CASE REPORT

Mosaic Trisomy 22 in a 14-Year-Old Adolescent: A Case Report

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Abstract

Complete trisomy 22 is the second most common chromosomal aneuploidy found in spontaneous abortions. However, mosaic trisomy 22 has a milder phenotype, which is compatible with life. The varied manifestations of trisomy depend on the distribution of the affected cells, making this diagnosis difficult. The authors report the clinical case of a 14-year-old adolescent observed for primary amenorrhea. On physical examination, mild dysmorphisms were noted and growth velocity was below percentile 25. An endocrine assessment revealed a hypergonadotropic hypogonadism, a hand radiograph showed delayed bone age, and a pelvic ultrasound showed infantile uterus and absent ovaries. She had a normal female blood karyotype. Blaschko lines were noticed on the upper extremities. Skin karyotype confirmed mosaic trisomy 22. Signs and symptoms in mosaic trisomy 22 can be unspecific. Dysmorphisms can be subtle and short stature is a common finding in other disorders. However, Blaschko lines, especially in association with postnatal growth failure, dysmorphias, and hemidystrophy should prompt this diagnosis.

Keywords: Abnormal Karyotype; Adolescent; Amenorrhea/etiology; Chromosome Disorders/complications; Chromosomes, Human, Pair 22; Mosaicism; Trisomy/diagnosis

Introduction

Chromosomal disorders are a major cause of spontaneous abortions.[1] Complete trisomy 22 has been identified as the second most common chromosomal aneuploidy in spontaneous abortions, occurring in 2.9% of cases.[2] Due to its characteristic malformations (microcephaly, cranial abnormalities, intrauterine growth retardation, congenital heart disease, and renal malformations), full trisomy 22 is almost incompatible with life and the postnatal survival rate is extremely low, with an average survival time of 4 days.[2,3] However, mosaic trisomy 22 can be compatible with life and, therefore, antenatal differentiation between both entities is crucial for genetic counseling regarding life-expectancy and complications.[2,4] The clinical features and symptoms will depend on the count and distribution of the cells with the extra chromosome 22.[2] The phenotype in patients with mosaicism is milder than full chromosomal aneuploidy and, therefore, it may be underdiagnosed in the presence of minimal physical features and normal neurodevelopment.[5]

Case Report

The authors report the clinical case of a 14-year-old Caucasian girl, second and last child born to a 35-year-old mother and a 37-year-old father. The parents were healthy and non-consanguineous and there was no family history of any genetic disorders nor a previous history of abortions. The mother had a previous pregnancy with a healthy daughter. In the context of increased nuchal translucency an amniocentesis was performed revealing a normal female karyotype (46,XX). This child was born prematurely at 31 weeks of gestation by elective cesarean delivery due to intrauterine growth restriction. The birth weight was 1020 g (percentile 10 based on Fenton curves). She was admitted to the neonatal intensive care unit at birth due to prematurity and very low birth weight. She was diagnosed with bronchopulmonary dysplasia and atrial septal defect. Despite her medical history, she was a healthy child with normal neurodevelopmental milestones and thriving well until the age of 9 years.

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Due to lower limb asymmetry (left leg longer 29 mm), she was evaluated by a pediatric orthopedic surgeon and remained in a watchful waiting approach.

A progressive decline in the growth rate was noted since the age of 9 years, and at the age of 14 years, her growth rate was 2.2 cm/year (percentile 10). At this point, she was observed in the pediatric endocrinology department for primary amenorrhea and suspicion of Turner syndrome. On physical examination, the high palate, webbed neck, cubitus valgus, asymmetric lower limbs, and dysplastic toenails were noted. Her Tanner stage was B2 P3 and anthropometric measures were:

- Body mass index: 21 kg/m^2 (*z*-score 0.50, percentile 69);
- Height: 152.1 cm (*z*-score 1.11, percentile 13);
- Growth rate: < 4 cm/year (< percentile 25).

Hematological and biochemical analyses revealed a hypergonadotropic hypogonadism with estradiol < 5 pg/mL, luteinizing hormone (LH) 14.3 mUI/mL, and follicle stimulating hormone (FSH) 56.3 mUI/mL. Other endocrine assessments were within the normal value ranges (Table 1). Bone age assessment using a radiograph of the non-dominant hand showed delayed bone age (11 years for chronological age of 14 years old). The pelvic ultrasound revealed an infantile uterus, and the ovaries were not found. Later, she was submitted to a pelvic computerized tomography that confirmed the absence of both ovaries. The chromosomal assessment of the peripheral blood cells revealed a female karyotype (46,XX). The diagnosis of gonadal dysgenesis was made and hormonal therapy with transdermal estrogen was started. Menarche occurred after one year of hormone treatment. Her last pelvic ultrasound revealed a normal adult uterus.

During multidisciplinary follow-up, hypopigmented skin regions that followed the Blaschko lines on both arms were observed. These were more prominent during the summertime (Figs. 1 and 2). Karyotype on skin fibroblasts confirmed the clinical diagnosis of mosaicism: 47,XX,+22[19]/46,XX[17], and it was compatible with mosaic trisomy 22. Genetic counseling was offered to the patient and her family.

Discussion

Mosaic trisomy 22, a rare chromosomal disorder, was first described by Schinzel in 1981. This chromosomal anomaly has a predominance for the female gender (ratio 3:2).[5] Typical manifestations include intrauterine growth restriction and postnatal growth failure, which are found in more than 70% of the patients,[6] short stature,[7] and hemidystrophy including whole body asymmetry with a difference in the length of the lower extremities.[8] Dysmorphic features are found in more than 90% of patients, such as epicanthic folds, pre-auricular pits, and flat nasal bridge that are the most common findings,[6] hypertelorism, low-set ears, and abnormal palmar flexion creases, skin linear pigmentary changes along the Blaschko lines, genitourinary tract abnormalities, including cryptorchidism and hypospadias, hearing loss,[5,9] limb anomalies, such as cubitus valgus, clinodactyly, brachydactyly, syndactyly, and hypoplastic or dysplastic nails.[8] Congenital heart disease occurs in over 70% of patients and both atrial and ventricular septal defects are the most common findings.[6] Delayed or failed development of the secondary sexual characteristics during puberty due to ovarian dysgenesis and developmental delay is a common finding in mosaic trisomy 22.[5] However, up to 40% of all patients may have normal neurodevelopmental milestones.[5] Therefore, the severity of developmental delay is not correlated with the percentage of trisomic cells.[8]

Down, Turner, Noonan, and Russell Silver syndromes have been proposed as differential diagnoses due to some similarities shared with mosaic trisomy 22.[8]

Abnormal findings in fetal ultrasound or even the

Table 1. Endocrine assessment of the patient

Parameter (unit)	Measured values	Reference range
Estradiol (pg/mL)	< 5	Follicular phase 12.5-166
		Ovulation phase 85.8-498
		Luteal phase 43.8-211
Follicle stimulating hormone (mUI/mL)	56.3	0.4-15.1
Luteinizing hormone (mUI/mL)	14.3	Follicular phase 2.4-12.6
		Ovulation phase 14.0-95.6
		Luteal phase 1.0-11.4
Anti-Müllerian hormone (pmol/L)	0.16	12-15 years old 3.0-46.6
Thyroid stimulating hormone (µUI/mL)	2.82	0.32-5.0
Free thyroxine (ng/dL)	1.39	1.0-2.5

presence of mosaic trisomy 22 in the karyotype of amniotic fluid can suggest the diagnosis.[5] However, diagnosis should be confirmed postnatally through peripheral blood karyotype or other tissue samples (skin or buccal cell) karyotype if the blood karyotype is normal.[5] In fact, up to 30% of patients had blood lymphocytes mosaic karyotype while about 90% harbored skin mosaic karyotype.[5,6]

Initially, our patient was thought to have Turner syndrome based on mild dysmorphisms and some manifestations commonly seen in this syndrome, such as congenital heart defects and hypergonadotropic hypogonadism. However, this diagnosis was ruled out after a normal peripheral blood karyotype. This reinforces the fact that a normal karyotype cannot exclude the presence of a chromosomal anomaly, especially if a mosaic pattern is suspected. In our patient, the mosaic trisomy 22 was found after karyotype on skin fibroblast. Due to the high variable manifestations, the management of these patients requires a multidisciplinary team, including pediatricians, endocrinologists, orthopedic surgeons, cardiologists, ophthalmologists, clinical geneticists, and physical therapists.[5]

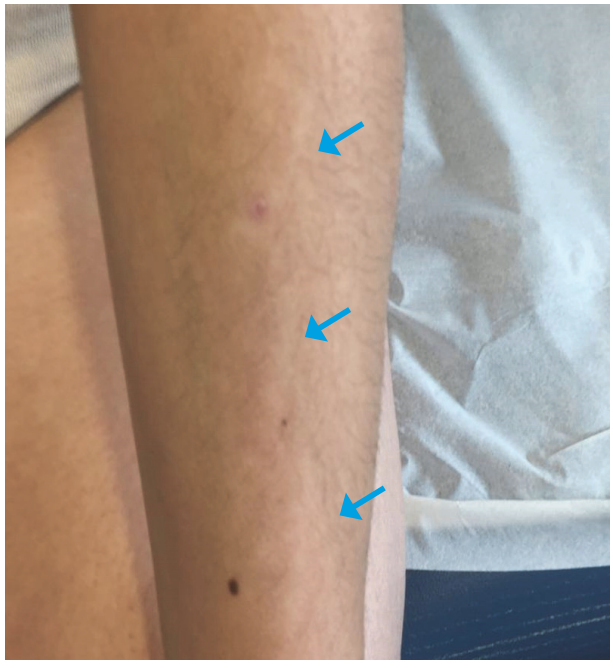

Figure 1. Blaschko lines (arrows) of the left upper extremity.

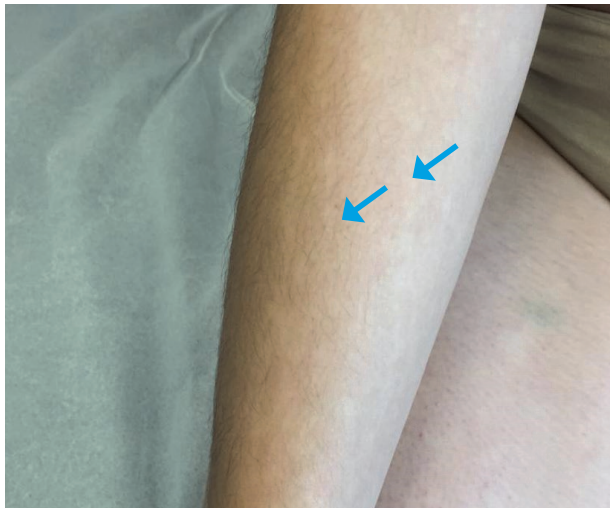

Figure 2. Blaschko lines (arrows) of the right upper extremity.

As somatic mosaicism is a post-zygotic event, the recurrence risk for parents is low, but higher than the general population because of the theoretical possibility of parental germline mosaicism. It is possible to offer prenatal testing for future pregnancies, and it should be discussed with the couple. Our patient herself had ovarian dysgenesis that will restrain her possibility for offspring.

The authors report this case to emphasize the value of team effort in search of the correct diagnosis as well as the importance of paying attention to the details and clues in every patient.

WHAT THIS CASE REPORT ADDS

- Mosaic trisomy 22 is a rare chromosomal disorder characterized by variable congenital malformations.
- Characteristic findings include craniofacial dysmorphias, growth and developmental delays, hemidystrophy and limb anomalies, congenital heart disease, genitourinary defects and skin pigmentary changes.
- Skin linear pigmentary changes along Blaschko lines are a sign of cutaneous mosaicism that can occur in several congenital or acquired conditions.
- A normal peripheral blood karyotype does not exclude the presence of a mosaic pattern chromosomal disorder.
- A multidisciplinary team is crucial for arriving at this diagnosis as well for the follow-up on these patients.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

References

1. Hassold T, Chen N, Funkhouser J, Jooss T, Manuel B, Matsuura J, et al. A cytogenetic study of 1000 spontaneous abortions. Ann Hum Genet 1980;44:151-78. doi: 10.1111/j.1469-1809.1980.tb00955.x.
2. Kalayinia S, Shahani T, Biglari A, Maleki M, Rokni-Zadeh H, Razavi Z, et al. Mosaic trisomy 22 in a 4-year-old boy with congenital heart disease and general hypotrophy: A case report. J Clin Lab Anal 2019;33:e22663. doi: 10.1002/jcla.22663.
3. Heinrich T, Nanda I, Rehn M, Zollner U, Frieauff E, Wirbelauer J, et al. Live-born trisomy 22: Patient report and review. Mol Syndromol 2013;3:262-9. doi: 10.1159/000346189.
4. Leclercq S, Baron X, Jacquemont ML, Cuillier F, Cartault F. Mosaic trisomy 22: Five new cases with variable outcomes. Implications for genetic counselling and clinical management. Prenat Diagn 2010;30:168-72. doi: 10.1002/pd.2427.
5. National Organization for Rare Disorders. Mosaic trisomy 22 [accessed 30 April 2020]. Available at: https://rarediseases.org
6. Abdelgadir D, Nowaczyk MJ, Li C. Trisomy 22 mosaicism and normal developmental outcome: Report of two patients and review of the literature. Am J Med Genet 2013;161A:1126-31. doi: 10.1002/ajmg.a.35812.
7. Saraiva JM, Matoso E, Garcia P, Bento G, Diogo L, Marques I. Cromossomopatia com cariotipo normal em linfócitos: Caso clínico. Acta Pediatr Port 2003;34:303-6.
8. Florez L, Lacassie Y. Mosaic trisomy 22: Report of a patient with normal intelligence. Am J Med Genet 2005;132A:223-5. doi: 10.1002/ajmg.a.30401.
9. Chen CP, Huang MC, Chern SR, Wu PS, Chen SW, Chuang TY, et al. Mosaic trisomy 22 at amniocentesis: Prenatal diagnosis and literature review. Taiwan J Obstet Gynecol 2019;58:692-7. doi: 10.1016/j.tjog.2019.07.020.
10. Crowe CA, Schwartz S, Black CJ, Jaswaney V. Mosaic trisomy 22: A case presentation and literature review of trisomy 22 phenotypes. Am J Med Genet 1997;71:406-13.

Trissomia 22 em Mosaico numa Adolescente de 14 Anos: Caso Clínico

Resumo:
A trissomia 22 é a segunda aneuploidia mais comum encontrada nos abortos espontâneos. Porém, a trissomia 22 em mosaico apresenta um fenótipo mais ligeiro, sendo compatível com a vida. As variadas manifestações da trissomia dependem da distribuição das células afetadas, dificultando o seu diagnóstico. Os autores relatam o caso clínico de uma adolescente de 14 anos observada por amenorreia primária. No exame físico, apresentava dismorfias e uma velocidade de crescimento inferior ao percentil 25. O estudo efetuado revelou hipogonadismo hipergonadotrófico, atraso na idade óssea, útero infantil e ausência dos ovários. Nos membros superiores apresentava linhas de Blaschko. O cariótipo de sangue periférico foi normal. O cariótipo de pele revelou trissomia 22 em mosaico. Os sinais e sintomas da trissomia em mosaico são inespecíficos. As dismorfias podem ser subtis e a baixa estatura é um achado comum noutras patologias. No entanto, a presença de linhas de Blaschko, especialmente associada a baixa estatura, dismorfias e hemidistrofia, devem sugerir este diagnóstico.

Palavras-chave: Adolescente; Alterações Cromossómicas/complicações; Amenorreia/etiologia; Cariótipo Anormal; Cromossomas Humanos Par 22; Mosaicismo; Trissomia/diagnóstico