CASE REPORT

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Intrapartum diagnostic of Roberts syndrome – case presentation

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Abstract

Roberts syndrome is a rare disease, with multiple limb and skeletal abnormalities (called "pseudothalidomide disease"). There are only around 150 cases described in literature. We present a case of Roberts syndrome, diagnosed in moment of delivery, after a pregnancy without prenatal follow-up. The stillborn baby was naturally delivered by a 17-year-old primiparous woman at 38 weeks of amenorrhea. The pregnancy was not followed due to socioeconomic and family situation, and no prenatal ultrasound was performed. The male baby has 2650 g and presented several morphological abnormalities and tight double umbilical abdominal loop. The macroscopic evaluation showed: dolichocephaly, hypoplastic inferior maxilla with micrognathia, antimongoloid palpebral slant, pterygium colli, abnormal and lower implanted ears, superior limbs phocomelia, syndactyly at lower left limb and tetradactyly in all limbs, bilateral cryptorchidism, pancreatic aplasia. Roberts syndrome is a rare genetic disease with recessive autosomal transmission generated by mutations in ESCO2 gene, located on chromosome 8. The disease should be easy to diagnose by antenatal ultrasound examination, but in our case, the lack of prenatal follow-up determined the diagnostic at term. We believe consider this case is an argument towards introducing ultrasound-screening compulsory to all pregnancies. To identify a possible genetic mutation, further investigations of the parents are in progress, but classically the disease has a recessive autosomal transmission.

Keywords: Roberts syndrome, prenatal ultrasound, congenital abnormalities.

Introduction

Roberts syndrome (synonyms: hypomelia-hypotrichosis-facial hemangioma syndrome, pseudothalidomide syndrome, Appelt–Gerken–Lenz syndrome, SC syndrome) [1] is a rare genetic disorder with pre and postnatal growth delays, and most typically malformations of the arms and craniofacial region, with autosomal recessive transmission. Its incidence is not known and not more 150 cases were described in literature [2].

In 1993, Van Den Bergh & Francke summarized the Roberts syndrome cases and identified only 100 reported cases [3].

This disease was first described in 1919 by John Roberts, but earlier reports of tetra phocomelia and facial anomalies are cited since 1670s [3].

Roberts syndrome was previously referred as "pseudothalidomide syndrome", based on the similarities regarding limb malformations with thalidomide syndrome patients [4]. There is no genotype–phenotype correlation established to date, and it was suggested that epigenetic factors might have a role in the clinical manifestations of the syndrome.

We present a recent case diagnosed moment of birth in "Elena Doamna" Maternity, Iassy, Romania.

Case report

The mother of the propositus was a 17-year-old primiparous presenting at 38 weeks of gestation, intrauterine fetal demise. No obstetrical or familial risk factors were detected. The pregnancy was not followed due to socio-economic and family situation, and no prenatal ultrasound was made.

After a normal length labor, she delivered a deceased male fetus with the following anthropometric features: weight 2650 g, length 53 cm; head circumference 37 cm, thoracic circumference 32 cm. During the delivery was identified a tight double umbilical abdominal loop. The postpartum evolution of the mother was uneventful.

The baby had multiple congenital anomalies, and the clinical evaluation showed a craniofacial dysmorphism with dolichocephaly, hypoplastic inferior maxilla with micrognathia (Figure 1), downslanted palpebral fissures, prominent beaked nose, pterygium colli (Figure 2), abnormal and lower implanted ears. Congenital anomalies of limbs were superior limbs phocomelia (superior limbs had a total length of 10 cm) (Figure 3), syndactyly at lower right limb (toes IV and V) and oligodactyly with tetradactyly in all the other limbs. The newborn has also a thoracic asymmetry with absence of ossification, and bilateral cryptorchidism.

The fetal autopsy was carried out and followed by histopathological examination. The external examination revealed several abnormal findings. At cranium were observed overlapped sutures, small anterior fontanella, blood collection at the parieto-occipital meninges, flattened circumvolutions.

Thorax examination revealed presence of 11 pairs of un-ossified and loose ribs, the last pair of ribs was floating, an interatrial communication of 0.2 cm, ductus arteriosus, incomplete lobulation between the middle and lower lobe in the left lung and incomplete lobulation between the upper and inferior lobe in the right lung, dark purple color of the lungs with absent crepitation.

Examination of the digestive tract revealed pancreas agenesia.

On gross examination, the placenta measured 18/12/4 cm in diameters, presenting few hemorrhagic areas; the umbilical cord measured 20/2 cm and was composed of three vessels.

Histopathological examination of the placenta and fetal tissues (lungs, placenta) was carried out, the fragments being fixed for 24 hours in buffered formalin and processed for paraffin embedding. Serial sections of 4–5 µm were dewaxed and stained with Hematoxylin–Eosin (HE) and trichromic Masson's technique. The microscopic examination confirmed the clinical diagnosis. The lung tissue revealed slightly thickened interalveolar septa, alveoli with eosinophilic granular debris and desquamated cells, rare macrophages (Figures 4 and 5). In the chorial plate of the placenta, there were vascular lumens with ectasia and thrombosis (Figure 6), perivillous and basal plate fibrin deposition, intervillous thrombi, microcalcifications (Figures 7 and 8).

For genetic analysis, genomic DNA was extracted from the paraffin embedding tissues stored after the histopathological examination. Full gene sequencing of the ESCO2 gene for the newborn and their normal parents was done. For the newborn, it was identified homozygosity for the c. 745_746delGT mutation of ESCO2 gene. Parents were heterozygous, presenting one normal variant and the c. 745_746delGT mutation of ESCO2 gene.

Based on the clinical findings corroborated with the anatomopathological examination and genetic analysis, the final diagnosis was established for this fetus and confirmed the initial suspicion of Roberts syndrome.

Discussion

Roberts syndrome is characterized by growth retardation (mild to severe), craniofacial anomalies (microcephaly, dolichocephaly, cleft palate, micrognathia, premaxillary prominence, microbrachycephaly, downslanted palpebral fissures, widely spaced eyes, exophthalmos, corneal clouding, ear malformations), limb malformations (bi-/tetra-phocomelia, hypomelia, oligodactyly with thumb aplasia, syndactyly, clinodactyly), more severe to the upper limbs [2].

Figure 1 – ***Macroscopic appearance of dolicocephaly, low implanted ears and micrognathia.***

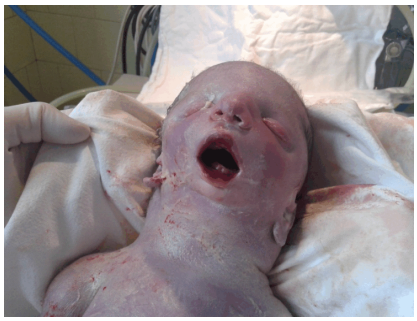

Figure 2 – ***Antimongoloid palpebral slant and pterygium colli.***

Figure 3 – ***Superior limb phocomelia, tetradactyly, syndactyly.***

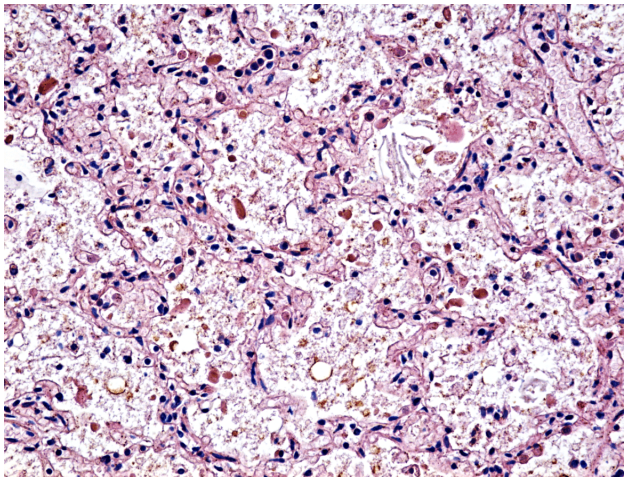

Figure 4 – ***Pulmonary alveolar proteinosis with interstitial thickening of the alveolar septa. HE staining, ×40.***

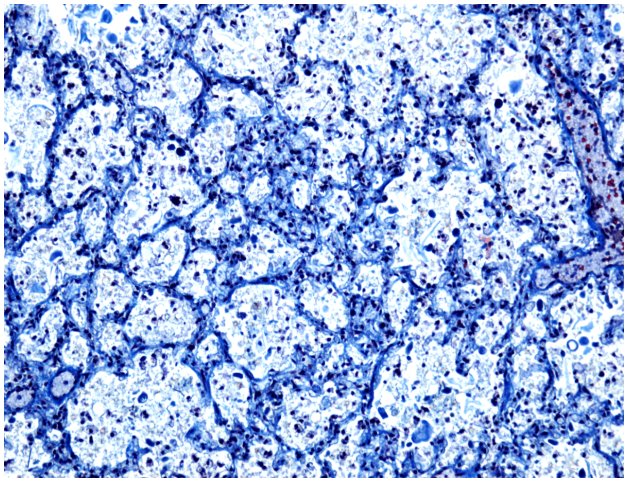

Figure 5 – ***Pulmonary alveolar proteinosis with interstitial thickening of the alveolar septa. Trichromic Masson's staining, ×40.***

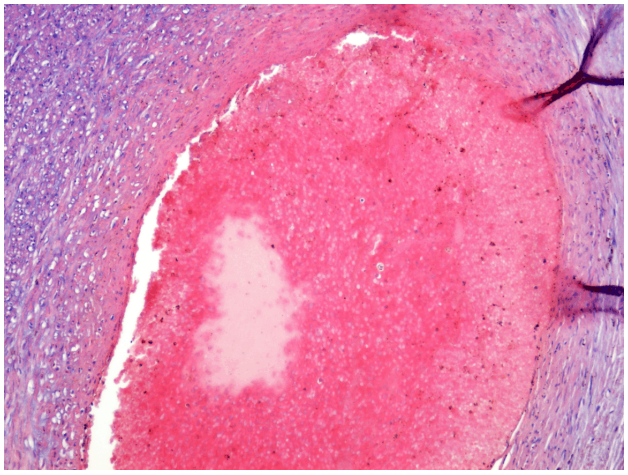

Figure 6 – ***Chorionic plate thrombosis. Recent thrombus, demonstrating few entrapped degenerating red cells. HE staining, ×40.***

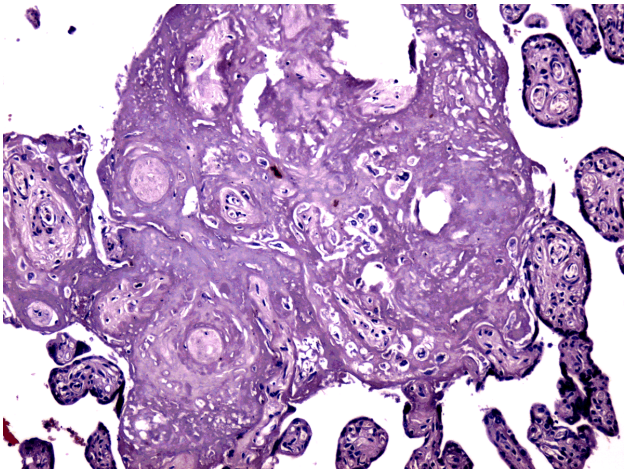

Figure 7 – ***Placental infarct. Avascular villi enmeshed in fibrinoid. HE staining, ×40.***

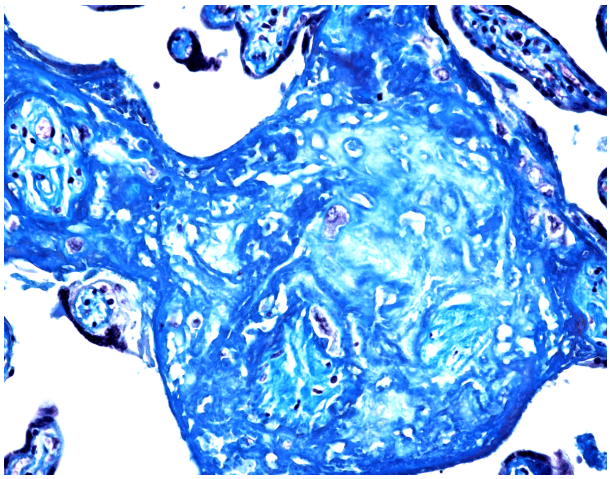

Figure 8 – ***Placental infarct. Avascular villi enmeshed in fibrinoid. Trichromic Masson staining, ×40).***

In our case, the histopathological examination revealed the architecture of the lungs abnormalities (thickened interalveolar septa, alveoli with eosinophilic granular debris and desquamated cells, rare macrophages) and the placental involvement (vascular lumens with ectasia and thrombosis, perivillous and basal plate fibrin deposition, intervillous thrombi, microcalcifications).

In less severe cases, altered physical and intellectual development is frequent. In severe cases, as the one depicted in this article, death occurs prenatally or immediately after birth [2].

Regarding its pathogenesis, the Roberts syndrome is caused by mutations in ESCO2, a gene which is located at 8p21.1, and encodes a protein with function of acetyltransferase essential in establishing sister chromatid cohesion during S phase and mitosis [5]. While the essential role of the cohesin complex in chromosome segregation has been well characterized, the protein codified by ESCO2 gene plays additional roles in DNA damage repair, chromosome condensation, and gene expression [6]. The normal ESCO2 gene product also has an important role in sister chromatid cohesion during mitosis [7]. The chromosomal analysis made in cases of Roberts syndrome revealed a characteristic premature centromere separation and separation of the heterochromatic regions in most chromosomes [8].

The molecular genetic testing allowed identification of 26 different gene mutations in ESCO2 gene [7]. The ESCO2 gene mutations can lead to loss of acetyltransferase activity, by truncation in the protein, or single amino acid changes in the protein [7, 9, 10]. ESCO2 mutations are correlated with lack of cohesion at heterochromatic regions impairing the mitotic cell division and affecting the cell proliferation. During embryogenesis, the ESCO2 mutations determine different structural defects by loss of genitor cells in several organs explaining the clinical manifestations of the syndrome.

Recent studies tried to explain the effect of the ESCO2 gene mutation on the embryogenesis [6, 7]. Roberts syndrome is considered a cohesinopathy, having similar pathogenic changing with Cornelia de Lange syndrome (CdLS) [6]. Cornelia de Lange syndrome and Roberts syndrome have some overlapping phenotypic features but the differential diagnosis is easy done between those two syndrome as they have well described phenotypes, that can be easily recognized. [11] The different transcriptional changes specific for Roberts syndrome are the result of translational defects and it was suggested that Roberts syndrome might be partially attributed to defects in translation [6]. Different clinical manifestations of Roberts syndrome were found to be present in several disorders associated with defects in ribosome biogenesis. A similar pathogenic pathway, implying the involvement of p53 and mTOR, was described in Treacher Collins syndrome [12], 5q- syndrome [13], Diamond–Blackfan anemia (DBA) [14], Shwachman–Bodian–Diamond syndrome (SBDS) [15], and dyskeratosis congenita [16], diseases that encompass some clinical features with Roberts syndrome: craniofacial, urogenital, cardiac and limbs anomalies.

By our knowledge, the ESCO2 gene mutation 745_746delGT was previously reported only in two cases [17]. Resta's report presented two fetuses, which exhibit severe malformations and growth retardation, first was aborted at 22 weeks and the second at 15 weeks of gestation [16]. For the first fetus, autopsy was not done. The second fetus was aborted at early gestational age and presented hypertelorism, low-set ears, bilateral cleft lip, and palate, micrognathia, hypomelia of the upper extremities, oligodactyly and clitoris hypertrophy [17].

In Resta's report was showed that a mutated full length mRNA was present in both fetuses [17]. Following that finding, it was performed Western blot analysis, which revealed the lack of the ESCO2-truncated protein in cells derived from those fetuses [17]. Apart from the cases reported previously by Resta *et al.*, in this case, the fetus was delivered at 38 weeks of gestation and a better characterization of the phenotype was possible [17].

Genetic testing of the carrier status for the parents was indicated in order to calculate the risk of having another child with Roberts syndrome for a future pregnancy. As the genetic analysis revealed the both parents are carriers of the c. 745_746delGT mutation of ESCO2 gene, genitors were informed that they have a 25% risk of having another affected child and were discussed options regarding a future pregnancy.

Conclusions

Our report presents a very rare case and brings information about the phenotype but also the histological anomalies associated with Roberts syndrome. We consider relevant to present the histopathological findings documented for this case, in order to add new information regarding the specific phenotype of Roberts syndrome. The particularities of our case are the presence of agenesis of several ribs and pancreas associated with absence of cleft palate/lip. Only two other cases exhibiting the same gene mutation were previously reported. In our case, the lack of prenatal follow-up delayed the diagnosis, although Roberts syndrome have some features that could be easily identified by prenatal ultrasonography. Thus, we believe that this case is an argument towards introducing ultrasound screening compulsory to all pregnancies.

Conflict of interests

The authors declare that they have no conflict of interests.

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