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Low-Level Trisomy 14 Mosaicism: A Carrier of an Isochromosome 14 and a Supernumerary Marker Chromosome 14

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Established Facts

- Trisomy 14 mosaicism is a rare condition characterised by a variety of clinical features.

Novel Insights

- A rare mechanism of trisomy rescue events is proposed as a compensation for full trisomy 14.
- This is the first case of mosaic trisomy 14 with 2 abnormal cell lines, one involving a bisatellited marker.

Keywords
Abnormal skin pigmentation · Array-CGH · Marker · Mosaic trisomy 14 · Short stature

Abstract
Trisomy 14 (T14) mosaicism is a rare chromosomal condition characterised by various clinical features, including developmental delay, growth impairment, and dysmorphism. Here, we report on a 12-year-old female referred for cytogenetic analysis due to short stature. Standard GTG-banding analysis on the patient's peripheral blood revealed mosaic T14 in the form of an i(14)(q10) in 3% of cells. Furthermore, a small supernumerary marker chromosome (sSMC) had been detected in the first trimester of pregnancy in chorionic villus sampling. A skin biopsy in the patient revealed the presence of a metacentric sSMC in 100% of cells. Cytogenetic and FISH studies showed that it was a de novo metacentric bisatellited sSMC derived from chromosomes 14 or 22. Oligonucleotide array-CGH using skin cells revealed no copy number variations. Studies for uniparental disomy 14 by microsatellite analysis confirmed biparental inheritance. To the best of our

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knowledge, this is the second report of a patient with 2 abnormal cell lines involving chromosome 14 in different tissues, one with mosaic T14 in the form of i(14)(q10) and one with an sSMC derived from chromosome 14, present in blood and skin, respectively. A rare mechanism of trisomy rescue events is proposed to explain the presence of the different cell lines in the tissues examined. This case highlights the importance of providing the cytogenetics laboratory with adequate clinical data to test for low mosaicism and analyse different tissues if necessary, thus contributing to the suitable clinical management of the patient.

Introduction

Trisomy 14 (T14) mosaicism is a well-known but rare chromosomal condition with approximately 40 cases reported to date [Salas-Labadía et al., 2014; Mohamed et al., 2020]. The most common clinical features are growth and psychomotor deficiency, developmental delay, and dysmorphic features. Dysmorphic features include dysplastic and/or malpositioned ears, cleft or high-arched palate, large mouth, hypertelorism, broad nasal bridge, and short neck [Shinawi et al., 2008; Salas-Labadía et al., 2014; Rodrigues et al., 2016]. Moreover, congenital heart disease, genitourinary abnormalities, body asymmetry, and abnormal skin pigmentation have also been reported [Shinawi et al., 2008]. Less frequent manifestations are diaphragmatic hernia, omphalocele, and severe scoliosis. Prenatally, clinical findings include increased nuchal translucency, cardiac defects, prominent forehead, micrognathia, enlarged posterior fossa, and talipes calcaneovalgus [Chen et al., 2013; He et al., 2014; Eventov-Friedman et al., 2015].

Full non-mosaic T14 is lethal to the embryo and hence, only mosaic cases have been reported co-existing with a normal (or abnormal) cell line. The most common type of abnormal cell line resulting in T14 mosaicism is free trisomy, followed by an isochromosome 14q, a robertsonian or non-homologous reciprocal translocation involving chromosome 14, and a ring chromosome 14 [Salas-Labadía et al., 2014]. Furthermore, more than 30 cases of small supernumerary marker chromosomes (sSMC) originating from chromosome 14 have been reported [Salas-Labadía et al., 2014; Wannenmacher et al., 2016]. T14 mosaicism individuals present with a variety of clinical signs, which could be due to tissue distribution, the proportion of trisomic cells involved, and the parental origin. However, no correlation between the proportion of the trisomic cell line identified in the blood and the severity of the clinical phenotype has been established [Fujimoto et al., 1992; Shinawi et al., 2008].

Here, we report on a 12-year-old female with short stature, in whom the cytogenetic study revealed low-level T14 mosaicism caused by an i(14)(q10) in the blood and an sSMC derived from chromosome 14 in the skin. Her medical history revealed that her mother had undergone chorionic villus sampling after a high-risk result during first-trimester prenatal screening. A metacentric bisatellited sSMC was then detected in 100% and in 30% of the cells in the direct and culture preparations, respectively. The finding was not confirmed by amniocentesis. In order to correlate the prenatal and postnatal cytogenetic findings with the phenotype, detailed cytogenetic, FISH, chromosomal microarray (CMA), and uniparental disomy 14 (UPD14) analyses were carried out in the peripheral blood and skin of the patient. Buccal smear tissue for FISH studies was not available. To the best of our knowledge, this is the fourteenth case of T14 mosaicism due to an acrocentric rearrangement [Turleau et al., 1980; Jenkins et al., 1981; Ozawa et al., 1984; Pangalos et al., 1984; Fujimoto et al., 1985; Antonarakis et al., 1993; Tunca et al., 2000; Shinawi et al., 2008; Von Sneidern and Lacassie, 2008; Wannenmacher et al., 2016; Mohamed et al., 2020], the fifth case regarding T14 where 2 different abnormal cell lines are seen in the same patient [Pangalos et al., 1984; Tzoufi et al., 2007; Salas-Labadía et al., 2014; Mohamed et al., 2020], the second case in which the abnormal cell lines do not co-exist but are present in different tissues [Pangalos et al., 1984], and the first case in which the marker initially identified prenatally is of bisatellited origin.

The present case shows the importance of correct clinical information when referring patients for cytogenetic investigation, using combined cytogenetic and molecular testing in making genotype-phenotype correlations, and the importance of having the result of prenatal cytogenetic studies that allows to suspect the presence of tissue-restricted mosaicism.

Case Report

The patient was first seen at the Paediatric Endocrine Unit at the age of 9 years 8 months due to her short stature. She was born to a 33-year-old G2P0 healthy mother and a 45-year-old healthy father, nonconsanguineous, with unremarkable family history, by caesarean section at 38 weeks of gestation with a birth weight of 3,370 g, length of 51 cm, and a head circumference of 34 cm. The patient walked at the age of 12 months and talked at 18 months. Her medi-

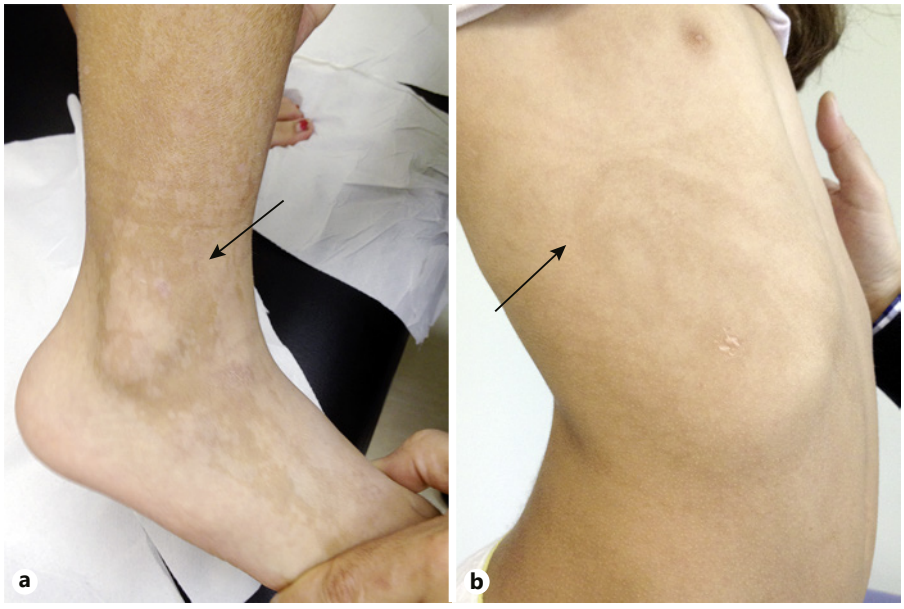

Fig. 1. Patient at 12 years, showing skin hyperpigmentation (arrows). **a** Skin hyperpigmentation of reticular and marble patterns on the right ankle and leg. **b** "S-shaped" Blaschko lines, exhibiting hyperpigmentation on the thoracic region.

cal history was remarkable for strabismus and frequent episodes of otitis media. She had a mild developmental delay with learning disabilities especially in mathematics whereas she was better at language and spelling. The clinical examination revealed a height of 120.5 cm (−2.5 SD for the WHO growth curves), while her target height was 160 cm (−0.5 SD), and a weight of 20.5 kg. Her bone age was 7.5 years, delayed by 2.17 years. She was prepubertal, with strabismus, low-set posteriorly rotated ears with increased anteroposterior distance, high-arched palate, large mouth, micrognathia, slightly webbed neck, small chest, and body asymmetry. Physical examination was remarkable for hyperpigmented lesions on her chest, abdomen, and legs. The lesion started by the end of the upper third of her chest down to her abdominal wall not crossing the middle line. She also had hyperpigmented lesions on her right gluteal region, thigh, outer surface of her tibia, and foot. Similar hyperpigmented areas were noticed on her left leg, especially on her foot (Fig. 1). A laboratory work-up of biochemistry, complete blood count, transglutaminase antibodies, thyroid function tests, cortisol, prolactin, and IGF-I was normal. A cytogenetic investigation was requested initially because of her short stature. Following the cytogenetic findings of low-level T14 mosaicism caused by an i(14q), a brain MRI, a renal and heart ultrasound, and an audiologic evaluation were normal. The patient was followed up to the age of 12 years. She had grown at the same SD (−2.5 SD) and was prepubertal.

Materials and Methods

Cytogenetic Analysis

Chromosome analysis of stimulated peripheral blood T-lymphocytes was performed by GTG-banding analysis using standard cytogenetic laboratory procedures. A 30-cell screen was initially performed to exclude sex chromosome mosaicism due to the patient's short stature. An abnormal cytogenetic finding in the first 30 cells analysed led to a total of 200 metaphases screened.

A fresh skin biopsy was obtained from the dark pigmented area of the right abdomen, and cytogenetic studies were carried out in skin fibroblast cultures. The cytogenetic investigation was performed in the same laboratory that had analysed the prenatal chorionic villus sample in the patient's mother. Conventional cytogenetic techniques were used for culturing skin fibroblasts. Chromosome analysis was carried out after GTG-banding on chromosomes from cultured skin fibroblasts. A total of 100 metaphases were analysed from 2 different cultures. CBG-banding and AgNOR-staining were performed to investigate the nature of the sSMC. The karyotype description was done according to ISCN [2016].

Parental blood chromosome testing was also performed using standard cytogenetic laboratory procedures.

FISH Analysis

FISH on cultured fibroblast metaphases allowed the investigation of the chromosomal origin of the sSMC detected in the skin. FISH analysis was performed on 100 cells using commercially available centromeric probes specific for acrocentric chromosomes 15 (Vysis, Abbott), 13/21 (Cytocell), and 14/22 (Cytocell). All FISH procedures followed the manufacturer's standard protocol.

Array-CGH

Array-CGH analysis aimed to delineate the sSMC's size and its gene content. DNA extracted from the skin biopsy was used, and analysis was performed using Cytochip Oligo 2 × 105K (Illumina, CA, USA). The array was scanned on a DNA Microarray Scanner (Agilent, CA, USA). Data were interpreted with BlueFuse Multi software (Illumina). All genomic coordinates were based on hg19/GRCh37.

UPD Studies by Microsatellite Analysis

QIAamp DNA Blood Mini Kit (QIAGEN) was used for DNA extraction from the patient's and her parents' peripheral blood.

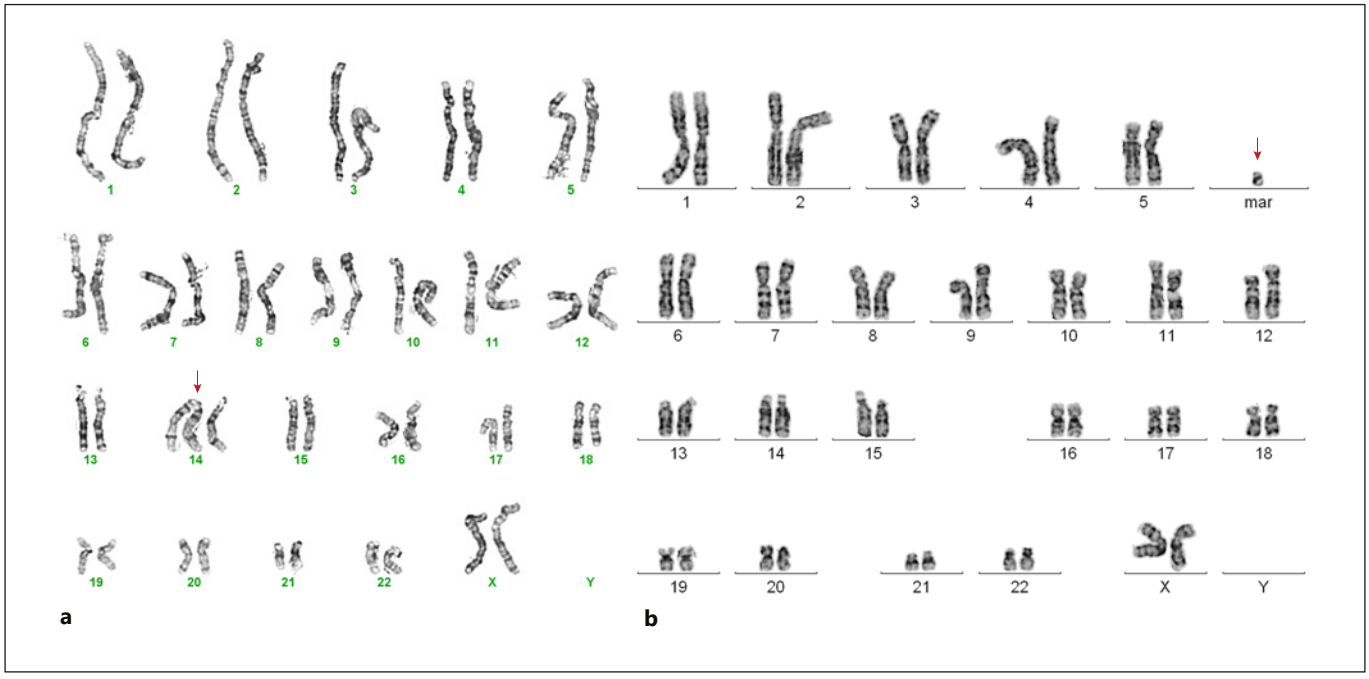

Fig. 2. Representative karyotypes of the patient. **a** 46,XX,i(14)(q10) from peripheral blood; **b** 47,XX,+mar from trophoblast cells, after chorionic villus sampling performed prenatally. The red arrows depict the isochromosome 14q (**a**) and the marker chromosome (**b**).

Seven microsatellite DNA polymorphisms due to either dinucleotide or tetranucleotide repeats from human chromosome 14 were detected by PCR amplification of genomic DNA [Dib et al., 1996]. These were in: D14S80 located in 14q12, D14S288 in 14q21.2, D14S43 and D14S53 in 14q24.3, D14S48 and D14S68 in 14q31.3, and D14S51 in 14q32.2.

Results

Cytogenetic analysis of peripheral blood showed a mosaic karyotype with 2 cell lines, mos 46,XX,i(14)(q10)[6]/46,XX[194], revealing a very low mosaic percentage of T14 (3%) (Fig. 2a). The karyotypes of the parents were 46,XX[100] and 46,XY[100] with no apparent chromosomal abnormalities.

Cytogenetic analysis of the skin fibroblasts revealed the presence of a metacentric bisatellited sSMC in all cells examined (47,XX,+mar). The morphology of the sSMC was compared to the sSMC seen prenatally in the same cytogenetic laboratory and was found to be the same. The prenatal cytogenetic investigation (Fig. 2b) had shown 30% mosaicism for the sSMC in the chorionic villus culture, but it was detected in all metaphases examined in the direct preparation. Other cytogenetic investigations in the fibroblasts included CBG-banding and AgNOR-staining, which confirmed the acrocentric origin of the sSMC.

FISH analysis in fibroblast cells using a probe specific for chromosomes 14/22 pericentromeric regions showed a positive fluorescence signal on the sSMC, suggestive of the chromosomal origin of the sSMC.

Normal array-CGH results in skin cells, despite the relatively large size of the marker and its ubiquitous presence in skin cells, suggested that the marker contained only heterochromatic material which is not detectable by CMA.

Microsatellite analysis of 7 chromosome 14 loci demonstrated inheritance of both maternal and paternal alleles along the length of chromosome 14 for all informative markers, indicating biparental inheritance.

Discussion

Our patient, a 12-year-old female, demonstrated clinical signs comparable to T14 mosaicism cases previously reported, including body asymmetry, developmental delay, and abnormal skin pigmentation [Shinawi et al., 2008; Salas-Labadía et al., 2014]. Postnatal peripheral

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blood samples from the patient showed very low mosaicism (3%) for T14 in the form of an i(14)(q10) (Fig. 2a). Her medical history revealed an sSMC which had been detected in chorionic villus samples in both direct and culture preparations, but had remained uncharacterised prenatally and not been confirmed by amniocentesis (Fig. 2b). Skin biopsy revealed an sSMC of chromosome 14 origin in all cells examined. CMA studies in the skin cells were normal, indicating that the marker contains no euchromatic chromosomal material, and UPD14 studies in the blood showed biparental inheritance.

Several mechanisms could explain the absence of the trisomic cell line from the patient's prenatal sample and skin biopsy, in conjunction with the absence of the sSMC from the peripheral blood. One possible mechanism involves a free-T14 zygote undergoing a T14 rescue event through transversal centromere division and isochromosome formation. This would lead to the formation of 2 cell lines; cell line A with 47 chromosomes with a supernumerary 14p isochromosome (sSMC), and cell line B with 47 chromosomes and 14q tetrasomy through the 14q isochromosome. Cell line A is the one observed prenatally in the trophoblast cells, in the skin, and probably in other tissues as well. Tetrasomy 14q in cell line B would hinder the survival of this cell, unless it went through a second rescue event, an anaphase lag. Consequently, a chromatid of chromosome 14 is eliminated in one daughter cell and a chromatid of i(14q) in the other. Through this "double anaphase lag" process cell line B would give rise to the normal 46,XX cells and the T14 cells observed in the patient. The selective advantage of the normal cell line would explain its relatively high frequency compared to the T14 cell line. This mechanism could explain why no cell line is detected with the 2 isochromosomes present in the same cell. The fact that our patient presents with clinical findings in multiple systems suggests that the rescue events occurred before the formation of the 3 germ layers (ectoderm, mesoderm, and endoderm). The presence of the sSMC in the trophoblast cells indicates that the rescue events must have occurred during the first cell divisions of the zygote.

Although the proposed mechanism explains the presence of the cell lines detected in the tissues examined, other possible mechanisms exist that might involve several trisomy rescue events or more complex karyotypes, both generating cell lines with karyotypes not seen in our case.

The initial paediatric referral of the patient was only due to short stature, and a standard 30-cell screen count was performed in order to exclude sex chromosome rearrangements. The presence of low-level T14 mosaicism could have easily been dismissed in the blood if an adequate number of metaphases had not been analysed in the initial culture. This prompted phenotype and clinical reassessment, revealed the prenatal findings, and suggested an autosomal rearrangement. In somatic cell mosaicism, peripheral blood analysis may not be sufficient or decisive, and chromosome analysis of cultured skin fibroblasts (light and dark areas) or other tissues is important for diagnosis [Pagon et al., 1979]. Aneuploid cells may either be under-represented in the peripheral blood or not respond well to mitotic stimuli. They may also decrease with age. Even in the skin tissue, aneuploid cells may not be seen if the specific biopsy contains only normal cells, or if there is a selection bias against them during tissue culture [Papavassiliou et al., 2009]. Thus, some cases of chromosomal mosaicism may present with a normal blood chromosome complement. This highlights the importance of a detailed clinical history.

Pigmentary anomalies are a frequent feature in T14 mosaicism and a common finding in individuals with any mosaic chromosomal abnormality, with hyperpigmentation usually appearing in adulthood, 6 months being the youngest age reported [Dallapiccola et al., 1984; Iglesias et al., 1997]. In our case, the presence of the 46,XX and the T14 cell lines in the skin cannot be ruled out considering that the sSMC does not contain important genetic material that could affect the patient's skin pigmentation. A second biopsy from the non-pigmented area could not be obtained from the patient, and this may constitute a limitation to our investigation.

Mild body asymmetry observed in our patient is also an indication of genetic mosaicism [Witters et al., 2004]. Other affected systems observed in cases with pigmentary mosaicism include the central nervous, musculoskeletal, and the ocular systems [Salas-Labadía et al., 2019]. Our patient presented with mild developmental delay and learning disabilities, scoliosis, and strabismus. Therefore, a multidisciplinary clinical approach is essential. Furthermore, the distal 14q region (14q11.2–14q22) is thought to be critical [Liehr, 2019], and genes involved in cardiomyopathy, neural deafness, and retinal degeneration are present in 14q11.2 [Salas-Labadía et al., 2014]. None of these clinical features were seen in our patient. Therefore, we hypothesise that the low-level T14 in the patient's blood might have contributed to some extent to her mild phenotype. Although different publications point to a specific "T14 mosaic syndrome," our case supports the idea of a "general chromosomal mosaic syndrome," as suggested by Von Sneidern and Lacassie [2008]. However, it is important to consider a multidisciplinary clinical

approach when a genotype-phenotype correlation is to be made.

In our case, CMA in skin fibroblasts did not show any gain of material, indicating that the sSMC consisted mostly of heterochromatin and satellite DNA. There are numerous reports in which new diagnostic technology helps reveal chromosome abnormalities that would be missed using time-consuming conventional cytogenetics, providing a more accurate estimate for the level of mosaicism [Cheung et al., 1988; Mitter et al., 2006; Eventov-Friedman et al., 2015; Hochstenbach et al., 2019]. However, had this case been prenatally analysed using CMA, the sSMC would have remained undetected, and in the scenario of UPD, an incomplete diagnosis would have been offered. Overall, when the phenotype is suggestive of a genetic aetiology, even though the technology used might not detect an abnormality, one should "zoom out" and look at the chromosomes [Pasquier et al., 2016].

This rare case of chromosome and tissue mosaicism, although not the first one to be reported, emphasises that diagnosis of chromosome mosaicism can be difficult (or fortuitous) depending on how mild the clinical features are. In cases of tissue mosaicism, cytogenetic analysis is still the gold-standard. Indeed, if we had not detected one abnormal cell in the first 30-cell count, the initial referral for short stature would not have prompted for further clinical and cytogenetic investigations. It is important to point out that a medical history of prenatal testing is essential in such cases; should this case have been handled in a different way, the patient would have been referred at an earlier age for the sSMC seen prenatally. The broad range of phenotypic findings, including developmental delay, pigment alterations, and body asymmetry, should alert detailed cytogenetic and molecular investigations in different tissues. This would contribute towards a diagnosis and enable accurate genetic counselling for the family.

Acknowledgement

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Statement of Ethics

Written informed consent was obtained from the parents of the patient for genetic testing and publication of her clinical pictures. Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

V.V., L.F., F.S., S.C.: design of the study, data acquisition, analysis, and interpretation. T.L.: analysis and interpretation of data, critical revision of important intellectual content. D.C., A.E.: acquisition and interpretation of data. E.A.: drafting the article, and critically revising intellectual content. E.G.S.: conception and design of the study, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. All authors read and approved the final manuscript.

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