cord, rotation of the body stalk, exencephaly and malrotated limbs, the theory of Daskalakis *et al.* (1997) that affirm the early amnion-rupture being the initial cause of passage of the lower part of the fetal body into the coelomic cavity [5]. Luehr *et al.* (2002) reported a high incidence of anomaly of 3.3 to 10 000 births, by teratogenic causes such as smoking, alcohol and various drugs [17].

Since BSA is a fatal disease, termination of pregnancy is usually suggested, but if present in twin gestations with only one affected fetus, as in our case, the unaffected fetus usually survives with no major complications, being however, at increased risk for a preterm delivery.

Conclusions

BSA is a rare plurimalformative syndrome with fatal prognosis. Much remains to be cleared up in terms of epidemiology, pathogenesis and risk factors especially in cases of twin pregnancies. Additional effort should focus on making an early and appropriate diagnosis in order to avert complications during pregnancy. A careful surveillance of the unaffected twin is crucial.

Conflict of interests

The authors declare that they have no conflict of interests.

Ethical concerns

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

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