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RESEARCH ARTICLE

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Mosaic trisomy 22 in a 4-year-old boy with congenital heart disease and general hypotrophy: A case report

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Background: Trisomy 22 mosaicism is a rare autosomal anomaly with survival compatibility. Recognition of the complete trisomy 22 which is incompatible with life from the mosaic form is critical for genetic counseling. Affected mosaic cases have prevalent clinical presentations such as webbed neck, developmental delay, abnormal ears, cardiac disorders, and microcephaly. Phenotype of these patients is milder than full chromosomal aneuploidy, and the severity of the phenotype depends on the count of trisomic cells. We describe a 4-year-old boy with mosaic trisomy 22 from healthy parents and no family history of any genetic disorders in the pedigree.

Method and Results: The patient had determined dysmorphic clinical features including facial asymmetry, cleft palate, gastroenteritis, hydronephrosis, developmental delay, genital anomalies, dysplastic toenails, flattened nasal bridge, congenital heart defect, hearing loss, cryptorchidism, and hypotonic muscle. He is the first reported with hypothyroidism and larynx wall thickness in worldwide and the first with atrial septal defect (ASD) from Iran. Chromosomal analyses using G-banding indicated a de novo Mos 47,XY,+22(6)/46,XY(44) karyotype with no other chromosomal structural changes.

Conclusions: Our observations confirm the importance of cytogenetic analyses for determining the cause of congenital anomalies and provide a useful genetic counseling. In addition, due to the fact that some of mosaic trisomy 22 features are unavoidable such as CHD and general hypotrophy, we suggest including echocardiography test for early diagnosis during the clinical assessment.

KEYWORDS

atrial septal defect, hypothyroidism, karyotype, mosaicism, trisomy

1 | INTRODUCTION

Complete trisomy 22, the second most common chromosomal aneuploidy, occurs in about 2.9% of spontaneous abortions.[1] It is extremely incompatible with life and the average survival of affected children is 4 days.[2] The incidence of trisomies 22 (both mosaic and non-mosaic forms) among miscarriage cases is 9-20 cases per 100 000.[3] Mosaic trisomy 22 is a rare anomaly which has prolonged survival compatibility; therefore, recognition of full trisomy 22 from the mosaic form is critical for genetic counseling. Affected mosaic cases have prevalent clinical presentations, such as webbed neck, developmental delay, abnormal ears, cardiac disorders including congenital heart diseases (CHDs), and microcephaly.[4] The diagnosis of a mosaic trisomy 22 is usually complicated for the present/absent of mosaicism in tissue or hematological cell lines; that is, not all patients of mosaic trisomy 22 are detectable in cultured blood cells,

the difference between various tissues in the mosaicism level, and the paternal/maternal uniparental disomy. Furthermore, establishing a trusty relevance between the mosaic trisomy 22 phenotype and karyotype is difficult.[5]

Congenital heart diseases are the common cause of pediatric mortalities which occur in 8 per 1000 live births. Atrial septal defect (ASD) often occurs in 7%-11% of CHD cases.[6] Overall, about 33%-42% of CHD are associated with chromosomal aneuploidy and the majority of the individuals with CHD having an aneuploidy harbors extracardiac deformities.[7] In published studies, documented mosaic trisomy 22 has been identified in patients with some of CHD types such as ventricular septal defect (VSD), pulmonary stenosis (PS), aortic stenosis (AS), and ASD.[1] Nevertheless, the spectrum of CHD related to mosaic trisomy 22 has not been well described.

Herein, we present a patient with ASD in addition to other previously reported symptoms of the mosaic trisomy 22.[8] To our knowledge, this is the first report of a mosaic trisomy 22 with ASD from Iran. Our finding indicates that patients with asymmetry and CHD should be surveyed for mosaic trisomy 22.

2 | MATERIALS AND METHODS

2.1 | Case clinical studies

This 4-year-old Iranian boy was the second and last child of the studied family. His younger brother was healthy and 12 years old. The parents were healthy and third-degree consanguineous. Father's age was 39 years and mother was 35 years old. In the last days of the pregnancy with the affected son, the mother had abnormal excessive weight gain. There was no family history of any genetic disorders in pedigree. Due to heart-stopping of the newborn during the spontaneous vaginal delivery, the patient was born by emergency cesarean section. The length, weight, and head circumference of the birth were 51 cm, 2400 g, and 32 cm, respectively. He was hospitalized at the age of 45 days because of failure in gaining sufficient weight and feeding problems, at that time, he was recognized by an echocardiogram to have ASD (Figure 1). The seizure co-occurred with heart-stopping once in the second month of the life but he had normal brain MRI (magnetic resonance imaging) and normal intelligence. At age 1 year, he underwent surgery for his large ASD.

The clinical findings were as below (Figure 2): the facial asymmetry was noticeable, the right-side ear was small and rotated; that is, hypoplasia of the antitragus, tragus, and lower helix, and audiological evaluations indicated both of ears had hearing loss. His right eye and eyelid were normal, but the left eye had esotropia and blepharoptosis. His growth was extremely slowly; at 3 years, length and weight were 78 cm and 8000 g, a late gain head control (at 8 months), lack of creep, talk, and walk. He suffered from cleft palate up to the age of 1 year, hypothyroidism, hydronephrosis, gastroenteritis, and dental anomaly. He had flattened nasal bridge, low hairline, no feet nails up to the age of 3½ years, flat hands nails, that is, dysplastic toenails, hypotonic muscle, and robust crying which were detected by laryngoscopy to have thickening in the larynx wall. He harbored hypospadias, unilateral cryptorchidism, and ambiguous genitalia, that is, at 2 months of age; moreover, genetic and endocrine examinations determined the baby sexual as male. In addition, on repeated hematology and biochemistry tests, the patient values were nearly in normal ranges as indicated in Table 1.[9,10]

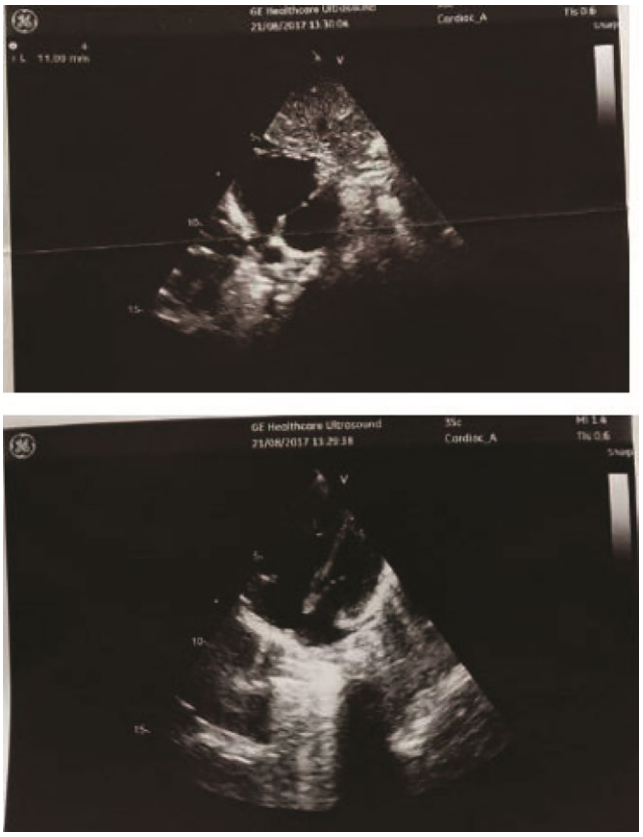

FIGURE 1 Cardiac defect analyses: the echocardiograph image indicating the atrial septal defect

2.2 | Cytogenetic analyses

With informed consent of the case parents, the karyotype (GTG-banding) of peripheral blood lymphocytes from the affected son and his parents was performed. Lymphocyte cells were cultured in medium with RPMI 1640, penicillin, fetal bovine serum (FBS), L-glutamin 200 mmol/L, and phytohemaglutinin (PHA). After 72 hours culture at 37°C, Colcemide was added to cultured tube and harvested base on the standard protocols.[11] Metaphase spreads were stained by Giemsa (G-banding), and 50 cells were analyzed at a resolution of 450-550 bands according to the lab protocol. The karyotype was described based on the International System for Human Cytogenetic Nomenclature (ISCN 2016).[12] This study was performed due to the Declaration of Helsinki Principles and was reviewed by the ethics committee of Rajaie Cardiovascular, Medical and Research Center.

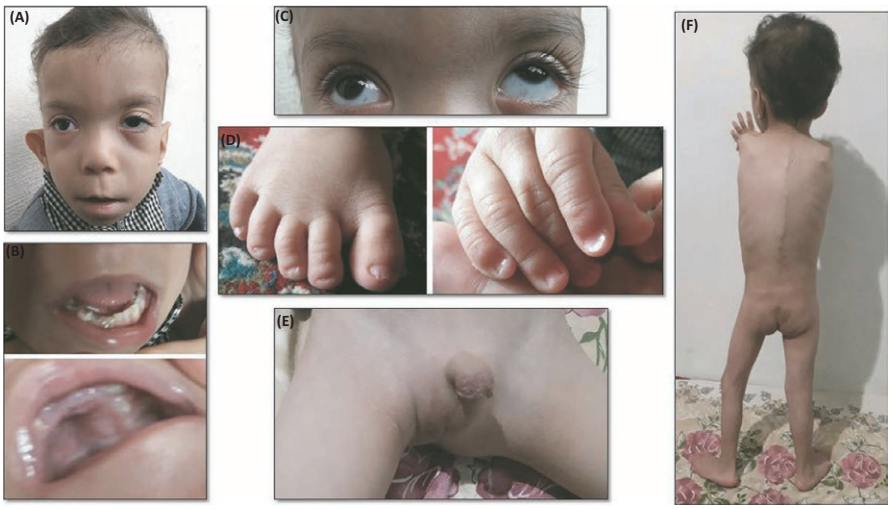

FIGURE 2 The patient at 4 years of age. A, Ear asymmetry and the flattened nasal bridge. B, Dental anomaly. C, Left eye: esotropia and blepharoptosis. D, Dysplastic toenails. E, Ambiguous genitalia. F, General hypotrophy

TABLE 1 Hematological and biochemical analyses of the patient

	Parameters (unit)	Measured values in the patient	Reference values
Hematology	White blood cell count (x10^3)	10.2	6.3-16.3
	Red blood cell count (x10^6)	4.6 (L)[d]	4.7-5.7
	Hemoglobin (g/dL)	12.5 (L)[d]	13.7-18.1
	Hematocrit (%)	37.5 (L)[d]	41.0-54.0
	Neutropenia (segs)x10^3	6.9	2.0-10.2
	Lymphocytes (x10^3)	5.8	3.1-7.9
	Platelet (x10^3)	156 (L)[d]	202-557
	MCV (fL)[a]	81.2	80.8-100.9
	MCH (pg)[b]	27.5	27.3-34.1
	MCHC (g/dL)[c]	33.9	32.0-36.0
Biochemistry	Sodium (mmol/L)	138	133-146
	Potassium (mmol/L)	4.7	3.5-6.5
	Glucose (mg/dL)	100	70-115
	Creatinine (mg/dL)	0.2 (L)[d]	0.6-1.4
	Uric acid (mg/dL)	8.5 (H)[d]	3.6-8.2
	Alanine aminotransferase (U/L)	12	5-40
	Aspartate aminotransferase (U/L)	42	5-45
	Troponin (μg/L)	6.44 (H)[*]	<0.16
	Alkaline phosphatase (U/L)	169	<269
	Blood urea nitrogen (mg/dL)	14	7-20
	C-reactive protein (mg/L)	2.5	0.3-5
	Total bilirubin (μmol/L)	6	2-14

[a]MCV, mean cell volume; fL = (Hct [in L/L]/RBC [in x1012/L]) x 1000.
[b]MCH, mean cell hemoglobin.
[c]MCHC, mean corpuscular hemoglobin concentration.[*]L, low; H, high.

3 | RESULT

Chromosomal assessment of peripheral blood cells (50 metaphases) from patient indicated a male karyotype which contained six clones with trisomy 22 and forty-four clones with a usual male karyotype. The mosaic trisomy 22 karyotype was determined as Mos 47,XY,+22 (6)/46,XY(44), as shown in Figure 3. No other chromosomal structural changes were found in the karyotype. Also, the parent's normal chromosomes were determined as 46, XY and 46, XX for the father and the mother, respectively.

4 | DISCUSSION

A 4-year-old boy presented in our study, harbored a de novo mosaic trisomy 22. Apparently, the existence of the additional chromosome 22 in some of the patient's metaphase spreads is the cause of clinical findings that determine the disease.[13] Our patient displayed the most of the known symptoms of this mosaicism including ear problem (facial and hearing), developmental delay, genital anomalies, dysplastic toenails, flattened nasal bridge, congenital heart defect, cryptorchidism, and hypotonic muscle.

This patient had large ASD without any other types of CHD, although the most published reports indicated complex CHD; our finding was somewhat similar to Abdelgadir et al[14] publication, that they determined ASD and tetralogy of Fallot (TOF) in their patients and Abdelmoula et al[13] study, which a patient with ASD, patent ductus arteriosus (PDA) and PS was reported. Our case had hypothyroidism, although he was thin and weak, to our knowledge, this clinical feature has not been previously described in mosaic trisomy 22 cases. In addition, we found no study reporting larynx wall thickness in trisomy 22 mosaicism observed in our patient. High maternal age is related to a risk of aneuploidy, and it should be concluded whether this subject is or is not related with trisomy 22 because the age of our patient mother was 31 and the average age of women pregnancy had increased over the past years. Although it appears that the patients with mosaic trisomy 22 are females more than males, whereas our patient karyotype and endocrine evaluation indicated male. The microcephaly and intellectual disability are often reported in mosaic patients with trisomy 22[15-18]; however, they were not observed in our case, and our patient had normal intelligent as assessed by the Raven test, similar to Lacassie et al[3] report which described a 5-year-old girl with normal intelligent. Phenotype in patients with mosaic chromosomal abnormality is milder than full chromosomal aneuploidy. In addition, mosaic trisomy 22 has various clinical features which the severity of these symptoms is varied depending on the count of extra chromosome 22 cells. The patients with low trisomy 22 spreads have fewer symptoms of the mosaic trisomy 22.[13] Therefore, it is possible that healthy mental phenotype in our case is related to the low level of the mosaicism (12%). Mosaicism occurs because of errors in the fetal mitosis division or is the result of father/mother uniparental disomy which the second

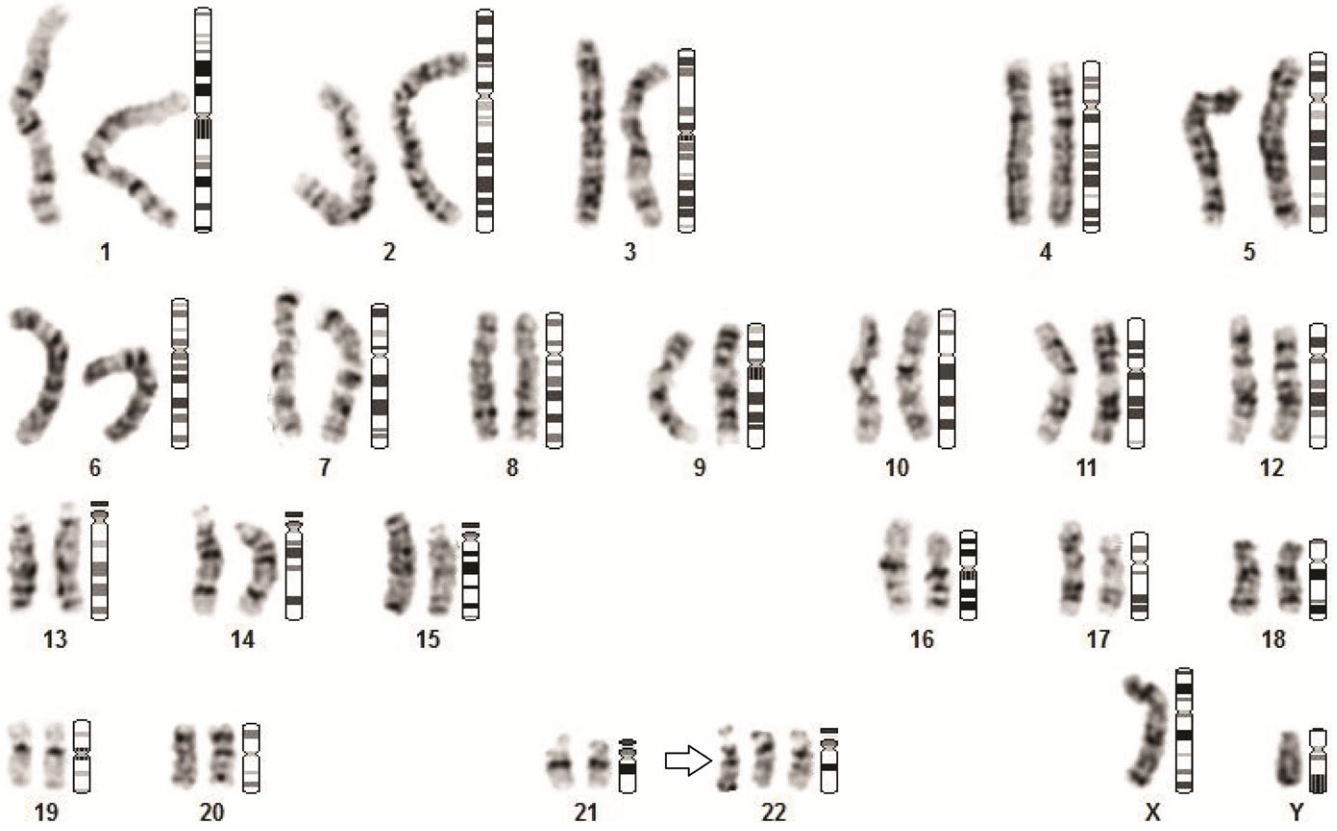

FIGURE 3 The karyotype indicating mosaic 47,XY,+22(6)/46,XY(44)

cause is a rare reason. However, it has been reported by Pater et al[19] that the maternal uniparental disomy has not any effect on patient features unless it happens in mosaic condition with a trisomy 22; in that time, the patient indicates some of the Turner syndrome characterizes. It is impossible to recognize the parental origin of the additional 22 in the patient without extragenetic investigation. The low-level mosaicism observed in our patient blood cells, with normal chromosome of the parents, resulting in concluding the postmeiotic nondisjunctional error occurred. When symptoms are present in the patient but the peripheral blood cells lacked mosaic trisomy 22, the evaluation of the tissue is necessary and important. In study of Abdelgadir et al[14] 30% of patients had blood lymphocytes mosaic karyotype while about 90% harbored skin mosaic karyotype. Furthermore, there are some publications reporting that mosaicism determined by blood cells is lower than tissue cells, that is, skin particularly.[18,20,21] In cases with low level of mosaicism, the FISH and molecular studies should be performed for confirmation.[22] As a limitation of our study, we were unable to survey any more mainly due to migration of this family to another remote place, but the present of more symptoms of the mosaic trisomy 22 in this patient can be a validation for our diagnosis.

In conclusion, chromosomal aneuploidy should be investigated in any child with multiple anomalies. Moreover, we think further tissue chromosomal evaluation in defined cases with normal blood karyotype is necessary. Regarding that some of mosaic trisomy 22 features are unavoidable such as CHD and general hypotrophy, we suggest including echocardiography test for early diagnosis during the clinical assessment. Moreover, these mosaic trisomy 22 indicative features may guide clinician to distinguish chromosomal mosaicism.

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