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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Autopsy findings in a fetus with monosomy 20 mosaicism

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SUMMARY

Introduction Mosaic monosomy 20 is a rare chromosomal aberration, without characteristic clinical features. We present a case of a fetus with monosomy 20 mosaicism revealed after prenatal ultrasound detection of anhydramnios and multiple anomalies.

Case outline The second pregnancy of a 33-year-old woman, was terminated at 23rd gestational week, because of the multiple fetal anomalies and anhydramnios, detected by ultrasound. The autopsy of a female fetus revealed multiple congenital anomalies: ventriculomegaly, bilateral choroid plexus cysts, perivascular gliosis in periventricular region of cerebri, hydropericardium, severe cardiomegaly, severe myocardial hypertrophy, hydrothorax, glandular/canalicular stage of fetal lung development, bilateral renal and ureter agenesis (Potter syndrome), bladder aplasia, agenesis of the uterus, fallopian tubes and proximal vagina and valgus deformity of left foot (*pes valgus*). Fetal growth was adequate for gestational age with no craniofacial dysmorphia or radiographically visible anomalies of the skeleton, without signs of infection. The umbilical cord was too long for gestational age – 48 cm. Analysis of fetal karyotype from fetal blood sampling revealed monosomy of chromosome 20 in 10% of analyzed cells in metaphase.

Conclusion Revealing the genetic basis of fetal anomalies is at outmost importance not only for further evaluation of pregnancy, but also for proper genetic informing of patients.

Keywords: fetus; autopsies; monosomy of chromosome 20

INTRODUCTION

Chromosomal mosaicism is the presence of two or more genetically distinct cell lines. It may occur in various genetic changes, including chromosomal aberrations, single-nucleotide variations or small insertions/deletions. Such changes can either go unnoticed or underlie genetic diseases. Chromosomal mosaicism may refer to the presence of two or more different abnormal cell lines (e.g., aneuploid/aneuploid), or a normal and an abnormal cell line (e.g., euploid/aneuploid) [1].

Mosaicism happens because a mutation occurs after the zygote is created. Frequent mitotic errors after fertilization contribute to prevalent aneuploidy in human embryos, including cell cycle dysregulation, defective chromatid cohesion, and centrosome overduplication [2, 3].

The fitness consequences of mosaicism are less precise than those of meiotic origin – aneuploidy. Just because an embryo is a mosaic does not mean those cell lines will propagate throughout development. The influence of mosaicism during development may depend on the degree of aneuploidy, the tissues involved, and the particular chromosome complement. While mosaicism is associated with adverse pregnancy outcomes, some mosaic embryos are viable, and low-level mosaicism may be a regular feature of human development [3].

Chromosomal mosaicism in pregnancies and live births has been reported for cytogenetic aberrations, including trisomies, monosomies, deletions, duplications and other rare alterations. Mosaicism with the loss of an entire autosome is extremely rare in liveborn babies.

We present a case of a fetus with monosomy 20 mosaicism revealed after prenatal ultrasound detection of anhydramnios and multiple anomalies.

Ethical approval was obtained by the Ethics Committee of the University Clinical Center of Serbia, and the study followed Helsinki Declaration principles (Number 68/14). Written consent was obtained from the patient to publish this case report and any accompanying images.

CASE REPORT

A 33-year-old woman, at 21st gestation week of her second pregnancy, was referred to our clinic because of multiple fetal abnormalities diagnosed at her prior hospital. The couple was both healthy and not consanguineous. They had one healthy child and no family history of genetic diseases or congenital malformations. The mother denied being exposed to teratogenic agents or irradiation during the pregnancy. First-trimester

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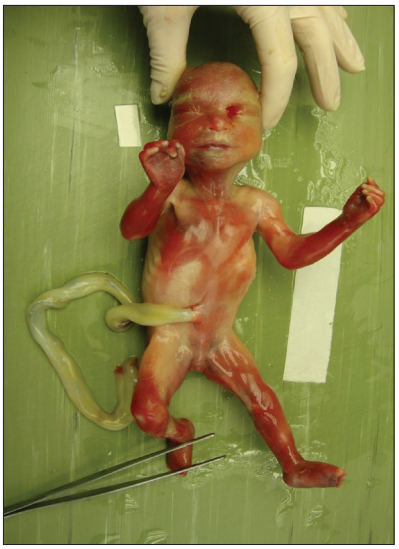

Figure 1. Phenotype of a fetus with monosomy 20 mosaicism

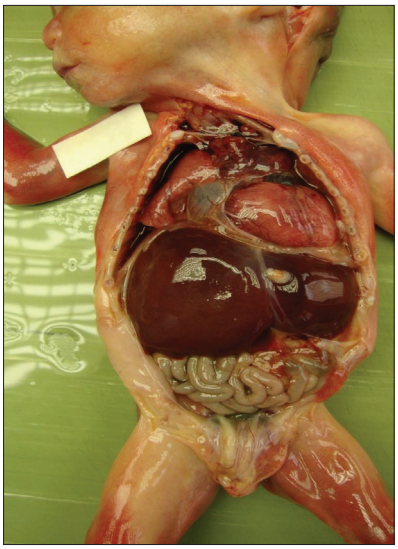

Figure 2. Cardiomegaly and hepatomagaly

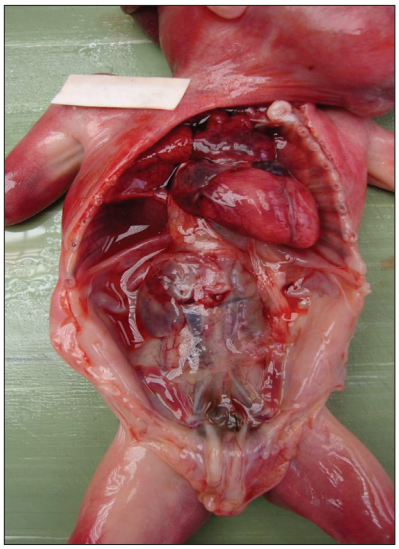

Figure 3. Bilateral renal and ureter agenesis, bladder aplasia, agenesis of the uterus, fallopian tubes, and proximal vagina

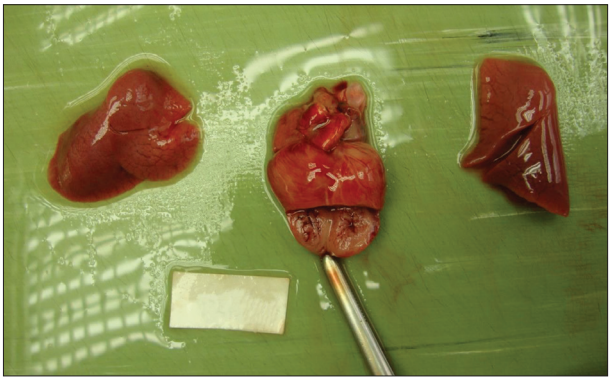

Figure 4. Severe cardiomegaly and myocardial hypertrophy

screening for aneuploidies revealed the low-risk range. No prenatal invasive test was indicated before the patient was observed.

At referral, a fetal comprehensive transabdominal ultrasound exam was performed at 22 weeks of gestation by two experienced maternal-fetal medicine physician sonographers.

Ultrasound examination showed an anhydramnios, ventriculomegaly, bilateral choroid plexus cysts, pleural effusions, fetal heart failure and bilateral renal agenesis.

A sample of fetal blood was analyzed for chromosome abnormalities. The sample was taken by cordocentesis and processed using standard techniques. All specimens were G-banded using trypsin – Giemsa. One hundred metaphase cells were analyzed for chromosomal constitution. In 10 cells (10%), monosomy of chromosome 20 was found, so the karyotype was 45, XX,-20/46, XX (10%:90%). In addition, the parental karyotypes were normal.

On the parent's demand, after genetic counselling and ethics committee approval, the pregnancy was terminated.

Autopsy of a female fetus after inducted abortion (with Prostaglandin E2 and Prostaglandin E3) revealed multiple anomalies: ventriculomegaly, bilateral choroid plexus cysts, perivascular gliosis in periventricular region of cerebri, hydropericardium, severe cardiomegaly, severe myocardial hypertrophy, hydrothorax, glandular/canalicular stage of fetal lung development, bilateral renal and ureter agenesis (Potter syndrome), bladder aplasia, agenesis of the uterus, fallopian tubes and proximal vagina and valgus deformity of left foot (*pes valgus*) (Figures 1–4). Fetal growth was adequate for gestational age with no craniofacial dysmorphia or radiographically visible skeleton anomalies without signs of infection. The umbilical cord was too long for the gestational age – 48 cm.

DISCUSSION

Historically, prenatal diagnosis has focused on detecting chromosomal abnormalities, particularly trisomy 21, using metaphase karyotype.

Pathological biomarkers of the fetus are routinely collected via percutaneous umbilical cord blood sampling. The key applications of this procedure are diagnosis and identification of fetal infections, karyotype analysis, diagnosis of hematologic conditions, fetal growth retardation, and metabolic analysis. This procedure has become more popular recently since it provides direct data on fetal blood status [4].

Clinical testing to determine the underlying etiological factors involved in fetal death currently involves the complex integration of family and obstetric history, radiographic imaging and macroscopic and histological examination of the body and placenta, along with laboratory investigations such as biochemistry, microbiology and genetic testing [5]. Failure to detect low-level mosaicism is a concern since microarrays for detecting genomic imbalances have supplanted karyotyping as the first genomic investigation for patients with developmental delay or multiple congenital anomalies.

A fetal autopsy is the backbone for fetal phenotyping in the molecular era and contributes to the limited data on fetal phenotypes of various genetic disorders. Reverse phenotyping requires detailing fetal characteristics, including dysmorphism, that may not be apparent on ultrasound. Thus, fetal autopsy plays an essential role in better understanding phenotypic and genotypic relationships and complements the field of molecular autopsy in diagnosing genetic diseases [6].

To our knowledge, only five cases of liveborns with monosomy 20 mosaicism have been previously reported. In most cases, only peripheral blood was sampled. The phenotype of patients with monosomy 20 mosaicism ranged from clinically normal to delayed motor and intellectual development, with mild dysmorphic signs and asymmetry. There were no common abnormalities except for an intergluteal cleft asymmetry. There was no correlation between the percentage of aneuploid cells in cultured lymphocytes and the severity of the phenotype in the five patients with monosomy 20 mosaicism, with the highest percentage (25%) found in a normal woman [7, 8].

Stefanou et al. [9] found a significant number of monosomy 20 cells (39 out of 50) in the urine sediment of a boy with bilateral vesicoureteric reflux. They suggested that monosomy 20 causes renal tract abnormalities and trisomy 20. Our case supports this thesis since the fetus we examined had bilateral agenesis of kidneys and ureters, with secondary aplasia of the bladder [9].

Mosaicism arises from mitotic errors occurring after fertilization, during post-zygotic development, usually after the first three cleavage divisions. The best-characterized types of mitotic errors resulting in mosaicism are sister chromatid malsegregations: anaphase lagging, mainly resulting in one normal and one monosomic daughter cell, and non-disjunction, leading to reciprocal trisomic and monosomic daughter cells [10]. The observation that monosomies are commonly found without reciprocal trisomies in mosaic embryos indicates that anaphase lagging might be more frequent than non-disjunction during mitotic errors [11, 12, 13]. The specific method by which mosaicism arises can result in distinctly different outcomes because the impact on fetal development depends on the percentage of mosaicism, specific chromosomes involved, monosomy versus trisomy and inclusion of complete or segmental chromosome mosaicism [11, 12, 13]. We assume that mosaicism anaphase lagging occurred in the case of monosomy 20. If the mosaicism resulted from a cell division error after fertilization, recurrence risk for the mosaic chromosome is very low**.**

The devastating impact of pregnancy loss, terminations and perinatal death on families and the wider community is often compounded by the uncertainty of the cause of death and the subsequent recurrence risk for future pregnancies [5].

We should agree with McCoy [3] that future research should focus on understanding the risks associated with various forms of mosaicism to guide the implementation of genetic screening approaches.

Percutaneous blood sampling allows direct access to the fetal circulation, thus spreading new prenatal diagnosis and therapy areas. Revealing the genetic basis of fetal anomalies is of foremost importance not only for further evaluation of pregnancy but also for proper genetic informing of patients. Identifying a genetic diagnosis in the fetus is valuable to aid in pregnancy management decisions and can be critical for the medical management of the newborn.

Conflict of interest: None declared.

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Аутопсијски налази фетуса са мозаичном монозомијом хромозома 20

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САЖЕТАК

Увод Мозаична монозомија хромозома 20 је ретка хромозомска аберација, која нема карактеристичну клиничку слику, будући да она зависи од процента аберантних ћелија у различитим ткивима.

Приказ болесника Друга трудноћа 33-годишње жене прекинута је у 23. гестацијској недељи због вишеструких аномалија плода и недостатка плодове воде, откривених ултразвучним прегледом. Аутопсијом плода женског пола утврђено је постојање вишеструких урођених аномалија: Потеров синдром – билатерална агенезија бубрега и уретера са секундарном аплазијом мокраћне бешике; агенезија утеруса и вагине; цисте хороидног плексуса; вентрикуломегалија. Плод је био одговарајућег интраутерусног раста за гестацијску старост, без краниофацијалне дисморфије, без радиолошки видљивих аномалија скелета, са знацима инсуфицијенције срца тешког степена, без знакова инфекције. Пупчана врпца била је превелике дужине за гестацијску старост – 48 *cm*. Анализа кариотипа плода из узорка феталне крви открила је монозомију хромозома 20 у 10% анализираних ћелија у метафази.

Закључак Утврђивање генетичке основе конгениталних аномалија важно је како ради даље евалуације трудноће, тако и због исправног генетичког информисања пацијената.

Кључне речи: фетус; аутопсија; монозомија хромозома 20