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CASE REPORT

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Turner syndrome due to Xp22.33 deletion with preserved gonadal function: case report

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Abstract

Turner syndrome (TS) is a chromosomal condition affecting 1 in 2000 females characterized by partial or complete loss of one of the X chromosomes. We describe an 11-year-old female who was recently diagnosed with TS. Karyotype revealed a deletion of the distal portion of chromosome X. Chromosome single nucleotide polymorphism (SNP) array revealed microdeletion of Xp22.33p22.12. Patient reached her menarche at age 11 years. Both the patient and her mother have short stature. Her mother, however, has a normal karyotype. This is one of few case reports of TS with microdeletion of Xp22.33 reported in the literature, with normal ovarian function and possible future transmission of the deletion to the next generations.

INTRODUCTION

Turner syndrome (TS) is a chromosomal condition affecting 1 in 2000 females characterized by partial or complete deletion of one of the X chromosomes [1]. About 50% of affected cases are monosomic for X chromosome (45,X) and tend to present with short stature/skeletal changes, a webbed neck, cardiovascular and renal abnormalities, gonadal dysgenesis and/or ovarian failure. For mosaic TS, the variability of the phenotype depends on the degree of mosaicism. Patients may experience normal pubertal development and can conceive spontaneously [2,3]. Females with partial X monosomy have variable phenotypes, but limited number of reports have described pregnancies and ovarian function for these individuals. Patients found to have deletions of the short arm of the X chromosome (Xp deletions) present with short stature, with or without other somatic traits common to TS. Due to preservation of fertility, mother-to-daughter transmission of terminal Xp deletion TS is possible and is considered to be familial TS [4,5]. Our patient presents with Xp deletion beyond Xp22.33. This Xp deletion has been reported once previously in the literature [4].

CASE REPORT

An 11-year, 9-month-old Hispanic female was referred to our endocrine–genetic clinic for evaluation of short stature. She was born to a healthy 21-year-old female. Pregnancy was complicated by decreased fetal movement; delivery was induced at 33 weeks of gestation with a birth weight of 2.27 kg (83rd percentile; Z-score, 0.94). Family history was unremarkable. Mother is 143.8 cm tall, and father is 165 cm, giving our patient a corrected mid-parental height of 148 cm, which is below the 3rd percentile (Z-score, −1.9).

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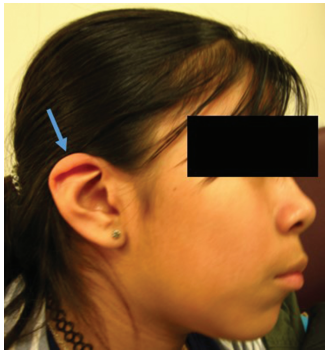

Figure 1: Lateral view of the face, showing underdeveloped auricle.

The patient measured 136.5 cm tall (5th percentile; Z-score, −1.6) and weighed 41.2 kg (50th percentile, Z-score, 0.15). She had pubarche and thelarche approximately at age 10, and she reached her menarche at 11 years. She has had regular menses. On physical exam, facial features included abnormally large and deformed ears with underdeveloped auricles (Fig. 1). Her oropharynx had an intact palate and had overlapped, malformed teeth. Low posterior hairline, mildly flexible joints and pes planus was noted. Breast and genitalia exam was compatible with Tanner stage III.

The patient was seen by cardiology team, had an echocardiogram (ECHO) done and no cardiovascular or respiratory abnormalities were noted.

Chromosome SNP array revealed a deletion of the distal portion of one X chromosome (46, X,del(X)p) (Fig. 2). Thyroid profile, IGF-1 and electrolytes were all normal. LH 2.7 mIU/ml (ranges by lab follicular phase, 2.1–10.9 mIU/ml; luteal phase, 1.2–12.9 mIU/ml), FSH 1.9 mIU/ml (ranges by lab follicular phase, 3.4–10.0 mIU/ml; luteal phase, 1.9–5.1 mIU/ml) were also normal. Her bone age described ~14 years versus chronological age of 12 years and 5 months. X-ray of the hand showed foreshortening of the fourth and borderline length of the fifth metacarpal bones with positive metacarpal sign for TS, with no associated Madelung deformity (Fig. 3). Renal ultrasound and ECHO were performed and found to be normal. A chromosome SNP array revealed a copy loss of 21.26 Mb on Xp 22.33p22.12 encompassing 253 genes. Due to short stature, a karyotype was performed on the patient's mother and was normal.

DISCUSSION

Our case describes a rare Xp deletion (Xp 22.33p22.12), found only in one previous case of familial TS. Similar to our case, Cho *et al.* [4] described a patient with short stature and shortening of the fourth/borderline fifth metacarpal bone in the hands. Lachlan *et al.* [5] reported a *de novo* case of Xp22.33p22.12 of a 16-year-old female with height in the 0.4th percentile, cubitus valgus, menarche at age 12.5 years, pigmented nevi and autism. Schwinger *et al.* [6] described a *de novo* terminal deletion of Xp, with breakpoint of Xp22.32 in a mother and daughter associated just with short stature and preserved fertility. Puusepp *et al.* [7] described a case of 16-year-old girl with short stature, normal puberty and epilepsy, found to have deletion of the distal part of Xp22.33 (including homeobox gene) and duplication of Xp22.12-p22.32, which is slightly similar to the mutation of our patient.

There are multiple chromosome abnormalities associated to TS, including, but not limited to 45,X (monosomic), mosaicism as 45,X/46,X + ring, 45,X/46,XX/47,XXX, 46X,Xq (interstitial long-arm deletions) and 46,X,Xp(short arm deletion) [8]. The prevalence of Xp deletion among TS patients has been reported to be ~2% [4]. Patients with partial Xp deletion have variable phenotypes including short stature and generally preserved ovarian function along with some other somatic features of TS. The short stature and skeletal features can be explained by a loss of function (haploinsufficiency) of the homeobox gene, *SHOX* gene in the pseudoautosomal region of Xp [8]. Uniquely, terminal Xp deletions can be inherited. It is thought that the genes located in the Xp are spared from the process of inactivation seen in girls with normal karyotype 46,XX since they are in an encoding region called pseudoautosomal region 1 and that is why the loss of one of the genes can have clinical importance [9]. Since ovarian function is preserved, the vertical transmission of this defect is possible.

Once the diagnosis of TS was made, the family had questions about the use of growth hormone (GH) to improve final height. GH is used to improve the final height of patients with TS. Park *et al.* [10] reported in their study of recombinant human GH therapy effect in linear growth in girls with TS showed greatest benefits when therapy started at a younger age and in the first year of treatment initiation. Stoklasova *et al.* [11] reported a family where six fertile women were affected in four sequential generations, presenting with short stature with mesomelic shortening of the limbs and no other typical findings of TS, with a karyotype with a combination of terminal Xp deletion and terminal Xq duplication: 46,X,rec(X)inv(p21.1q27.3). One was treated with GH with subsequent worsening of the body proportions. It was hypothesized that endogenous estrogen production and GH therapy promoted trunk growth, enhancing the disproportion. Estrogen's action at the growth plate may exacerbate the effects of *SHOX* haploinsufficiency, manifested as short stature and skeletal deformities. Based on her bone age, our patient was no longer growing and therefore was not a candidate for GH.

Regarding ovarian function, as of now, no evidence of premature ovarian failure exists in patients with Xp deletion. A previous study of a patient with the same Xp deletion reported that mother had normal ovarian function at the age of 37 years [4]. Stoklasova *et al.* [11] reported no premature ovarian failure in their subjects, with a subject reaching menopause at 50.3 years of age. Knowing that Xp deletion is seen in hereditary TS, it is recommended that mothers of girls found to have Xp deletions should be tested [11]. The mother of our patient was found to have a normal karyotype.

Our case presents a girl with a *de novo* Xp deletion having short stature and normal puberty.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

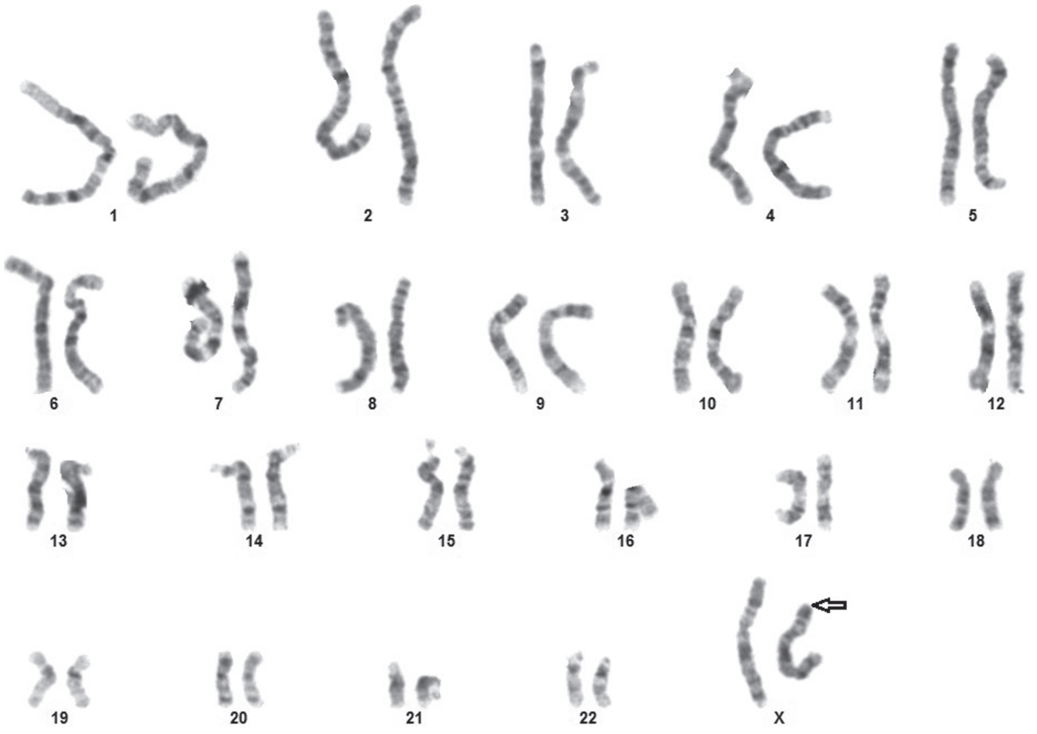

Figure 2: Patient's karyogram demonstrates large piece of short arm of the X chromosome missing (black arrow).

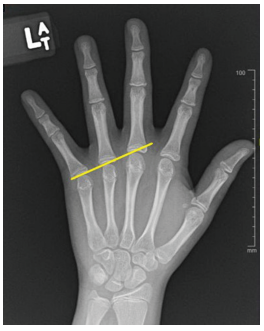

Figure 3: Radiograph showing foreshortening of the fourth metacarpal with positive metacarpal sign (yellow line).

FUNDING

No funding was secured for this study.

ETHICAL APPROVAL

No ethical approval required.

CONSENT

The patient/parent has given written consent for publication of this case report.

GUARANTOR

Zohra Shad.

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