Spontaneous puberty in an adolescent girl with a combined structural anomaly of the X chromosome

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Abstract

Structural anomalies of the X chromosome represent a significant cause of reproductive dysfunction and primary amenorrhea. The coexistence of large-scale deletion and duplication within the same X chromosome is rare and associated with marked clinical variability. In this context, spontaneous pubertal development represents an unusual and rarely reported finding. Advances in cytogenetic and molecular techniques, particularly chromosomal microarray analysis, have improved the detection of combined of chromosomal rearrangements and are essential for accurate diagnosis.

Case Presentation

We report a 16-year-old adolescent girl presenting with primary amenorrhea and spontaneous but incomplete pubertal development. Physical examination revealed height 152 cm, with minor dysmorphic features, including a low posterior hairline and high-arched palate. Tanner staging corresponded to B4P4Ax3Me0, with normal female external genitalia. Hormonal evaluation demonstrated hypergonadotropic hypogonadism with elevated FSH and LH and low estradiol levels. Pelvic ultrasound revealed a hypoplastic uterus and small ovaries without visible follicles. Cytogenetic analysis identified a structural anomaly of the X chromosome (46,X,del(X)(q21)). Chromosomal microarray analysis confirmed a combined rearrangement consisting of a heterozygous ~70 Mb deletion at Xq21.2–q28 and a heterozygous ~51 Mb duplication at Xp22.33–p11.2. Despite the presence of a terminal Xq deletion, height delay was not observed, as the patient's stature was consistent with familial height.

Conclusion

This case highlights the importance of integrated cytogenetic and molecular analysis in patients with DSD. Combined X chromosome copy number variations can result in diverse clinical phenotypes, requiring careful genetic counseling, evaluation of X chromosome inactivation, and multidisciplinary management. Early diagnosis and comprehensive care may improve outcomes, while ongoing advances in genetic research will further refine understanding and guide targeted diagnostic strategies.
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Keywords: Differences in Sex Development (DSD); X Chromosome Anomalies; Xq Deletion; Xp Duplication; Primary Amenorrhea; Spontaneous Puberty.

Introduction

Differences in sex development (DSD) are defined as congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. The estimated incidence is approximately 1 in 4,500–5,500 live births [1,2].

Anomalies of the X chromosome, including both numerical and structural alterations, represent a major genetic cause of reproductive dysfunction and are frequently identified in individuals presenting with gonadal dysgenesis and impaired ovarian development [3,4,5].

At the biological level, the X chromosome plays a critical role in ovarian function and somatic growth. Structural alterations may disrupt key genomic regions involved in ovarian development, including loci associated with premature ovarian insufficiency (POI), leading to impaired folliculogenesis, accelerated oocyte depletion, and gonadal dysfunction [5,6,7,8]. As a result, affected individuals may present with a spectrum of reproductive anomalies, including delayed or incomplete pubertal development, primary or secondary amenorrhea and early loss of ovarian function [9,10].

Importantly, the clinical variability observed in individuals with X chromosome anomalies reflects the underlying heterogeneity of genetic alterations, including differences in type (e.g., deletions, duplications, or complex rearrangements), genomic location, and extent of chromosomal imbalance. These factors influence gene dosage, disrupt critical loci involved in ovarian development, and are further modulated by variability in X chromosome inactivation, collectively contributing to the wide spectrum of phenotypic presentations [10,11,12,13].

Advances in cytogenetic and molecular genetic techniques have significantly improved the detection and characterization of X chromosome anomalies. The appli-

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cation of high-resolution karyotyping, fluorescence in situ hybridization (FISH), and chromosomal microarray analysis (CMA) has enabled the identification of complex and previously unrecognized structural rearrangements and mosaic patterns. These methodological advances have been instrumental in elucidating atypical clinical presentations and refining genotype–phenotype correlations [10,14,15,16].

This genetic and cytogenetic heterogeneity is reflected in the diversity of karyotypic patterns observed in affected individuals. Monosomy X (45,X) accounts for approximately 40–50% of cases, while Turner syndrome variants include mosaic and structural anomalies of the X chromosome. Mosaic karyotypes such as 45,X/46,XX are observed in approximately 15–25% of cases, whereas 45,X/47,XXX or 45,X/46,XX/47,XXX karyotypes occur in approximately 3%. Structural anomalies of the X chromosome, including isochromosomes (e.g., 46,X,i(Xq)) and isodicentric chromosomes (e.g., 46,X,idic(Xp)), account for approximately 15%, while ring X chromosomes (45,X/46,X,r(X)) and terminal deletions of the short arm (e.g., 46,XX,del(Xp11)) are relatively rare [17,18].

Combined structural anomalies of the X chromosome, characterized by the coexistence of deletions and duplications involving different chromosomal regions, are rare and associated with marked clinical heterogeneity. While similar rearrangements have been reported, the coexistence of extensive Xq deletion and Xp duplication within a single karyotype is exceptionally uncommon, and to our knowledge, cases with identical breakpoints have not been previously described [19,20,21]. Therefore, detailed characterization of such cases is essential for advancing understanding of their genetic and clinical implications

Case report

A 16-year-old patient was admitted for evaluation of primary amenorrhea. The patient exhibited spontaneous but incomplete pubertal development. Her height was 152 cm, weight 52 kg, and body mass index (BMI) 22 kg/m². The father's height was 160 cm and the mother's 154 cm. Physical examination revealed a low posterior hairline and a high-arched palate.

Sexual development according to Tanner staging corresponded to B4P4Ax3Me0. Pubic hair distribution was of the female type. External genitalia were normally developed, with no signs of virilization; the clitoris was not enlarged, and the labia majora and minora were normally developed (Fig.1).

Hormonal evaluation revealed elevated gonadotropin levels: follicle-stimulating hormone (FSH) 37.6 mIU/mL (reference range: 3.2–15.0 mIU/mL) and luteinizing hormone (LH) 22.5 mIU/mL (reference range: 0.8–10.0 mIU/mL), with low estradiol (E2) at 11.8 pg/mL (reference range: 28–178 pg/mL). Prolactin (PRL) was 16.3 IU/L (reference range: 4.79–23.30 IU/L), thyroid-stimulating hormone (TSH) 1.9 mIU/mL (reference range: 0.27–4.20 mIU/mL), and the HOMA index was 3.0 (reference value: ≤2.5).

Pelvic ultrasound examination demonstrated a hypoplastic uterus measuring 24 × 10 × 23 mm, with a volume of 2.8 cm³ and a body-to-cervix ratio of 1:1. The endometrial thickness was 1.4 mm. The right ovary measured 18 × 10 × 11 mm (volume 0.5 cm³), and the left ovary measured 20 × 10 × 12 mm (volume 1.2 cm³). No follicles were visualized in the ovaries.

Breast ultrasound examination revealed no anomalies of the skin, subcutaneous tissue, or retromammary space. The glandular component was poorly developed and predominantly localized in the periareolar region, with a predominance of adipose tissue in both breasts.

Cytogenetic analysis demonstrated a female karyotype with a structural anomaly of the X chromosome: 46,X,del (X)(q21), indicating deletion of the long arm of the X chromosome. For further characterization, chromosomal microarray analysis (CMA) was performed, confirming a combined structural anomaly consisting of a heterozygous ~70 Mb deletion at Xq21.2-q28 and a heterozygous ~51 Mb duplication at Xp22.33-p11.2. (Fig.2)

Results and discussion

Large-scale copy number variations involving both arms of the X chromosome are rare but clinically significant. In the present case, chromosomal microarray analysis identified a combined structural rearrangement consisting of a ~70 Mb deletion at Xq21.2-q28 and a ~51 Mb duplication at Xp22.33-p11.2. This combination results in partial monosomy of the long arm and partial trisomy of the short arm of the X chromosome, leading to substantial gene dosage imbalance [6,22,23].

The Xq21.2-q28 deletion encompasses multiple dosage-sensitive genes, including MECP2, FMR1, IDS, and loci associated with premature ovarian insufficiency (POI). Alterations in this region have been linked to neurodevelopmental disorders, metabolic conditions, and, importantly, gonadal dysfunction[6,7,8,21,24]. In females, phenotypic expression is often modulated by X chromosome inactivation; however, skewed inactivation or escape from inactivation may result in clinically significant manifestations. In the present case, the endocrine profile characterized by elevated gonadotropins and low estradiol is consistent with hypergonadotropic hypogonadism and supports the role of the Xq deletion in impaired ovarian function[21,24]. Structural anomalies of the X chromosome, including large deletions of the long arm, are increasingly recognized as Turner syndrome variants, based on phenotypic features and the functional consequences of X chromosome haploinsufficiency [1,2]. In this context, the present case may be considered a Turner syndrome variant, given the presence of gonadal dysfunction and associated phenotypic findings.

The duplication at Xp22.33–p11.2 includes genes such as SHOX, STS, and NLGN4X, which are involved in growth regulation, steroid metabolism, and neurodevelopment. Variations in SHOX dosage are known to influence linear growth, while NLGN4X has been associated with neurodevelopmental variability [6,25,26]. Although duplications of this region are less extensively characterized than deletions, they may exert modifying effects on the clinical phenotype through altered gene dosage[27,28,29].

The coexistence of a large terminal Xq deletion and a

substantial Xp duplication represents a rare and complex chromosomal rearrangement, likely resulting from an unbalanced structural event. Previous studies have shown that combined copy number variations affecting both arms of the X chromosome are associated with marked phenotypic heterogeneity, influenced by gene content, extent of chromosomal imbalance, and patterns of X chromosome inactivation[6,22,30].

In the present case, despite the presence of a terminal Xq deletion, which is typically associated with growth retardation, height delay cannot be considered, as the patient's stature is consistent with familial height, given that both parents are of short stature. The concomitant duplication of the Xp22.33–p11.2 region, including the SHOX gene, may have contributed to the relatively preserved growth pattern[25,26,27].

A particularly notable feature of this case is the presence of spontaneous pubertal development despite significant structural anomalies of the X chromosome. Deletions involving the Xq region are generally associated with gonadal dysgenesis and absent or incomplete puberty. However, the observed partial pubertal development suggests residual ovarian function, which appears insufficient to support complete pubertal progression and the onset of menarche [6,7,8,21]. This may be explained by variability in X chromosome inactivation, partial preservation of functional ovarian tissue, or compensatory effects of the duplicated Xp region.

Overall, this case highlights the complexity of genotype–phenotype correlations in X chromosome anomalies. The combination of opposing genomic imbalances, including loss of genetic material from the long arm and gain of material from the short arm, may result in a partially compensated phenotype, leading to atypical clinical presentations [6,8,10,11].

In conclusion, this case highlights the importance of integrated cytogenetic and molecular analysis in patients with DSD. Combined X chromosome copy number variations can result in diverse clinical phenotypes, requiring careful genetic counseling, evaluation of X chromosome inactivation, and multidisciplinary management. Early diagnosis, comprehensive medical care, and appropriate long-term support may help mitigate the impact of these genetic imbalances, improving quality of life and developmental outcomes, while ongoing advances in genetic research will further refine our understanding and guide targeted diagnostic strategies.

Patient Consent

Consent to publication was obtained from the patient and patient's legal guardian before publication submission.

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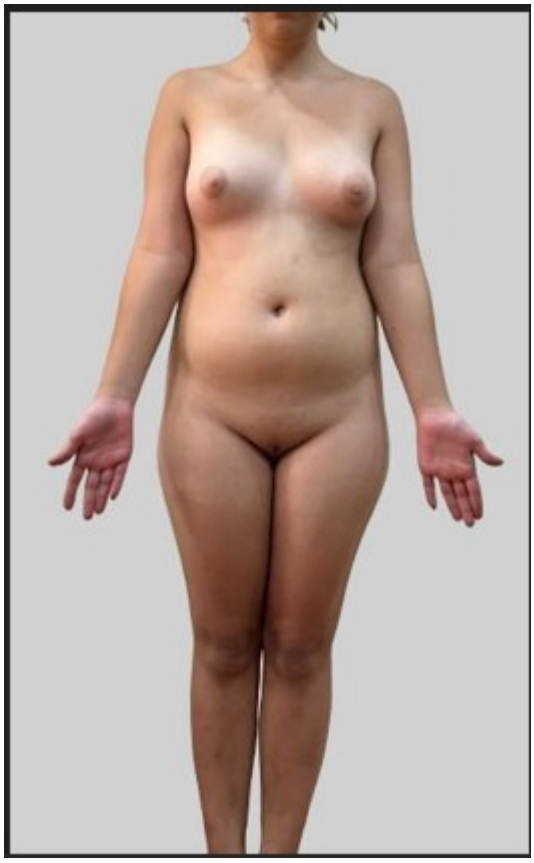

Fig. 1 Phenotypic appearance of a 16-year-old adolescent girl with spontaneous pubertal development, without signs of virilization

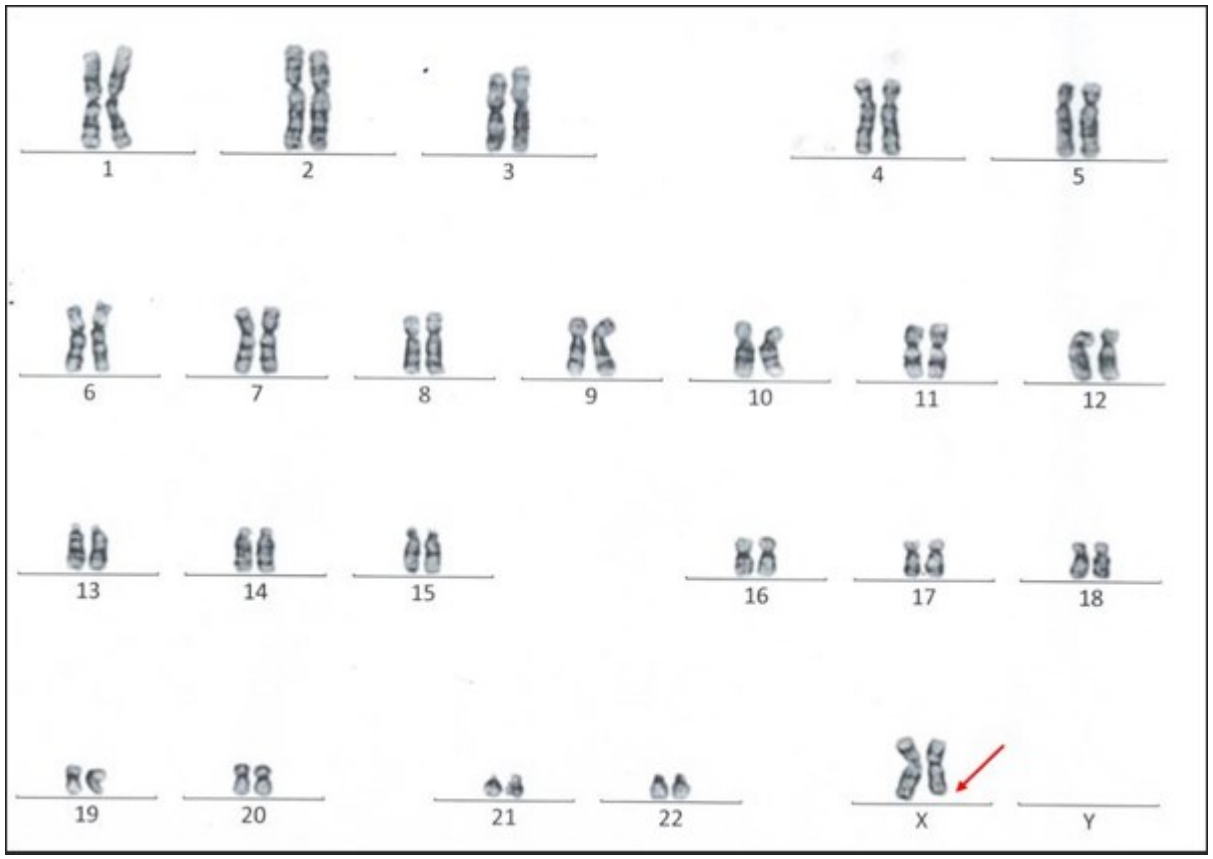

Fig. 2 Karyotype 46,X,del(X)(q21) in a 16-year-old adolescent girl with primary amenorrhea and spontaneous pubertal development.

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