Diagnostic Dilemma in a 46-XY Female

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CASE PRESENTATION

A previously healthy phenotypic female presented with primary amenorrhea at 17-years-of-age. She had thelarche onset at age 10 and she progressed to Tanner Stage V breast development. She had no symptoms to suggest virilization or adrenal insufficiency. She had symptoms of pelvic fullness. Family history was negative for amenorrhea or fertility concerns.

Physical examination revealed a tall (height 187.3cm, 100th percentile) and lean body habitus. She has broad hands and long fingers. Pubertal assessment showed Tanner Stage V breast development and Tanner Stage V pubic hair, Prader score 0. An examination under anesthesia demonstrated a normal appearance of the vagina, cervix, uterus and fallopian tubes.

INVESTIGATIONS

Karyotype: 46, XY (1-22), (X,Y) x1

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>pmol/L</td>
<td>145</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.5-2.0 nmol/L</td>
<td>3.9 (High)</td>
</tr>
<tr>
<td>FSH</td>
<td>U/L</td>
<td>43.3 (High)</td>
</tr>
<tr>
<td>LH</td>
<td>U/L</td>
<td>14.6</td>
</tr>
<tr>
<td>AMH</td>
<td>pmol/L</td>
<td>269.5</td>
</tr>
<tr>
<td>DHEAS</td>
<td>&lt;11.0 umol/L</td>
<td>7.9</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>&lt;12.9 nmol/L</td>
<td>4.9</td>
</tr>
<tr>
<td>HCG</td>
<td>&lt;5 U/L</td>
<td>81 (High)</td>
</tr>
</tbody>
</table>

Table 1. Initial biochemical investigations. FSH: follicle stimulating hormone, LH: luteinizing hormone, AMH: anti-Mullerian hormone, DHEAS: dehydroepiandrosterone, HCG: human chorionic gonadotropin.

Imaging: Pelvic MRI showed large bilateral adnexal masses (left 9.4 cm, right 8.3 cm, see Figure 2), a normal appearing uterus and a slightly thickened endometrium.

Pathology: Pathology identified bilateral dysgerminomas arising from gonadoblastomas, with no metastases.

CLINICAL COURSE

Adjuvant chemotherapy was not required and tumor markers normalized post-operatively. After resection, she developed symptoms of hypoestrogenism and required estrogen replacement.

Genetic testing identified a heterozygous pathogenic variant in the POR gene, a rare cause of congenital adrenal hyperplasia. The phenotypic presentation of homozygous PORD is variable and manifestations include DSD, glucocorticoid deficiency and skeletal dysplasia. Biochemical evaluation showed no evidence of adrenal insufficiency.

DIFFERENTIAL DIAGNOSIS

The most frequent identifiable causes of 46-XY females are Androgen Insensitivity Syndrome (AIS) and Gonadal Dysgenesis. There were aspects of our patients clinic presentation that were consistent with each.

Figure 1. Intraoperative findings of bilateral dysgerminomas

Figure 2. Pelvic MRI of bilateral adnexal masses

DISCUSSION

Despite progressive understanding of DSD and the increasing role of genetic testing, challenges in diagnosis persist. We suspect partial gonadal dysgenesis and we hypothesize that there was adequate function of dysgenetic gonads for full thelarche, before malignant transformation. The dysgerminomas then produced testosterone, accounting for elevated levels but minimal virilization.

The identified heterozygous mutation for PORD is insufficient to explain her phenotype; however, we question if she has a secondary, unidentified compounding mutation. She has no clinical or biochemical features to suggest PORD.

This case highlights the challenges in diagnosing patients with 46 XY DSD and reinforces the value of a multi-disciplinary approach including genetic and endocrine expertise in diagnostic evaluation.

References and Acknowledgements


We extend our sincere gratitude to our patient and her family for giving us permission to share her story and photographs.