

A Rare Case of Double Trisomy Mosaicism: 47,XXX/47,XX,+8

Jae Hee Lee¹, Heung Sik Kim² and Jung Sook Ha^{1*}

¹Departments of Laboratory Medicine, ²Pediatrics, Keimyung University School of Medicine, Daegu, Korea

Double trisomy mosaicism of two different cell lines is extremely rare, particularly those that involve constitutional trisomy 8. We report a case of 47,XXX/47,XX,+8 in a 12-year-old female presenting with several skeletal anomalies. She exhibited distinct phenotypic features such as tall stature, deviation of the left middle finger, webbing of both thumbs and flexion deformities of the both third and fifth distal intermediate phalanges. A mild impulse-control disorder was observed, without mental retardation. Chromosomal and fluorescence in situ hybridization analysis demonstrated double trisomy mosaicism both on lymphocytes and buccal epithelial cells.

Key words: Double trisomy mosaicism, Trisomy 8, Trisomy X

Introduction

Constitutional trisomy 8 mosaicism (T8M) is a relatively common chromosomal abnormality with an estimated frequency of about 1:25,000 to 1:50,000 births.¹⁾ The phenotype of T8M exhibits marked variability including genitourinary abnormalities, multiple skeletal abnormalities, some congenital cardiovascular disorders, deep palmar and plantar creases, some solid neoplastic and hematological lesions, mental retardation, and intracranial abnormalities. The majority of the reported cases are mosaics with a normal cell line component.²⁾ Double mosaicism involving sex chromosome aneuploidy and trisomy 8 is an extremely rare event. To date, only seven cases of combinations of sex chromosome aneuploidy with trisomy 8 have been reported: two different cell lines (45,X/48,XXY,+8, 47,XXY/47,XY,+8, 48,XXYY/47,XY,+8, 45,X/47,XY,+8), three different cell lines (45,X/46,X,+8/47,XX,+8), and four different cell lines (45,X/46,XX/47,XXX/47,XX,+8).³⁻⁷⁾ We report a case of double trisomy, trisomy 8 and X, in a 12-year-old female with skeletal abnormalities and tall stature.

Case

A 12-year-old female presented at our hospital with a chief complaint of recurrent respiratory infections over the past six years. She was born to healthy, non-consanguineous parents at term by cesarean section at a local hospital. When she was born, the mother was 38 years old and the father was 38 years old. Her birth weight and height were not recorded. At presentation, she weighed 54 kg (75-90th centile) and was 169.2 cm (> 97th percentile) tall. She had several skeletal deformities including deviation of the left middle finger, webbing of both thumbs and bilateral flexion deformities of the third to fifth distal interphalangeal joints; deep furrowing of the palms or soles was not present (Fig. 1). Facial abnormalities such as hypertelorism, prominent low lip, dysmorphism of ears and nose, and cleft lip were not observed. The rest of physical examination revealed no abnormalities except above described features. A mild impulse-control problem was observed, but mental retardation was not

Received: 12 September 2013, Revised: 14 October 2013, Accepted: 11 November 2013, Published: 31 December 2013

*Corresponding author: Jung Sook Ha, M.D.

Department of Laboratory Medicine, Keimyung University School of Medicine 56 Dalseong-ro, Jung-gu, Daegu, Korea

Tel: +82-53-250-7266, Fax: +82-53-250-7275, E-mail : ksksmom@dsmc.or.kr

Conflict of interest: We declare that we do not have any conflicts of interests.

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

© Copyright 2013 by the Korean Society of Medical Genetics

www.e-kjgm.org

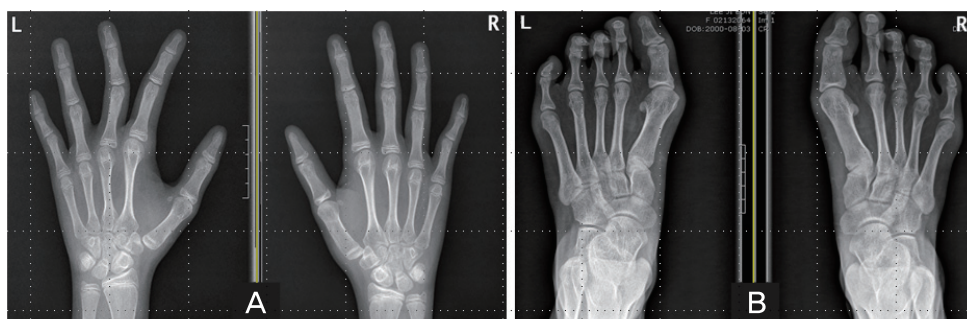


Fig. 1. The X-ray images of patient's both hands and feet 47,XXX/47,XX,+8. Her left hands show the deviation of left middle finger (A) and her feet show the flexion deformities of both 3-5th distal interphalangeal joints (B).

detected. Her menarche occurred at age 9 with subsequent regular menses. Her complete blood count (CBC), urinalysis, liver function tests, renal function and total IgG, IgA, IgM tests were within normal limits. Before undergoing cytogenetic study, written informed consent was obtained from patient's parents. A conventional cytogenetic analysis on peripheral lymphocytes demonstrated: 47,XXX[35]/47,XX,+8[15]. However, a normal 46,XX cell line was not detected. Fluorescence in situ hybridization (FISH) was performed on peripheral lymphocytes and epithelial cells obtained from a buccal swab, using the probes of X, Y, and CEP 8 (Abbott Laboratories, IL, USA) according to the manufacturer's instructions. The hybridization pattern in lymphocytes revealed that 51% of analyzed 500 interphase cells were trisomy X. The remaining 49% cells were trisomy 8 (Fig. 2). In the buccal epithelial cells, signal patterns of trisomy X and trisomy 8 in 500 interphase cells were 75% and 25%, respectively. None of the analyzed cells exhibited a normal signal pattern. Chromosomal analysis of both parents revealed normal karyotypes.

Discussion

Non-mosaic trisomy 8 is generally incompatible with life, but T8M is known to demonstrate extreme clinical variability, ranging from normal to extensive deformities such as facial dysmorphism (prominent forehead, large, inverted low lip, low-set, dysplastic ears, and a wide prominent nasal bridge), multiple skeletal and joint anomalies (contractures of the fingers and toes, vertebral anomalies, and absent or hypoplastic patellae), urogenital malformations, congenital heart defects, and agenesis of the corpus callosum.²⁾ The intelligence of patients with T8M is usually in the mild to moderate retarded range; however, normal intelligence has been reported in about 10% of cases.⁹⁾

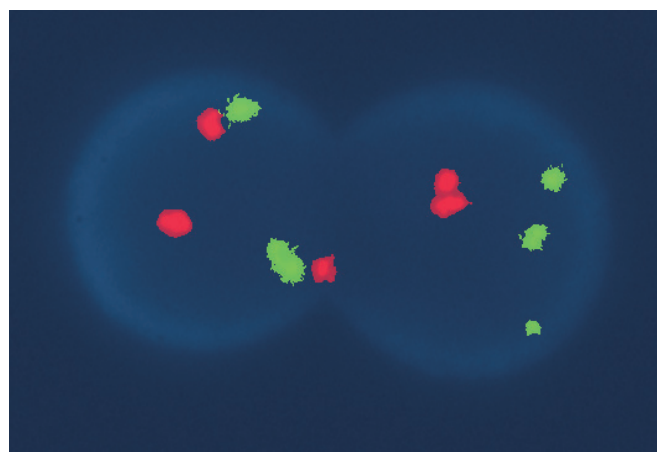


Fig. 2. Fluorescence in situ hybridization was performed using probes for chromosome X (CEP X, spectrum green) and chromosome 8 (CEP 8, spectrum orange). Two interphase cells show double trisomy mosaicism: the left cell displays disomy X and trisomy 8, and the right cell displays trisomy X and disomy 8.

Triple X syndrome has no significant facial dysmorphism or striking physical features however, minor physical findings can be present in some individuals tall stature, hypertelorism, clinodactyly and congenital heart and genitourinary anomalies.⁹⁾ Length and weight at birth is usually normal for gestational age, however, stature typically increases in early childhood, and by adolescence most girls with 47,XXX are at or above the 75th percentile for height.⁹⁾

The prominent phenotypic changes of our patient are skeletal abnormalities. But, other facial anomalies related to the characteristics of trisomy 8 were not observed. This mild phenotypic presentation might be due to the mixture of the 47,XXX cell line, because triple X is usually have milder phenotype than trisomy 8. Although this case had a higher proportion of 47,XXX than 47,XX,+8 cell line, the degree of mosaicism is not generally related to the phenotypic severity.²⁾ The tall stature of our case is a characteristic feature of triple X, and rare in trisomy 8. Therefore, our patient's phenotypic features might be affected by both

trisomy 8 and trisomy X. For the mild psychotic problem without mental retardation, close long-term follow up focused on identifying minor intellectual changes are indicated for this case.

For recurrent infection, few has been known about the relationship between immunity and T8M or triple X. Although a few reports mentioned the dysfunction of trisomic 8-positive natural killer cells and the correlation between T8M and hematologic disorders,¹⁰⁻¹⁴⁾ these opinions cannot be sufficient for immunocompromised status.

The mechanisms for the occurrence of aneuploidy in humans can be divided according to the stage of cell division, mitosis and meiosis. Nondisjunction leading to autosomal and sexual trisomies generally occurs during meiosis.^{15,16)} However, the etiology of T8M appears to differ from that of common autosomal trisomies. Karadima et al. performed a molecular study of 26 probands with trisomy 8/T8M and reported that 20 cases were probably due to postzygotic duplication.²⁾

Our case was a double trisomy, which consisted of two apparently unrelated aneuploid cell lines in the same individual. Based on previous reports, the most probable theory regarding double trisomy is two independent postzygotic nondisjunctions occurring in a normal 46,XX zygote. However, any normal 46,XX cells was not detected in this case. Therefore, it is highly possible that nondisjunction took place during early embryogenesis. Another theory may be considered, independent loss of chromosome X and 8 each in a 48,XXX,+8 as trisomic rescue. However, the latter mechanism is even rarer than that of the former.

To establish the origins of trisomic cells, molecular genetic analysis using DNA must be conducted. Unfortunately, we could not discover the origin of double trisomy 8 and X.

In conclusion, we report a case of constitutional 47,XXX/47,XX,+8 mosaicism showing distinct skeletal anomalies and tall stature. To understand the consequences of this double aneuploidy, further intense investigation is needed.

References

1. Wisniewska M, Mazurek M. Trisomy 8 mosaicism syndrome. *J Appl Genet* 2002;43:115-8.
2. Karadima G, Bugge M, Nicolaidis P, Vassilopoulos D, Avramopoulos D, Grigoriadou M, et al. Origin of nondisjunction in trisomy 8 and trisomy 8 mosaicism. *Eur J Hum Genet* 1998;6:432-8.
3. Gafter U, Shabtal F, Kahn Y, Halbrecht I, Djaldetti M. Aplastic anemia followed by leukemia in congenital trisomy 8 mosaicism. *Clin Genet* 1976;9:134-42.
4. Hoovers JM, Oorthuys JW, de Visser M. Mosaic 47,XY,+8/48,XXYY in a mentally non-retarded man with phenotypical and neurological abnormalities. *Clin Genet* 1989;35:446-9.
5. Schofield B, Babu A, Punaes-Morejon D, Popescu S, Leiter E, Franklin B, et al. Double mosaic aneuploidy: 45,X/47,XY,+8 in a male infant. *Am J Med Genet* 1992;44:7-10.
6. DeBrasi D, Genardi M, D'Agostino A, Calvieri F, Tozzi C, Varrone S, et al. Double autosomal/gonosomal mosaic aneuploidy: study of nondisjunction in two cases with trisomy of chromosome 8. *Hum Genet* 1995;95:519-25.
7. Cogulu O, Tirpan C, Ozkinay F, GunDuz C, Ozkinay C. The second case with 47,XY,+8[38]/45,X0. *Turk J Pediatr* 2002;44:86-9.
8. Baidas S, Chen TJ, Kolev V, Wong LJ, Imholt J, Qin N, et al. Constitutional trisomy 8 mosaicism due to meiosis II non-dysjunction in a phenotypically normal woman with hematologic abnormalities. *Am J Med Genet A* 2004;124A:383-7.
9. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. A review of trisomy X[47,XXX]. *Orphanet J Rare Dis* 2010;5:8.
10. Marti S, Galan FM, Casero JM, Merino J, Rubio G. Characterization of trisomic natural killer cell abnormalities in a patient with constitutional trisomy 8 mosaicism. *Pediatr Hematol Oncol* 2008;25:135-46.
11. Cornaglia-Ferraris P, Ghio R, Barabino A, Perlino GF, Maggio A, Parodi MT, et al. Diminished in vitro colony forming capacity of bone marrow cells in a case of chromosome 8 trisomy (mosaic): Criteria for "high risk" pre-leukemia syndrome. *Boll Ist Sieroter Milan* 1981;60:69-73.
12. Gafter U, Shabtal F, Kahn Y, Halbrecht I, Djaldetti M. Aplastic anemia followed by leukemia in congenital trisomy 8 mosaicism. Ultrastructural studies of polymorphonuclear cells in peripheral blood. *Clin Genet* 1976;9:134-42.
13. Heim S, Mitelman F. Numerical chromosome aberrations in human neoplasia. *Cancer Genet Cytogenet* 1986;22:99-108.
14. Seghezzi L, Maserati E, Minelli A, Dellavecchia C, Addis P, Locatelli F, et al. Constitutional trisomy 8 as first mutation in multistep carcinogenesis: clinical, cytogenetic, and molecular data on three cases. *Genes Chromosomes Cancer* 1996;17:94-101.
15. Pangalos C, Avramopoulos D, Blouin JL, Raoul O, deBlois MC, Prieur M, et al. Understanding the mechanism(s) of mosaic trisomy 21 by using DNA polymorphism analysis. *Am J Hum Genet* 1994;54:473-81.
16. Robinson WP, Binkert F, Bernasconi F, Lorda-Sanchez I, Werder EA, Schinzel AA. Molecular studies of chromosomal mosaicism: relative frequency of chromosome gain or loss and possible role of cell selection. *Am J Hum Genet* 1995;56:444-51.