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Bifid cardiac apex in Pallister-Killian syndrome: case report

Bifidno srce u sindromu Pallister-Killian: prikaz slučaja

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Abstract. ***Aim:*** Pallister-Killian syndrome (PKS) is a rare chromosomal disorder, caused by tissue-limited mosaicism for an isochromosome 12p. Prenatal diagnosis of PKS is generally incidental. Although clinical presentation of PKS varies, cytogenetic findings are constant, and include a tetrasomy of chromosome 12p. We report a case of prenatally diagnosed PKS with unique dysmorphic feature: bifid cardiac apex, a type of morphology that has not been documented before. ***Case presentation:*** Our patient was the 38-year-old pregnant woman who underwent amniocentesis. Cytogenetic analysis of amniotic fluid detected a mosaic karyotype with a supernumerary chromosome (SMC) in 64 % of fetal amniocytes. To determine the chromosomal origin of SMC, fluorescence *in situ* hybridization was performed and tetrasomy 12p was confirmed: mos 47,XY,+mar[18]/46,XY[10].ishi(12p)(8M16/SP6++,CEP12+,VIJyRM2196-). Ultrasound examination showed a fetus with cleft lip, echogenic focus in the left ventricle of the heart and shortened fetal long bones. After receiving a genetic counseling for PKS, the woman requested a termination of pregnancy. A postmortem inspection of the fetus revealed a complex heart anomaly that includes bifid cardiac apex and ventricular septal defect. ***Conclusions:*** This report expands the clinical manifestations of PKS with a unique feature of bifid cardiac apex, and highlights the targeted prenatal diagnosis of PKS if specific ultrasound markers are present.

Key words: bifid cardiac apex; Pallister Killian syndrome; prenatal diagnosis; ultrasound examination

Sažetak. ***Cilj:*** Sindrom Pallister-Killian (PKS) rijedak je kromosomski poremećaj uzrokovan tkivno ograničenim mozaicizmom za prekobrojni izokromosom 12p. Prenatalno se dijagnoza PKS-a postavlja uglavnom slučajno. Iako je težina kliničke slike različita i varira od vrlo blage do izrazito teške, citogenetički nalaz uvijek uključuje tetrasomiju 12p. Ovim radom prikazan je prenatalno dijagnosticirani PKS s jedinstvenim dismorfološkim obilježjem: bifidnim srcem, koje do sada nije opisano u literaturi, kao dio kliničke slike ovoga sindroma. ***Prikaz slučaja:*** Tridesetosmogodišnja trudnica upućena je na amniocentezu. GTG metodom oprugavanja kromosoma utvrđen je aberirani mozaični muški kariotip s malim prekobrojnim marker kromosomom (engl. *small supernumerary marker chromosome*, sSMC) u 64 % fetalnih amniocita. Za određivanje podrijetla marker kromosoma korištena je metoda fluorescentne *in situ* hibridizacije te je utvrđena tetrasomija 12p: mos 47,XY,+mar[18]/46,XY[10].ishi(12p)(8M16/SP6++,CEP12+,VIJyRM2196-). Nalaz ultrazvuka ukazao je na fetus s rascjepom usne, ehogenim fokusom u lijevoj srčanoj klijetki te skraćenim dugim kostima. Po genetičkom savjetovanju, trudnica se odlučila za prekid trudnoće. Obdukcijom fetusa otkrivena je kompleksna srčana anomalija koja uključuje bifidno srce te ventrikularni septalni defekt. ***Zaključci:*** Ovaj prikaz slučaja prvi put opisuje jedinstveno dismorfološko obilježje bifidnog srca u PKS-u te naglašava važnost ciljanog pristupa u prenatalnoj dijagnostici PKS-a, ako postoje specifični ultrazvučni biljezi.

Ključne riječi: bifidno srce; sindrom Pallister-Killian; prenatalna dijagnostika; ultrazvuk

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INTRODUCTION

Pallister-Killian syndrome (PKS; OMIM #601803) is a sporadic, rare chromosomal disorder, caused by tissue-limited mosaicism for an isochromosome 12p (i12p)[1]. In PKS, percentage of cells including the isochromosome is dependent upon the tissue examined, and does not correlate with the severity of the syndrome[2]. In most cases it is of prezygotic maternal origin, although paternal and postzygotic origin is also possible[3-5]. Studies by Wenger et al. (1988)[6] and Wilkens et al. (2012)[7] reviewed parental ages from published case reports, and showed a link between increasing parental (maternal, rather than paternal) age and the risk of PKS.

Prenatal diagnosis of PKS is generally incidental at karyotyping in case of fetal anomaly detection or advanced maternal age[8]. However, PKS can be suspected in the presence of ultrasound anomalies among which are congenital diaphragmatic hernia and rhizomelic micromelia most common[9]. Recent reports described several more typical characteristics: a flat profile, a small nose, and a prominent upper „Pallister" lip[9,10].

This report expands the clinical manifestations of PKS with a unique feature of bifid cardiac apex, and highlights the targeted diagnosis of Pallister-Killian syndrome in a second and third trimester of pregnancy if specific ultrasound markers are present.

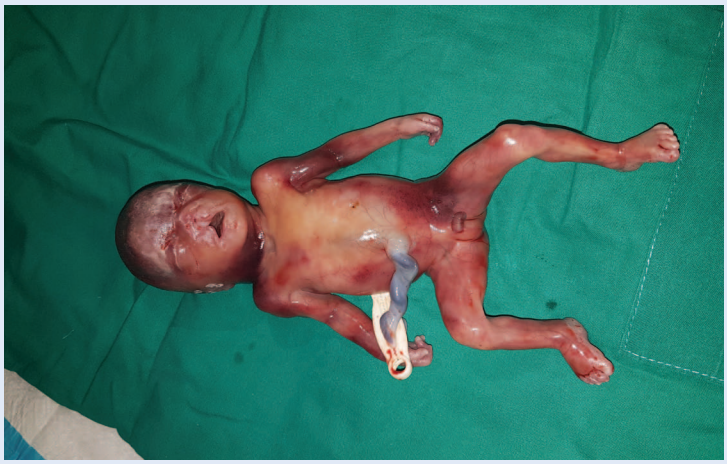

Figure 1. Autopsy finding – frontal view

Although clinical presentation of PKS varies, cytogenetic findings are constant, and include a tetrasomy of chromosome 12p diagnosed by chorionic villus sampling, amniocentesis or cordocentesis[11].

We report a case of prenatally diagnosed PKS with unique dysmorphic feature: bifid cardiac apex, a type of morphology that has not been documented ever before in the literature, along with other anomalies more common in PKS. Moreover, our case emphasizes the importance of a detailed ultrasound examination and chromosomal analyses in providing a precise and rapid prenatal diagnosis.

CASE PRESENTATION

Our patient was the 38-year-old pregnant woman (G3P2) who underwent amniocentesis at 18 weeks and 1 days' gestation upon of an ultrasonographic imaging of fetal cleft lip and advanced maternal age. Patient's medical history was negative for any relevant diseases, combined test showed no risk for trisomies, and previous ultrasound examinations were normal.

Cytogenetic analysis (G-banding) of amniotic fluid detected a male mosaic karyotype with a supernumerary chromosome (SMC) in 18/28 (64 %) of fetal amniocytes. To determine the chromosomal origin of SMC, fluorescence *in situ* hybridization (FISH) was performed on metaphase spread chromosomes using commercial centromeric probe (D12Z1) and TOTELVysionTM Multicolor DNA Probe for chromosome 12 (Vysis®, Abbott Laboratories, Abbott Park, Illinois, U.S.A.). Mosaicism of tetrasomy 12p was confirmed: mos 47,XY,+mar[18]/46,XY[10].ish i(12p)(8M16/SP6++, CEP12+, VIJyRM2196-).

At 21 weeks and 2 days' gestation the woman was referred to the Department of gynaecology and obstetrics for a detailed ultrasound examination and a genetic counseling. Ultrasound examination revealed a male fetus with abnormal facial profile: large and protruded forehead, flat nasal bridge and cleft lip. Moreover, it showed an echogenic focus in the left ventricle of the heart and shortened fetal long bones: humerus 27.5mm, tibia 26.4mm (both measures less than the 3rd percentile for gestational age), with a

discrepancy in femur length (L:33.3mm; R:27.6mm).

After receiving a genetic counseling for PKS, the woman requested a termination of pregnancy due to medical reasons, which was carried out at 21 weeks and 4 days' gestation. A postmortem inspection and autopsy of the fetus were as: flattened face profile, telecanthus, unilateral cleft lip and palate, low-set abnormal ears, short neck and congenital right hand deformity due to abnormal position in the womb (Figure 1). In addition, it showed a complex heart anomaly that includes bifid cardiac apex and ventricular septal defect, along with a sternum caved-in appereance.

DISCUSSION

Our case describes for the first time, as far as we known, bifid cardiac apex in PKS. This cardiac anomaly is one of the rarest congenital morphologies in humans, and occurs as a consequence of a disturbed union of the two ventricles at the apex of the heart[12]. It could be an isolated finding or combined with other heart defects, as in our case where is ventricular septal defect present. Although several genes on 12p are known to be involved in the development of heart during embryogenesis, including *FOXM1*, *FOXJ2,* and *KRAS*, the exact molecular mechanism of their function is stil unknown[13]. Considering the fact that other heart defects are commonly seen in PKS, especially septal defects (atrial or ventricular), bicuspid aortic valve and aortic dilatation[13], investigation of the aforementioned genes could be beneficial in verifying their involvement in the wide spectrum of abnormal cardiac phenotype in PKS.

Since the first prenatal description of PKS in 1985[14], less than one hundred prenatal cases have been published, mostly declared as incidental findings[8]. This could be explained by phenotypic variability on ultrasound scans or due to the mosaic distribution of the 12p isochromosome in different tissues[15]. However, early and precise prenatal diagnosis of PKS is essential for appropriate and timely genetic counseling and management, as it poses significant emotional and financial burden for parents. While Wilson et al. (1994)[16] recommends it in all fetuses with diaphragmatic hernia, short femur, and polyhydramnios, Paladini et al. (2000)[9] suggests prenatal diagnosis based on similar ultrasound findings (diaphragmatic hernia, rhizomelic limb shortening) and abnormal facial profile. Furthermore, the recent study by Salzano et al. (2018)[17] provides guidelines for early recognition of the distinctive prenatal profile and consideration of a diagnosis of PKS, which are based on prenatal data from 86 published reports and their group of 114 PKS patients. Among the suggested ultrasound markers in second trimester that are highly indicative of PKS, our case met one major and three minor criteria (Table 1).

Accurate diagnosis of fetuses with PKS is critical for appropriate genetic counseling and clinical management.

However, final diagnosis of PKS is impossible without adequate chromosomal analyses. Thomas Liehr provided suggestions for ideal SMC management, that include detection by cytoge-

Table 1. Ultrasound markers in second trimester highly indicative of Pallister Killian syndrome*

Ultrasound markers	
Major criteria	**Minor criteria**
Congenital diaphragmatic hernia	Facial profile
Femur shortening	Congenital heart defects
Polyhydramnios	Thickened nuchal fold
Fetal macrosomia	Calico-pelvic dilatation
Ventriculomegaly	Polydactily
	Cleft palate

*according to Salzano et al. (2018)[16]

netic analyses, followed by the addition of targeted fluorescence *in situ* hybridization (FISH) or other molecular genetic analyses such as array comparative genomic hybridization (aCGH) to make an accurate diagnosis[19].

CONCLUSIONS

This report expands the clinical manifestations of PKS with a unique feature of bifid cardiac apex, and highlights the targeted diagnosis of Pallister-Killian syndrome in a second and third trimester of pregnancy if specific ultrasound markers are present. Accurate diagnosis of fetuses with PKS is critical for appropriate genetic counseling and clinical management.

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Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. **Informed consent:** Informed consent was obtained from the patient involved in the study. **Guidelines:** Our report is in accordance with the CARE guideline available through the EQUATOR network (http://www.equator-network.org/) and COPE guidelines (http://publicationethics.org/).

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