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Case Report

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Abstract

Introduction

This case report provides genetic insights into prepubertal gynecomastia through the comprehensive analysis of a rare 45,X[2]/46,X,+mar[28] karyotype. Gynecomastia, characterized by the enlargement of male breast, is typically physiological in pubertal cases but necessitates thorough evaluation in severe instances. Prepubertal gynecomastia is exceptionally rare, and the limited literature results in a deficit of etiological and management data.

Case report

The case involves an eight years and six months old male child with prepubertal bilateral gynecomastia and short stature, presenting a karyotype of 45,X[2]/46,X,+mar[28], with the additional marker chromosome originating from the Y chromosome, revealing Yq microdeletions. The patient's clinical progression, chromosomal analysis, and molecular findings are detailed, emphasizing the importance of karyotyping in prepubertal gynecomastia cases.

Conclusion

In prepubertal gynecomastia cases, karyotyping is crucial to identify potential chromosomal abnormalities contributing to the condition. Particularly, cases with Yq deletion should be closely monitored, especially for short stature.

Introduction

Gynecomastia is described by the enlargement of breast, either on one or both sides, in male individuals. Typically, pubertal gynecomastia is commonly bilateral and considered a physiological phenomenon in the majority of cases. However, a complete endocrine and oncologic evaluation is required in cases where breast enlargement is ≥ grade 3 to exclude fundamental pathologic disorders. Opposed to pubertal gynecomastia, there are only a few compiled case reports related to prepubertal gynecomastia; hence, this condition is exceedingly rare in the medical literature. Consequently, data related to the etiology and management strategies for this condition are deficient [1–3].

The age distribution of gynecomastia reveals three distinct peaks. Due to the transmission of estrogens across the placenta, palpable breast tissue expands in 60–90% of newborns during the neonatal period, marking the first peak. The second peak of breast tissue development during puberty is attributed to a disproportion between androgens and estrogens in the breast tissue. The adult male population exhibits the final peak, with males between the ages of 50 and 80 having the highest frequency[2]. Prepubescent gynecomastia is uncommon, in contrast to gynecomastia in teenage and adult boys. Prepubescent gynecomastia is categorized as idiopathic in 90% of instances, and a particular etiology is rarely found. Therefore, more research into the conditions' genesis is advised, especially to avoid endocrine or
neoplastic problems. Gynecomastia is caused by stimulation of breast tissue by a range of endocrinopathies, which are mostly caused by an increase in the ratio of circulating estrogens to androgens [3].

This report presents an infrequent case involving a boy diagnosed with prepubertal bilateral gynecomastia and short stature, characterized by a 45,X[2]/46,X,+mar[28] karyotype. The origin of the additional marker chromosome was identified as emanating from the Y chromosome, revealing Yq microdeletions.

**Case Report**

An eight years and six months old male child was admitted to the endocrinology service due to the onset of pubic hair development. His height measured 128.2 cm (25–50 percentile; -0.24 standard deviations), with an ideal weight percentage of 111. In the initial physical examination, testicular volume was 2 ml/2 ml, pubic hair was classified as Tanner III, and there was no axillary hair. The first laboratory assessment revealed TSH at 3.12 mU/L, sT4 at 1.21 ng/dL, total testosterone at 0.14 ng/dL, DHEAS at 70 µg/dL, 11-deoxycorticosterone (11DOC) at 2.7 ng/dL, 17-hydroxy progesterone (17 OHP) at 0.98 ng/dL, cortisol at 24.4, and adrenocorticotropic hormone (ACTH) at 23.9 pg/mL.

During the 12 years and 11 months of follow-up, the patient experienced obesity and a decline in height percentile, with a height of 146.2 cm (3–10 percentile; -1.46 standard deviations) and an ideal weight percentage of 138. The growth velocity was 3.2 cm/year. In the subsequent physical examination, testicular volume remained at 2 ml/2 ml, pubic hair advanced to Tanner IV, and bilateral gynecomastia (right breast Tanner II, left breast Tanner II) was observed. Laboratory results indicated alpha-fetoprotein (AFP) < 1.7 ng/mL, estradiol (E2) < 11.8 ng/dL, beta-hCG < 2, prolactin at 21.9 ng/mL, follicle-stimulating hormone (FSH) at 1.26 IU/L, luteinizing hormone (LH) at 0.36 IU/L, total testosterone at 17.11 ng/dL, DHEAS at 135 µg/dL, 11 DOC at 0.58 ng/dL, 17OHP at 0.69 ng/dL, TSH at 2.4 mU/L, sT4 at 1.19 ng/dL, cortisol at 30.9, and ACTH at 7.12 pg/mL (Table 1). Breast ultrasound revealed left 38x15 mm and right 15x4 mm fibroglandular tissue. Chromosome analysis was requested due to the presence of prepubertal gynecomastia.
Table 1. Hormonal evaluation of the patient

<table>
<thead>
<tr>
<th></th>
<th>8 years 6 months</th>
<th>12 years 11 months</th>
<th>14 years 2 months</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU/L)</td>
<td>1.26</td>
<td>1.59</td>
<td></td>
<td>1.2-19.2</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>0.36</td>
<td>2.84</td>
<td></td>
<td>1.24-8.62</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>&lt;11,8</td>
<td></td>
<td></td>
<td>&lt;10</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>0.14</td>
<td>17.11</td>
<td>134.6</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>23.9</td>
<td>7.12</td>
<td>7.08</td>
<td></td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>24.4</td>
<td>30.9</td>
<td>16</td>
<td>6.7-22.6</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>21.9</td>
<td>16.68</td>
<td></td>
<td>4.79-23.3</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>1.21</td>
<td>1.19</td>
<td>0.92</td>
<td>0.6-1.12</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>3.12</td>
<td>2.4</td>
<td>1.46</td>
<td>0.5-5</td>
</tr>
<tr>
<td>Alfa-fetoprotein (ng/mL)</td>
<td>&lt;1,7</td>
<td></td>
<td></td>
<td>0.5-5.5</td>
</tr>
<tr>
<td>BetaHcg (mIU/mL)</td>
<td>&lt;2</td>
<td></td>
<td></td>
<td>&lt;2</td>
</tr>
<tr>
<td>17OHP (ng/mL)</td>
<td>0.98</td>
<td>0.69</td>
<td></td>
<td>0-0.63</td>
</tr>
<tr>
<td>11DOC (ng/dL)</td>
<td>2.72</td>
<td>0.58</td>
<td></td>
<td>0-3.44</td>
</tr>
<tr>
<td>DHEAS (µg/dL)</td>
<td>70.5</td>
<td>135</td>
<td></td>
<td>80-560</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td></td>
<td>22.9</td>
<td>10-57</td>
<td></td>
</tr>
<tr>
<td>IGF-BP3 (µg/mL)</td>
<td></td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatomedin-C (ng/mL)</td>
<td></td>
<td>311</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-DOPA peak GH (ng/mL)</td>
<td></td>
<td>2.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine peak GH (ng/mL)</td>
<td></td>
<td>3.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chromosomal analysis

Subsequent FISH analysis (nucish) reported the presence of DXZ1 x 1, Yp11.31 x 0, and DYZ1 x 0 signals in 5 out of 50 interphases, while in the remaining 45 interphases, the signals were DXZ1 x 1, Yp11.31 x 1, and DYZ1 x 0. Notably, no signal was obtained with the probe attached to the Yq11.31 region in any of the analyzed cells. Family screening was reported as normal. Further molecular analysis of the Y
chromosome demonstrated deletions in the AZFb and AZFc regions. Subsequently, the refined chromosomal analysis identified the karyotype as 45,X[2]/46,X,+der(Y)del(Y)(q11.22q11.23)[28] (Fig. 1).

At the last follow-up of the patient at 14 years and 2 months, the height was measured at 153 cm (3–10 percentile; -1.54 standard deviations), with an ideal weight percentage of 121. The physical examination revealed testicular volume at 8 ml/8 ml, pubic hair classified as Tanner IV, and bilateral gynecomastia (right breast Tanner III, left breast Tanner III). Laboratory evaluation, as presented in Table 1, indicated low growth hormone values in Growth Hormone Provocation tests. The L-DOPA peak growth hormone value was 2.76 ng/mL, and the clonidine peak growth hormone value was 3.08 ng/mL (Table 1). Consequently, the patient commenced growth hormone (GH) treatment.

Discussion

In the present case, the male karyotype 46,X,+mar is a rare presentation where the testicles lack the usual structural Y chromosome in their non-mosaic karyotypes. An aberrant chromosome in a structure that cannot be identified using traditional cytogenetic karyotype analysis is known as a marker chromosome (mar). A marker chromosome's intact genetic material and information are what give it relevance. Growth changes, skeletal development, spermatogenesis, and fertility are all impacted by Yq deletions. Consequently, it is essential to use cytogenetic molecular techniques in order to clarify the genetic and clinical features of the marker chromosome [4–6].

Increased adipose tissue aromatase activity in obesity cases can lead to the alteration of androgens to estrogens and the development of gynecomastia [2]. Einav-Bachar et al. reported that 31% of patients with prepubertal gynecomastia were obese[1]. Gynecomastia in prepubescent individuals may occur due to exposure to medications and chemical substances with estrogenic or antiandrogenic effects, either systemically, autocrinally, or paracrinally. This excludes systemic conditions such as estrogen- or androgen-secreting tumors, liver dysfunction, hyperthyroidism, etc., which can either elevate estrogen production or impede its metabolism [2, 7, 8].

Three prepubertal boys were found by Felner and White to have bilateral gynecomastia as a result of their mothers' topical estrogen cream use, which served as an indirect source of estrogen exposure [9]. Gynecomastia returned in all three patients when the moms stopped using the lotion. Three prepubertal boys experienced bilateral gynecomastia after using lavender oil, according to Henley et al. [7]. The condition resolved after the causal substance was removed. The subject in our research had no prior exposure to chemicals or history of systemic illness.

Teenagers ages 13 or 14 are typically the ones that experience pubertal gynecomastia, which manifests as unilateral or bilateral, momentarily painful, rubbery, or hard masses in a concentric area. Most patients relapse after a year or two. An endocrine examination should be taken into consideration if the disease lasts longer than two years and is notably worse than B3, according to a cohort research [10]. Elevated aromatase activity, neoplasms in the adrenal or testicular regions, partial androgen insensitivity syndrome, and conditions related to disorders of sex differentiation (DSD), including 46,XX testicular
(SRY+)-associated hypogonadism, and Klinefelter syndrome, are some of the factors contributing to the enduring and conspicuous cases of gynecomastia [11]. Consequently, karyotyping was performed in the present case due to clinical features suggestive of DSD. Interestingly, the karyotype revealed 45,X[2]/46,X,+mar[28]. FISH analysis showed nucish (DXZ1 x 1, Yp11.31 x 0, DYZ1 x 0)[5/50] /(DXZ1 x 1, Yp11.31 x 1, DYZ1 x 0)[45/50]. Signals from the DXZ1 and SRY regions were observed in 45 out of 50 interphase nuclei, while no signal was detected with the probe targeting the Yq11.31 region in these cells. In the remaining 5 cells, a single signal from the DXZ1 region was identified.

The present individual, with 46,X,+mar, exhibits obesity and short stature, which are consistent with comparable clinical symptoms reported in earlier studies (Table 2). It is important to remember that 46,X,del(Yq) is linked to co-occurring diseases such as gynecomastia, low stature, and intellectual incapacity, as well as spermatogenic maturation arrest, tiny testes with testicular lesions, sertoli cell-only syndrome, tubular hyalinization, and spermatogenic maturation arrest [12].

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Karyotype</th>
<th>Comorbidities</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi et al.</td>
<td>1 yr</td>
<td>46,X,+mar</td>
<td>Abnormal external genitalia, hypospadias</td>
<td>SRY+, 46,X,der(9p)</td>
</tr>
<tr>
<td>Calzolari et al.</td>
<td>11 yr</td>
<td>46,X,+mar</td>
<td>Obesity, short stature(&lt;10p), bilateral cryptorchidism, coarctation of the aorta</td>
<td>SRY+, 46,X,del(Y)(p11.3–q11.21)</td>
</tr>
<tr>
<td>Graham and Bacino</td>
<td>10yr 10mo</td>
<td>46,X,+mar</td>
<td>Short stature(&lt;5p), developmental delay, bilateral cryptorchidism, bilateral hearing loss, webbed neck, low posterior hairline, mild brachydactyly, short 4th, and 5th metatarsals, murmur</td>
<td>SRY+, 46,X,der(Y)del(Y)(p11.23)del(Y)(q11.23)</td>
</tr>
<tr>
<td>Ki Eun Kim et al.</td>
<td>15 yr</td>
<td>46,X,+mar</td>
<td>Short stature, mild intellectual disability, a small fallus, a knuckle-dimple sign, the fourth toe of left foot, short 4th and 5th metacarpal and 4th metatarsal bones</td>
<td>46,X,der(Y)del(Y)(q11.21q11.222)del(Y)(q11.23qter)</td>
</tr>
</tbody>
</table>

Short stature has been associated with the Yq11 region, which is well-known for the anti-Turner effect, controlling growth control, tooth development, and fertility, especially through Y-specific growth control regions [13]. Interestingly, in certain circumstances, microdeletions of the Yq chromosome have been linked to a variety of phenotype combinations, such as cubitus valgus, short height, a webbed neck, shorter fourth and fifth metacarpals, pigmented nevi, a low posterior hairline, and gynecomastia [5, 6].
Conclusion

In conclusion, karyotyping is crucial in the assessment of prepubertal gynecomastia. Additionally, when conventional banding techniques reveal a marker chromosome instead of a typical sex chromosome, comprehensive endocrine assessments, incorporating cytogenetic and DNA molecular analyses, become essential. These evaluations are undertaken to ascertain the presence of a sex chromosome or SRY and to identify any structural aberrations or breakpoints in the marker chromosome.

Declarations

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Conflict of interest: The authors declare no conflicts of interest.

Patient consent statement: Consent for the inclusion of this patient and their family in this report has been obtained.

Ethical Approval: Not applicable

Availability of data: Data can be requested directly from the authors.

References


Figures
Figure 1

See image above for figure legend