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Case Report

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First trimester diagnosis of an unusual case of double aneuploidy with karyotype 48,XXY,+18 (Klinefelter-Edwards syndromes)

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Abstract

Objective: Double aneuploidy cases involving autosomal and sex chromosomes are very rare. Therefore, it is difficult to determine the clinical features and prognosis of these cases. In this case, a fetus with 48,XYY,+18 karyotype is presented.

Case: Cystic hygroma, cleft lip and palate, and clubbed foot were detected in the prenatal ultrasonographic evaluation of a 31-year-old pregnant woman at 13 weeks of gestation. Chorionic villus sampling revealed double aneuploidy including Klinefelter and Edwards syndromes. The molecular result was consistent with the occurrence of nondisjunction error involving chromosome 18 in maternal meiosis I (mat MI) but the finding of the extra X chromosome could not be fully explained. Post-abortion fetal pathology specimen confirmed prenatal diagnosis.

Conclusion: Double aneuploidy cases may rarely present with structural anomalies due to maternal meiosis error, without advanced maternal age, as in this case.

Keywords: Klinefelter, Edwards, trisomy 18, 48XXY, double aneuploidy, structural anomaly, meiosis nondisjunction, case report.

Introduction

Autosomal trisomy is a genetic disorder that occurs as a result of nondisjunction in the maternal meiotic phase. Trisomy 13, 18 and 21 are the most commonly diagnosed types of autosomal trisomy. Sex chromosome trisomies such as XXX (triple X syndrome), XXY (Klinefelter syndrome) and XYY (XYY syndrome) are caused by parental meiotic nondisjunction or postzygotic nondisjunction. These chromosomal aberrations are seen very rarely as double aneuploidy with an incidence of less than 1 in 30,000 births.[1] Clinical features and prognosis are not well known in such cases, due to the scarce availability of follow-up data and the limited number of cases reported in the literature. In this case report, a prenatally diagnosed fetus with 48,XYY,+18 karyotype is presented.

Case Report

A 31-year-old, gravida 2, abort 1 woman was referred to the Perinatology Outpatient Clinic of Tepecik Training and Research Hospital due to fetal cystic hygroma at 13 weeks gestation. Prenatal ultrasonographic examination revealed cystic hygroma, cleft lip and palate, and clubfoot (**Fig. 1**). QF-PCR examination of chorionic villus sampling material detected the chromosome 18 markers as 1:1:1 and 2:1. This result was compatible with Trisomy 18. QF-PCR result of the patient's sex chromosomes was also found to be consistent with XXY. Afterward, FISH analysis was performed on the chorionic villus sampling material, and probes related to chromosome 18 had 3 detected signals, probes related to

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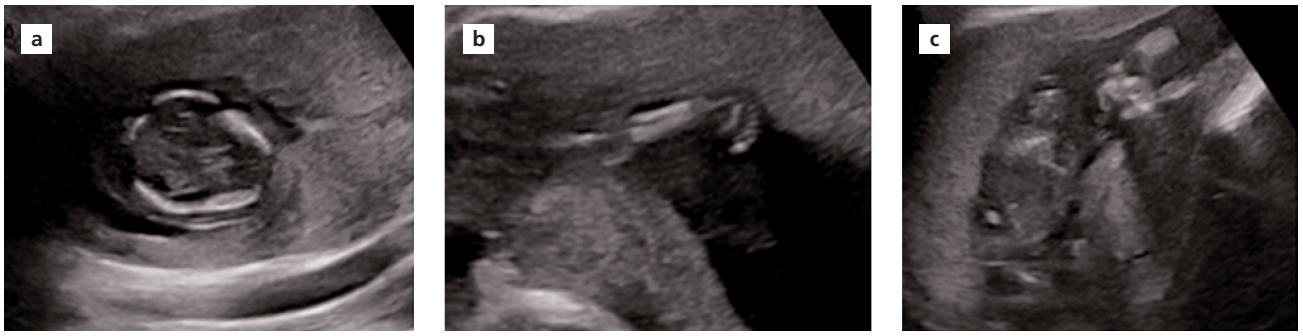

Fig. 1. Prenatal ultrasound findings at 14 weeks of gestation. (**a**) Cystic hygroma, (**b**) clubbed foot, (**c**) cleft lip and palate.

chromosome X had 2 detected signals, and probes related to chromosome Y had 1 detected signal. These studies showed that the prenatal result is consistent with 48,XXY,+18 (**Figs. 2** and **3**). Chromosome analysis was performed from the mother and father's peripheral blood. Both of mother and father's peripheral blood chromosomal analyses showed a normal karyotype. The molecular results, along with the 48,XXY,+18 karyotype, were compatible with the occurrence of nondisjunction error involving chromosome 18 in maternal meiosis I (mat MI) but the finding of the extra X chromosome could not be fully explained. Nondisjunction of XXY chromosome might be related to maternal meiosis 1 or maternal meiosis 2 (mat MI or MII) (**Table 1**). The parents opted for termination of pregnancy at 14 weeks of gestation. Images of the anatomic specimen were not available as termination was performed elsewhere. Postabortion fetal pathology specimen evaluation confirmed prenatal diagnosis.

Discussion

The present case was prenatally identified with two aneuploidies involving Klinefelter syndrome and trisomy 18 and ultrasound findings with cleft lip and palate, clubbed foot, and cystic hygroma. The occurrence of double aneuploidy in the same fetus is known to be an uncommon phenomenon. The first case with autosomal and sex chromosomal anomalies (48,XXY,+21) was presented by Ford et al. in 1959.[2] Since double aneuploidy cases usually result in abortion, there are few cases reported in the literature. Diego-Alvarez et al. reported the rate of double aneuploidy 2.18% among 321 karyotyped spontaneous abortions between 4 and 24 weeks of gestation.[3] However, the expected frequency of double aneuploidy among very early spontaneous abortions is thought to be higher than the observed one. Therefore, the occurrence of clinically undetected pregnancy losses might be the main reason of the scarcity of data on such rare aneuploidies. Furthermore, advances in ultrasonographic devices and screening for aneuploidy over the years provide improvements in the prenatal diagnosis of these cases.

The most frequently reported double aneuploidies in live births involve sex chromosomes combined with either trisomy, 13, 18, or 21.[4] Thus far, a total of 16 case reports in the literature described the combination of trisomy 18 and Klinefelter syndrome. The diagnosis

Table 1. Molecular analysis of 18 and X chromosomes with polymorphic markers. mat MI, maternal meiosis I nondisjunction error; mat MII, maternal meiosis II nondisjunction error.

Locus	18C	18D	18B	18M	18J	XY2	X3	X9	Xq26.2
Fetus	321-325-325	364-371-388	209-209-216	369-369-384	457-457-461	193-209-209	286-286	331-331	144-148
Maternal	325-325	371-388	209-216	368-384	457-461	197-209	286-286	331-331	144-148
Paternal	320-320	362-406	215-236	368-371	457-464	192-203	293	325	147
Result	mat MI						mat MI or MII		

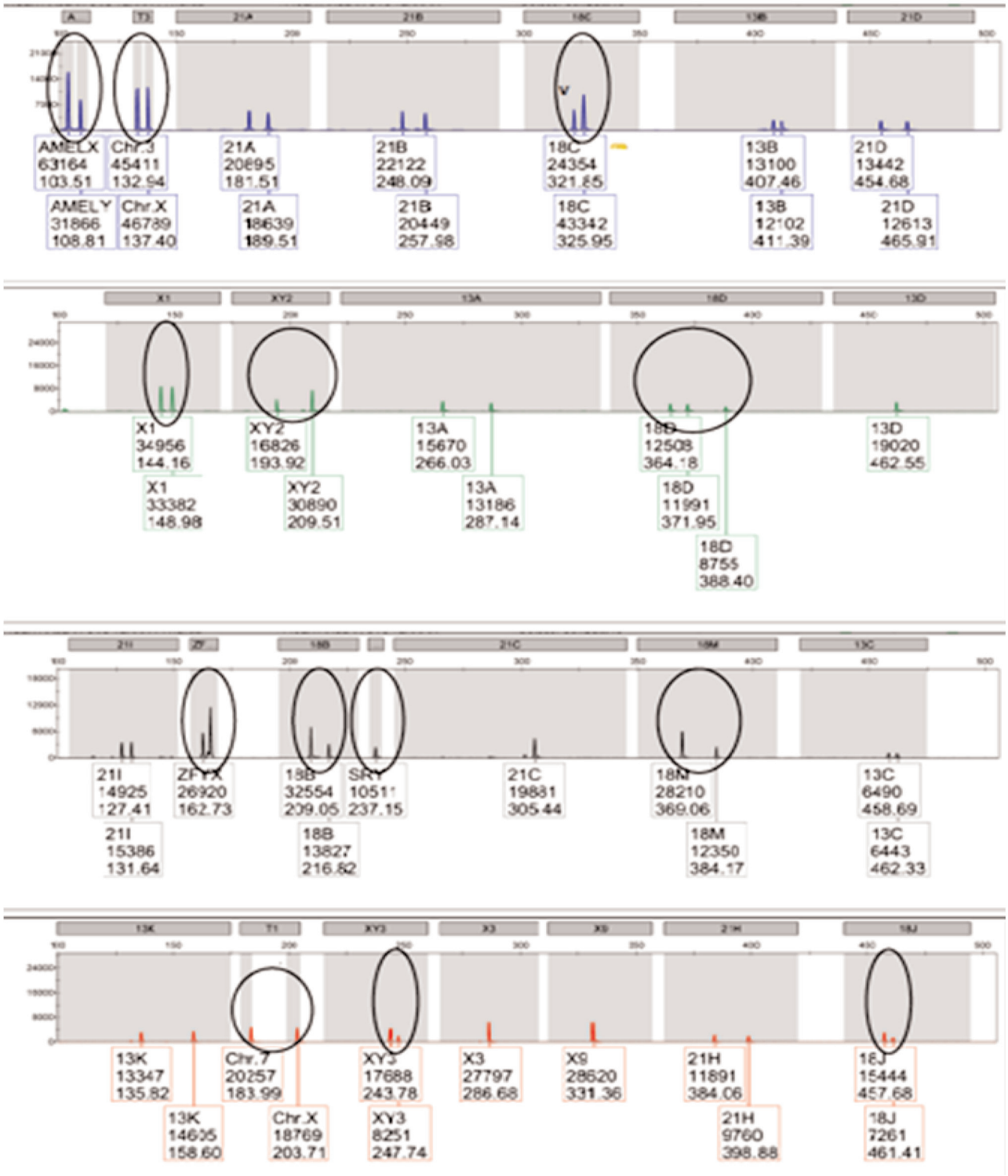

Fig. 2. Positive quantitative fluorescent polymerase chain reaction results with extra short tandem repeat markers in 48,XXY,+18: Trisomy 18 is identified by a trisomic diallelic pattern for D18S978, D18S535, GATA178F11, and D18S976 (≥1.8) and a trisomic triallelic pattern for D18S386 (1:1:1). XXY is identified by a trisomic diallelic pattern for Amelogenin, T3:3X,XY2,ZFYX,T1:7X and XY3.

was made postnatally in most of the cases. Only four (%25) of these fetuses were diagnosed during the prenatal period (**Table 2**). Van Ravenswaaij-Arts et al. performed amniocentesis at 31 weeks of gestation, due to polyhydramnios and fetal growth retardation, bilateral cleft lip on ultrasound. The sample analyzed revealed a 48,XXY,+18 karyotype that was initially misinterpreted as pseudomosaicism.[5] Komwilaisak et al. reported a 33-week fetus with ultrasound findings of large for the date, single umbilical artery with the absence of the left umbilical artery, polyhydramnios, and fetal growth restriction. Karyotyping from the cordocentesis led to the diagnosis of 48,XXY/+18, which was confirmed after delivery of the fetus.[6] Begam et al. presented a case of 34 weeks with several markers of chromosomal anomalies including choroid plexus cyst, severe asymmetrical intrauterine growth restriction, strawberry-shaped head, micrognathia, cerebellar hypoplasia, membranous ventricular septal defect, bilateral clubfeet, clinodactyly, and pectus excavatum. Amniocentesis and cytogenetic analysis of their case revealed double aneuploidy of both trisomy 18 and Klinefelter syndrome, 48,XXY+18.[7] Chen et al. delivered a fetus at 22 weeks of gestation with clenched hands, arthrogryposis of the left wrist, aplasia of the left thumb, micrognathia, low-set ears, hypertelorism, rocker-bottom feet, and a normal penis. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 48,XXY,+18.[8]

Taken together, infants or fetuses with a karyotype of 48,XXY,+18 may present typical abnormalities of trisomy 18 and Klinefelter syndrome. The most common findings were growth restriction, heart defects, micrognathia,[8] suggesting the clinical picture is dominated by the symptoms associated with trisomy 18. Among all prenatally detected cases, the diagnoses were possible in the second or third trimester of pregnancy. In literature, however, this is the first reported case of 48,XXY,+18 syndrome detected in the first trimester of pregnancy by chorion villus sampling. Most of the mentioned findings in previous cases were not present in our case due to the diagnosis in the early weeks of gestation. But it should also be kept in mind that some associated structural anomalies of 48,XXY,+18 syndrome could be demonstrated before routine mid-trimester anomaly scan.

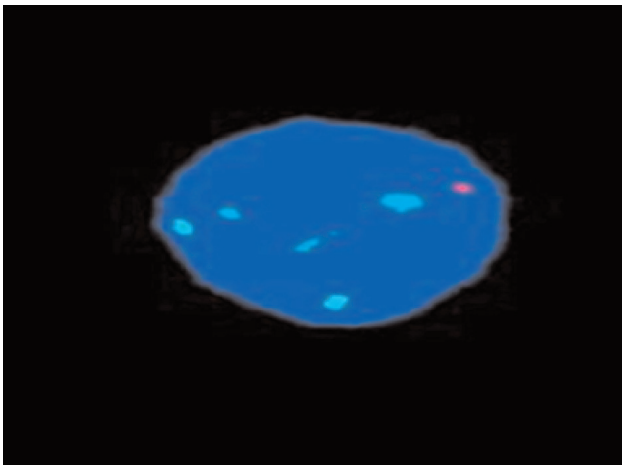

Fig. 3. Interphase FISH analysis of direct chorionic villus sampling preparation demonstrating centromere-specific probe signals for chromosomes 18, X and Y. All 20 interphase cells analyzes contained two signals for X, one signal for Y and three signal for 18. These results are consistent with Klinefelter syndrome with Edwards syndrome.

It has been found that the extra chromosomes in double aneuploidy are almost always of maternal origin. Similarly, extra chromosomes in our case were originated from meiosis 1 for chromosome 18 and meiosis 1 and 2 for chromosome X. The most proposed explanation for the cause of nondisjunction was advanced maternal age. It has been demonstrated that maternal age in double trisomy cases is significantly higher than that for single trisomy cases.[9] In contrast to the literature, we did not find maternal age as a contributing factor for the development of nondisjunction.

There was great variation in neonatal survival of fetuses with a double aneuploidy. Hou reported a case with the longest survival. In his report, a male fetus was delivered at 39 weeks of gestation with growth restriction and multiple structural anomalies including VSD, PDA, PS, facial dysmorphism, micrognathia, microcephaly, single umbilical artery, congenital diaphragmatic hernia, left renal hypoplasia, right hydronephrosis, clenched hands, clinodactyly, inguinal hernia, high-arched palate, and cryptorchidism. Cytogenetic analysis of that case revealed double aneuploidy of both trisomy 18 and Klinefelter syndrome, 48,XXY+18, and remained alive up to 21 months. All other antenatally reported cases were terminated or resulted in neonatal death.[8]

Table 2. Clinical findings of cases diagnosed with prenatal Edwards and Klinefelter (48,XXY,+18).

Authors	Karyotype	Maternal age (y)	Paternal age (y)	Major abnormalities and outcome	Parental origin of aneuploidy	Cell stage of nondisjunction Chr. 18	Cell stage of nondisjunction Chr. X
Van Ravenswaaij-Arts et al.[5]	47,XY,+3/48, XXY,+18/46,XY	26	NA	Prenatal ultrasound at 31 weeks: • IUGR, polyhydramnios, and bilateral cleft lip. Amniosentesis: • Delivery at 38 weeks, 1746 g, bilateral cleft lip and palate, micropenis, cryptorchidism, ventriculomegaly, camptodactyly, an atrioventricular septal defect, hypoplasia of cerebellar vermis, facial dysmorphism, clenched hands, and neonatal death (10 days).	NA	PZM (suspected)	PZM (suspected)
Komwilaisak et al.[6]	48,XXY,+18	21	NA	Prenatal ultrasound at 33 weeks: • IUGR, polyhydramnios, single umbilical artery, micrognathia, bilateral club hands, clenched hands, and rocker-bottom feet. Cordosentesis: • Delivery at 38 weeks, 2200 g, microcephaly, bilateral cataracts, microtia, micropenis, undescended testicles, two-vessel cord, facial dysmorphism, and neonatal death (18 days).	NA	NA	NA
Begam et al.[7]	48,XXY,+ 18	NA	NA	Prenatal ultrasound at 34 weeks: • IUGR, choroid plexus cysts, cerebellar hypoplasia, ventricular septal defect, club feet, clinodactyly, and pectus excavatum. Amniocentesis: • Facial dysmorphism, clenched hands, and neonatal death (2 days).	NA	NA	NA
Chen et al.[8]	48,XXY,+18	42	43	Prenatal ultrasound at 18 weeks: • Choroid plexus cysts. Prenatal ultrasound at 22 weeks: • A flexion contracture, • Deformity of left wrist, and absence of left thumb. Amniocentesis: • Termination at 22 weeks, 332 g, facial dysmorphism, micrognathia, arthrogryposis of left wrist, aplasia of left thumb, clenched hands, and a normal penis.	Maternal	MI	MII or PZM
Present case	48,XXY,+18	31	NA	Prenatal ultrasound at 14 weeks: • Cleft lip and palate, pes equinovarus and cystic hygroma. • Termination at 14 weeks, NA.	Maternal	MI	MI or MII

Chr: chromosome; **IUGR:** intrauterin growth restriction; **MI:** meiosis I nondisjunction error; **MII:** meiosis II nondisjunction error; **NA:** not available; **PZM:** postzygotic mitotic error.

Conclusion

In conclusion, we presented a rare case of double aneuploidy (48,XXY,+18) with cystic hygroma, cleft lip and palate, and clubfoot diagnosed at early weeks of gestation. In this case, extra chromosomes were of maternal origin but not associated with advanced maternal age. Therefore, the possibility of this rare chromosomal abnormality should be considered in the differential diagnosis of structural malformations in the first trimester of pregnancy even in the absence of advanced maternal age.

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