Ductus venosus agenesis as a marker of Pallister-Killian syndrome

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Objective
The ductus venosus (DV) is a shunt that allows the direct flow of well-oxygenated blood from the umbilical vein (UV) to the coronary and cerebral circulation through the foramen ovale. Its agenesis has been associated with chromosomal abnormalities and rare genetic syndromes, structural defects, IUGR and even antepartum fetal demise. Pallister-Killian Syndrome (PKS) is a rare and sporadic disease with specific tissue mosaic distribution of an additional 12p isochromosome that associates severe mental retardation as well as multiple and varied malformations. Prenatal diagnosis is difficult as there are no associated identification signs. The tissue mosaicism linked to this syndrome and the decrease of the abnormal clone carrier of the isochromosome p12 after successive trypsinizations of cultured cells makes the diagnosis even more challenging. We present the case of a 27.5 weeks pregnant woman with a fetal ductus venosus agenesis (DVA) as the only one marker. To our knowledge this is the first case reporting a DVA as a guide sign to diagnose a complex condition as Pallister-Killian syndrome. We also underscore the key role of new genetic techniques as microarrays to avoid misdiagnosis when only a subtle sonographic sign is present in complex conditions like this.

Methods
We report the case of a 38-year-old woman, who was 27.5 weeks pregnant and without antecedents of interest or consanguinity with her partner. The patient was referred to us from a private clinic for ductus venosus agenesis, polyhydramnios and small fetal stomach with suspicion of oesophageal atresia. The patient was controlled outside of our unit until that moment; however, her first trimester combined screening results presented a low-risk. Our exploration showed a bifurcation of the umbilical vein, giving rise to a normal hepatic-portal portion and another varicose portion of 5.2 mm, which ran intrahepatic, describing a curved path in the form of an intrahepatic "C". This joined to the suprahepatic veins and drained into the inferior vena cava (IVC), giving rise to an umbilical-IVC portosystemic shunt. The fetal stomach was normal, with a 27 Amniotic Fluid Index. Echocardiography showed a cardiac axis displaced to the left, with the wall of the right ventricle thickened, especially at the level of tricuspid valve implantation. The Tei-Index was 0.59, indicating mild diastolic dysfunction. The rest of the examination was normal, with estimated fetal weight in the 77th percentile. Abruption was offered, requesting Array-CGH and molecular study through a massive panel sequencing of 16 genes related to Noonan Spectrum Disorders (RASophathies), finding no pathogenic mutations in the sequences analysed. The analysis by array-CGH of the DNA extracted from uncultivated amniocytes obtained a result of arr [hg19] 12p13p11 (222,688-34,345,726) x4 and male genomic pattern. A gain of chromosomal material was detected in the entire short arm of chromosome 12, compatible with an isochromosome 12p, diagnosis of Pallister-Killian Syndrome (PKS). After obtaining the result, we proceeded to perform karyotype from a sample of amniotic fluid kept in culture in the Genetics Service to visualize the 12p isochromosome and confirm this finding. To our surprise, however, 3 weeks after its extraction, the result of the culture was that of a normal karyotype. The couple was informed of these results, deciding to terminate the pregnancy.

Results
There are no pathognomonic echographic indicators for PKS. The most frequent sonographic indicators are polyhydramnios (84%), congenital diaphragmatic hernia (16%) and micromelia mainly of rhizomelic type (10%). The cytogenetic diagnosis of PKS is especially difficult due to the peculiarity of tissue-dependent mosaicism that it presents: in fact, although it is common to identify the 12p isochromosome in fibroblast cultures, it is rarely identified in blood lymphocytes and cytogenetic discordances have been described between placental and fetal tissues. This variability could reflect a selective proliferative advantage of normal diploid cells over the tetrasomal cells during embryogenesis9,12, although variable tissue-dependent mechanisms have also been postulated for the selection of cell lines in vivo or in vitro. In vivo, the loss of i(12p) has been shown with the aging of patients in bone marrow, fibroblasts and lymphocytes, whilst in vitro, a progressive decrease of the abnormal clone carrier of the isochromosome p12 has been observed after successive trypsinizations of cultured cells, independently of the tissue that is analyzed. This loss of the abnormal clone in successive cultures has special importance from the point of view of prenatal diagnosis, especially in those cases in which the cells grow slowly in the culture and repeated trypsinizations are necessary, since this can lead to false diagnoses.

Conclusion
In this case none of the typical clinical manifestations reported in the literature of Pallister Killian syndrome was present: the guide sign for the prenatal diagnosis was DVA. Considering that DVA is a subtle sign that can be associated with complex syndromes, we encourage the search of genetic conditions associated to this finding, using the microarrays as the first choice diagnostic technique, complementing it with conventional karyotype if necessary to improve diagnosis. It is even more important in rare genetic conditions such as PKS, as the rapid loss of the i(12p) in the course of amniocyte subculturing could lead to misdiagnosis.