A Dual Gender Rare Case with 47,XY, +18/46,XX Karyotype: Chimera or Mosaic?

Ravindran Ankathil1 Foong Eva1 Zulaikha Abu Bakar1 Nazihah Mohd Yunus1 Nurul Alia Nawi1 Aziati Annuar1 Cheng Yi Ting1 Sarina Sulong1

1Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

J Child Sci 2021;11:e41–e44.

Abstract

Our objective is to report one rare case of dual gender chimerism involving abnormal male trisomy 18 and normal female karyotype. The baby was born full term with birth weight of 1.8 kg, not vigorous with light meconium stained liquor and Apgar score of 51, 85 and 910. Parents are 40 years old and mother is G6P5+1. The baby had clinical features of Edwards syndrome, and a blood sample was sent to Human Genome Centre, Universiti Sains Malaysia, Malaysia for cytogenetic analysis. Conventional cytogenetic analysis results showed two distinct sex discordant genetic cell lines XY and XX in 90:10 ratio. The male genetic cell line XY also showed trisomy 18 (47,XY, +18) consistent with clinical diagnosis of male Edwards syndrome, whereas the second genetic cell line showed normal 46,XX female. The present case was reported as dual gender chimera with chi 47,XY, +18/46,XX karyotype pattern. To the best of available knowledge, dual gender chimerism with abnormal male trisomy 18 and normal female karyotype has not been reported so far, and this case is reported for its rarity and as the first report.

Keywords

► chimerism
► dual gender
► liveborn
► trisomy 18

Introduction

Individuals who have two or more distinct populations of cells in the body can either be labeled as a mosaic or chimera depending on the mechanism of formation of these different cell lines. Mosaicism is referred to when the different cell lines arise from the same zygote, usually resulting from inaccurate segregation during mitosis. On the other hand, the different cell lines in chimera originate from different zygotes in which two zygotes fuse into one during an early embryonic stage producing a mixture of completely unrelated two cell lineages.1 Human chimeraism is a rare genetic condition. It is expected that many chimeras are in fact healthy and are almost never detected, especially if both zygotes are of the same genetic sex unless they exhibit abnormalities such as mismatched eyes color, partly-colored hair, uneven skin pigmentation, or hermaphroditic genitalia. Otherwise, many are incidentally identified by blood group or paternity/maternity testing or other clinical investigations related to health issues. Chimerism is often recognized cytogenetically when they are of dual gender. Dual gender chimeras (46,XX/46,XY cell lines) account for 13% of true hermaphrodites and are diagnosed at birth due to ambiguous external genitalia.2 Rarely dual gender chimerism has also been reported in cases in which a normal cell lineage (disomy) coexists with an abnormal (trisomy) one, each causing a distinct sex chromosome complement. Few rare disomy/trisomy chimeras with normal trisomy 21 and normal disomy karyotypes were reported.2 Here we report an extremely rare case of dual gender trisomy/disomy chimeraism with abnormal male trisomy 18 and normal female karyotype.

received September 20, 2020
accepted after revision November 27, 2020

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany
DOI https://doi.org/10.1055/s-0040-1722275.
ISSN 2474-5871.
Case History

A full-term baby boy was born to a 40-year-old woman who was gravida 6 para 5. She had a history of non-identical male twin pregnancy in the year 2000 and one abortion in the year 2014. The proband was born via spontaneous vaginal delivery, and the labor was uneventful. He was born not vigorous with Apgar score of 5 at 1 minute, 8 at 5 minutes, and 9 at 10 minutes (5, 8, and 9); he required resuscitation. He had low birth weight of 1.87 kg and appeared dysmorphic with wide anterior fontanelle, flat occiput, triangular facies, hypertelorism, depressed nasal bridge, micrognathia, under-developed left ear, low set ears, wide spaced nipple, trisomy hands, bilaterally flexed wrist, and bilateral rocker bottom feet. Examination of the genitalia revealed small prepuce, left descended testes, and right undescended testes. Right testis was palpable at right inguinal region. He was clinically diagnosed to have Edwards syndrome, and his peripheral blood sample was sent for cytogenetic analysis. Family counseling was performed and the child was managed conservatively, but he died 6 days postbirth.

Conventional Cytogenetic Analysis and Results

G-Banding Using Trypsin and Giemsa (GTG)-banded chromosomal analysis performed on 80 GTG banded metaphases revealed chi 47,XY,+18 [72]/46,XX [8] (Figs. 1 and 2) karyotype pattern with dual gender cell lines XY and XX in 90:10 ratio. The cytogenetic result was consistent with dual gender chimerism involving abnormal male trisomy 18 (Edwards syndrome) karyotype and a normal female 46,XX karyotype pattern.

Discussion

Dual gender chimeras are very rare, as symptomatic chimera with high proportion of trisomic chimeric cells in the body are unlikely to survive. Only a few chimera cases of trisomy 21 and normal karyotype have been reported. To the best of our knowledge, dual gender chimerism with abnormal male trisomy 18 coexisting with normal female karyotype has not been reported so far, and this case is reported for its rarity and as the first report. Trisomy 18 is the second most common autosomal trisomy syndrome after trisomy 21 and accounts for high frequency of fetal loss and infant mortality. A possible explanation on the rarity of dual gender chimera with trisomy 18 and normal karyotype may be that the chimera is asymptomatic due to the low proportion of trisomic chimeric cells in the body and due to the trisomic chimeric cells being confined to only certain organs. Another possibility is that the chimera is unable to survive due to the high proportion of trisomic chimeric cells in the body involving nearly every organ system in the body.

Sex-discordant XX/XY chimeras can have variable genital phenotypes, ranging from a normal male or female phenotype to different degrees of ambiguous genitalia based on the percentage and location of the abnormal cells present in the body. In a study by Madan on 50 individuals with a 46,XX/46,XY karyotype, only 28 were either true hermaphrodites or had

Fig. 1 Karyotype of the newborn dual gender chimeric child showing 47,XY, +18 karyotype pattern.
ambiguous genitalia. Van Bever et al also reported a phenotypically male patient presented at the age of 19 with a painless right scrotal mass and subsequently diagnosed with 46,XX/46,XY ovotesticular disorders of sex development (OT-DSD). Overall, 10 to 33% of patients with OT-DSD have the 46,XX/46,XY karyotype pattern. The present case is a phenotypically male baby whose peripheral blood CCA showed dual gender chimerism involving 90% abnormal male trisomy 18 (Edwards syndrome) karyotype and 10% normal female 46,XX karyotype pattern.

Human chimeras have been broadly divided into two groups, namely naturally acquired chimerism and artificial chimerism. Naturally acquired chimerism takes place in utero, whereas artificial chimerism is acquired following blood transfusion or following organ, stem cell, and bone marrow transplantation. Naturally acquired microchimerism commonly occurs during pregnancy when the placenta is imperfect, and there is reciprocal exchange of cells between a mother and her child. This often leads to the stable engraftment of hematopoietic and nonhematopoietic stem cells in both parties resulting in fetal-maternal chimera.

Examples of naturally acquired macrochimerism are blood chimera, tetragametic chimera, parthenogenetic chimeras, gynogenetic chimera, and androgenetic chimeras. Blood chimera, also known as twin chimera, occurs when there is blood anastomoses formed between the placentas of dizygotic twins, allowing exchange of cells and genetic material between the fraternal twins via in utero. The transfer of stem cells between the developing embryos lead to one or both of the embryos containing two genetically distinct cell populations. Subsequent to the first identification of human blood chimera in 1953, more human blood chimera has been identified.

Meanwhile, postzygotic fusion of the two different embryos can give rise to tetragametic or dispermic chimerism. This condition arises from four gametes: two eggs fertilized by two sperms, resulting in dizygotic twins who fuse into one individual. When a woman is pregnant with fraternal twins and one of the embryo dies very early on, the other surviving embryo can “absorb” its twin’s cells, a process known as vanishing twin syndrome. The fetus who survives will end up with two sets of DNA. As the fetus develops, he/she possess organs that have different sets of chromosomes. In addition, postzygotic fusion of a fertilized ovum with a fertilized second polar body also can produce tetragametic chimeras. Parthenogenetic (trigametic) chimeras, gynogenetic chimeras, and androgenetic chimeras also are resulted from endoreplication of one of the gametic genomes.

Sex chromosome discordance is also observed in patients with mosaicism. In mosaicism, two or more separate cell lines originate from single zygote. It is a consequence of errors in segregation which either resulted from nondisjunction or anaphase lag. In the present case, the possibility of nondisjunction resulting in 48,XXY, +18 zygote followed by somatic loss of an X chromosome and separately, loss of an Y chromosome and chromosome 18 which resulted in the 47,XY,+18/46,XX mosaic karyotype cannot be ruled out. Unfortunately, further molecular investigations could not be initiated as the baby passed away. Had DNA been available, molecular analysis such as SNP array analysis and...
microsatellite marker analysis could have been performed to investigate the parental origin of this patient’s genome. With this, the dual gender cell lines which result either from chimerism or from mosaicism could have been determined. Once chimerism was confirmed, the type of chimerism also could have been determined. In view of no molecular analysis available to support possibility of mosaicism, we concluded this patient as dual gender tetragametic chimera.

We propose two postulations on the origin of this dual gender chimera. One strong possibility is that the mother had an undiagnosed fraternal twin pregnancy, and the female embryo died in utero in very early stage of pregnancy. Some of the cells of this female embryo might have been absorbed by the surviving twin. The second possibility is that this could be a blood chimera as the diagnosis was made by conventional cytogenetic analysis where cells from leucocytes were used for examination. The possibility is that only exchange of hematopoietic stem cells had occurred between the twins in utero before the female embryo died in utero. If that was the case, only the hematopoietic cell lines might have had dual gender sets of different DNA. The only method to differentiate both the condition is by examining other tissues in the body for the presence of different sets of DNA. Unfortunately, this could not be done as this newborn passed away after a few days of life and before the completion of cytogenetic analysis.

Research suggests that the incidence of vanishing twin syndrome occurs before the 12th week of pregnancy in around 36% of pregnancies with two gestations and more than 50% of pregnancies with three or more gestations. The incidence of chimerism further increases due to assisted fertility procedures involving artificially induced ovulation. This leads to increased frequency of twinning in all pregnancies. In in vitro fertilization, some feto-maternal specialists tend to transfer more than one embryo into the uterus to increase the chance of successful implantation. Thus, the frequency of twinning increases.

In this chimera, the surviving fetus happened to be the abnormal male trisomy18 and not the normal female. As chromosomal aneuploidies are the most common etiology for pregnancy loss, the male twin with trisomy 18 was expected to undergo spontaneous abortion, and the normal female twin was expected to survive. It is presumed that this female twin might have had a lethal de novo mutation which lead to death in early pregnancy.

The parents have been counseled on the nature, consequences, and general management of children with Edwards syndrome. However, the chimeric child passed away a few days after birth. The parents were also informed on the probability and risk of occurrence of other aneuploidy in future pregnancies in view of advanced maternal age. Information and importance of fetal aneuploidy testing to screen for common aneuploidies in future pregnancies was offered to this couple.

Conflict of Interest
None declared.

Acknowledgments
The authors would like to thank all staff of Cytogenetic Laboratory of the Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia for their technical assistance in chromosome analysis.

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