Case Report

Gonadoblastoma with Dysgerminoma Presenting as Virilizing Disorder in a Young Child with 46, XX Karyotype: A Case Report and Review of the Literature

Prathamesh Chandrapattan¹, Amitabh Jena¹, Rashmi Patnayak², Swayamsidha Mangaraj³, Sujata Naik², and Saroj Panda⁴

¹Department of Surgical Oncology, IMS & SUM Medical College and Hospital, Bhubaneswar, Odisha, India
²Department of Pathology, IMS and SUM Medical College and Hospital, Bhubaneswar, Odisha, India
³Department of Endocrinology, IMS & SUM Medical College and Hospital, Bhubaneswar, Odisha, India
⁴Department of Medical Oncology, IMS & SUM Medical College and Hospital, Bhubaneswar, Odisha, India

Correspondence should be addressed to Swayamsidha Mangaraj; drsmangaraj@gmail.com

Received 24 December 2021; Revised 25 March 2022; Accepted 22 April 2022; Published 23 May 2022

1. Introduction

Various inherited and acquired causes can lead to hyperandrogenism and its resultant manifestations in a female child. In young children, androgen-producing ovarian and adrenal tumors can lead to features of virilization in a relatively short span of time. Gonadoblastoma is a relatively rare ovarian tumor comprised of sex cord and primitive germ cell components. Though being benign by themselves, they are frequently associated with invasive germ cell malignant tumors [1]. These tumors are frequently seen among individuals with 46, XY gonadal dysgenesis. However, they have been rarely described in individuals with normal 46, XX karyotype [1–6]. This presentation is even rarer in children less than ten years, and only one such case has been previously reported [5]. We present an interesting case of a young girl who presented with features of virilization and contrasexual pubertal development. A detailed clinical evaluation along with supportive biochemical and radiological findings pointed to the presence of a virilizing ovarian tumor. The patient underwent right salpingo-oophorectomy, pelvic node dissection, and infracolic omentectomy. The excised tumor was confirmed to be gonadoblastoma which was overgrown by dysgerminoma on histopathological evaluation. The presence of associated malignant tumors (like dysgerminoma) should always be ruled out in cases of gonadoblastoma.

2. Case Report

A nine-year-old girl presented for evaluation of progressively increased hair growth over androgen-dependent areas,
deepening of voice, and abdominal distension. The patient had first episode of bleeding per vaginum at the age of 7 years and 6 months. Following it, she had an irregular menstrual bleeding pattern for the next five months. Subsequently, the bleeding episodes had ceased on its own without any drug intake, and she was amenorrhoeic for the last one year. However, no medical consultation or evaluation was done at that point of time for this precocious pubertal event. The parents had also noticed a significant height gain in comparison with her peers in the preceding one and half years. There was no history of any chronic drug intake or prior surgery. There was no history of a similar disorder in any family member. She was born out of a nonconsanguineous marriage and delivered at term by normal vaginal delivery. The perinatal period was uneventful. On clinical examination, the girl was thin built with muscular appearance. Her anthropometric parameters were as follows: height of 145 cm (>97th percentile) and weight of 41 kg (90th–97th percentile). She had evidence of virilization characterized by a significant degree of hirsutism (Ferriman–Gallaway score of 16/36), clitoromegaly (clitoral length 16 mm and clitoral index 56 nm²), and lack of breast development. No Turner syndrome stigmata were noted. Her vitals were within a normal range. On abdominal palpation, a mobile abdominal mass (around 10 cm × 10 cm) was noted in the right lower abdomen with the presence of shifting dullness and bulging flanks. Ultrasonography of the abdomen and pelvis revealed a large lobulated adnexal mass (around 11 cm × 6 × 9 cm) arising from the right ovary along with ascites. The left ovary was morphologically normal. A pubertal uterus (dimension of around 7.5 cm × 5 cm × 3.6 cm) with a normal endometrial echogenicity of 3 mm was also noted. Her bone age was advanced by two years in contrast to her chronological age. Contrast enhanced computed tomography revealed a large lobulated solid mass of size 11.9 cm × 6.5 cm × 9.4 cm arising from the right ovary, morphologically normal looking left ovary, and presence of gross ascites (Figure 1). The right ovarian mass was characterized by heterogeneous postcontrast enhancement and punctuate internal calcification along with multiple intratumor tortuous vascular channels (Figure 1). Serum lactate dehydrogenase (LDH) (361 U/L, normal: 140–280 U/L), serum beta human chorionic gonadotropin (hCG) (447.2 mIU/ml, normal: <5.0 mIU/ml), and CA-125 (56.93 U/ml, normal: <35 U/ml) levels were elevated. Serum alpha-fetoprotein (AFP) level (4.2 ng/ml, normal: <5.8 ng/ml) was normal. Hormonal evaluation revealed significantly elevated levels of serum testosterone (12.51 ng/ml, normal: 0.06–0.52 ng/ml), low luteinizing hormone level (0.26 mIU/ml, normal: >0.6 mIU/ml for pubertal response), and slightly elevated estradiol level (30 pg/ml, normal: <20 pg/ml). Serum dehydroepiandrosterone sulphate (DHEAS) levels were within a normal range. Karyotype analysis from peripheral blood sample revealed a normal female 46, XX pattern. Fluorescence in situ hybridization (FISH) from peripheral blood did not reveal any Y chromosome material. Based on the above clinical, biochemical, and supportive radiological findings, a diagnosis of virilizing ovarian tumor leading to conrasexual puberty was considered. Intraoperative findings revealed a 15 cm × 10 cm firm and lobulated mass arising from the right ovary whereas the left ovary appeared morphologically normal. The patient underwent right salpingo-oophorectomy, pelvic lymph node dissection, and infracolic omentectomy along with left ovarian biopsy (Figure 2). Around three liters of straw-coloured ascitic fluid was drained. The patient had an uneventful recovery in the postoperative period. Ascitic fluid cytology was negative for malignant cells. Histopathologic examination of excised tumor revealed greyish yellow tumor with focal areas of myxoid changes and haemorrhage with an intact capsule. The tumor cells were present in sheets and nests separated by fibrous septa with lymphoid infiltration. Occasional primordial follicles were also seen in between. The tumoral cells were large with prominent nucleoli and mitotic activity. At places, bizarre tumor cells with areas of calcification (suggested of burned out gonadoblastoma) were seen. Regional lymph node assessment revealed reactive hyperplasia. Based on the above characteristic findings, a diagnosis of dysgerminoma associated with burned out gonadoblastoma was made (Figure 3). The left ovary biopsy sample revealed normal ovarian histology. Pathological staging was pT1aN0Mx. However, a cytogenetic study for assessing Y chromosome material from affected ovarian tumor tissue was not performed. The patient was started on chemotherapy comprising of bleomycin, etoposide, and cisplatin combination for four cycles. The virilization features decreased over the course of next three months with significant improvement in hirsutism, voice change, and other physical characteristics. The patient is on regular follow-up for the past one year with no evidence of tumor recurrence till now and menstrual cycles have not resumed. The hormonal evaluation revealed normalization of testosterone levels (0.2 ng/ml) and normal early pubertal gonadotropin levels.

3. Discussion

The diagnosis of virilization in a young girl can be clinically challenging at times. The causes include various inherited and acquired conditions such as disorders of sex development (DSD), virilizing ovarian tumors, adrenal tumors, and exogenous androgen exposure. DSD such as various forms of congenital adrenal hyperplasia (CAH), ovotesticular DSD, and aromatase deficiency can present with features of hyperandrogenism in females. They can be distinguished from other tumoral causes of virilization by the presence of genital ambiguity since birth, presence of associated findings (maternal virilization during pregnancy in case of aromatase deficiency, history of salt wasting in certain forms of CAH), usually slower rate of androgenization in contrast to virilizing tumors and characteristic hormonal profile. Similarly, ovarian and adrenal tumors are usually characterized by rapid progression and more severe virilization in affected individuals. The presence of cushingoid features in addition to signs of virilization may point towards the presence of underlying adrenocortical carcinoma. Elevated androgen levels (serum testosterone level of more than 2 ng/ml and serum dehydroepiandrosterone sulphate level of more than 8 μg/mL) are characteristic of virilizing ovarian and
Adrenal tumors, and these tumors may be identified by necessary dedicated imaging studies. The common age of presentation of gonadoblastomas is in the second and third decade [7]. The common clinical manifestations of these ovarian tumors include hirsutism, virilization, menstrual abnormalities, and abdominal pain/distension [7]. The characteristic features of virilization seen in gonadoblastomas are due to excessive production of testosterone by these tumors [1, 8]. On the other hand, ovarian dysgerminomas are usually hormonally inert. Rarely ovarian dysgerminoma can be associated with elevated estradiol levels due to the presence of syncytiotrophoblastic giant cells or due to malignant transformation [9]. Pure gonadoblastomas are usually small in size but may acquire large size due to invasive component overgrowth [8]. Around 40% or more cases of gonadoblastoma are bilateral [7, 10, 11]. The pathological hallmark of these tumors is the presence of sex cord and primitive germ cell components. The presence of calcification serves as an important diagnostic clue [2, 7, 8, 10].

It is customary to rule out the presence of invasive malignancy in every case of gonadoblastoma. This is due to the fact that malignant germ cell tumors are associated with 50–60% of gonadoblastomas. The most common malignancy is pure dysgerminoma, whereas other variants include immature teratoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma [3, 4, 7, 12]. Gonadoblastomas are found among 25–30% of patients with XY gonadal dysgenesis and among 15–20% of patients with 45, X/46, XY karyotype [2]. This finding underscores the importance of karyotype analysis. Normal 46, XX karyotype is observed in rare cases [1–6]. Hence, cytogenetic assessment of Y chromosome in blood/affected tissue is advocated. In our case, although we had conducted FISH analysis from peripheral blood, we could not do cytogenetic assessment of Y chromosome from affected tissue. Pure gonadoblastomas are benign in nature, and it has been reported that cases with dysgerminomas also have a favorable prognosis [3]. However, association of other tumor types such as the yolk sac tumor may have unfavorable prognosis [3, 13]. We have summarized relevant cases of patients having 46, XX karyotype and gonadoblastoma described in the literature in Table 1 [1, 3–6, 8, 10, 11, 14–17]. Our case is unique as
Table 1: Summary of similar cases published in the literature with gonadoblastoma and normal 46, XX karyotype.

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year</th>
<th>Clinical presentation</th>
<th>Age in years</th>
<th>Precocity</th>
<th>Karyotyping</th>
<th>Laterality</th>
<th>Management</th>
<th>Additional findings in histopathology (in addition to gonadoblastoma)</th>
<th>Adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erhan et al.</td>
<td>1992</td>
<td>Abdominal mass</td>
<td>26</td>
<td>No</td>
<td>46, XX</td>
<td>Right</td>
<td>TAH + BSO</td>
<td>Dysgerminoma</td>
<td>Combination chemotherapy</td>
</tr>
<tr>
<td>Obata et al.</td>
<td>1995</td>
<td>Abdominal pain</td>
<td>10</td>
<td>No</td>
<td>46, XX</td>
<td>Bilateral</td>
<td>B/L oophorectomy</td>
<td>Left with dysgerminoma, right with yolk sac tumour</td>
<td>Combination chemotherapy</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>2000</td>
<td>Abdominal mass</td>
<td>27</td>
<td>No</td>
<td>46, XX</td>
<td>Unilateral</td>
<td>USO + chemotherapy + later TAH + USO + LND + omentectomy</td>
<td>Choriocarcinoma, embryonal carcinoma, yolk sac tumor, immature teratoma, and dysgerminoma</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Erdemoglu &amp; Ozen</td>
<td>2007</td>
<td>Abdominal mass</td>
<td>19</td>
<td>No</td>
<td>46, XX</td>
<td>Unilateral</td>
<td>Unilateral oophorectomy</td>
<td>Endodermal sinus tumor</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Gorosito et al.</td>
<td>2010</td>
<td>Pregnancy with ovarian mass</td>
<td>17</td>
<td>No</td>
<td>46, XX</td>
<td>Left</td>
<td>Left oophorectomy</td>
<td>Dysgerminoma</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Yilmaz et al.</td>
<td>2010</td>
<td>Abdominal distention with mass</td>
<td>20</td>
<td>No</td>
<td>46, XX</td>
<td>Bilateral</td>
<td>BSO</td>
<td>Dysgerminoma</td>
<td>Chemotherapy (bleomycin, etoposide, and cisplatin) and radiation</td>
</tr>
<tr>
<td>Esin et al.</td>
<td>2011</td>
<td>Irregular vaginal bleeding and pelvic pain</td>
<td>15</td>
<td>No</td>
<td>46, XX</td>
<td>Left</td>
<td>Left oophorectomy with right ovary wedge biopsy</td>
<td>Dysgerminoma</td>
<td>—</td>
</tr>
<tr>
<td>Kanagal et al.</td>
<td>2013</td>
<td>Abdominal distention and mass</td>
<td>14</td>
<td>No</td>
<td>46, XX</td>
<td>Left</td>
<td>USO + cytoreductive surgery + right ovarian wedge biopsy</td>
<td>Mixed germ cells and sex cord cell derivatives</td>
<td>Combination chemotherapy</td>
</tr>
<tr>
<td>Kulkarni et al.</td>
<td>2016</td>
<td>Abdominal pain</td>
<td>20</td>
<td>No</td>
<td>46, XX</td>
<td>Left</td>
<td>USO + omental biopsy</td>
<td>Dysgerminoma</td>
<td>—</td>
</tr>
<tr>
<td>McCuaig et al.</td>
<td>2017</td>
<td>Oligomenorrhea and menorrhagia</td>
<td>20</td>
<td>No</td>
<td>46, XX</td>
<td>Left</td>
<td>USO</td>
<td>Dysgerminoma with syncytiotrophoblastic differentiation</td>
<td>Observation</td>
</tr>
<tr>
<td>Roth et al.</td>
<td>2019</td>
<td>Abdominal pain and mass</td>
<td>9</td>
<td>No</td>
<td>46, XX</td>
<td>Right</td>
<td>USO</td>
<td>Malignant mixed germ cell tumour</td>
<td>Cisplatin based combination chemotherapy</td>
</tr>
<tr>
<td>Rafeey et al.</td>
<td>2020</td>
<td>Abdominal pain and mass</td>
<td>10</td>
<td>No</td>
<td>46, XX</td>
<td>Bilateral</td>
<td>USO with cytoreduction with right ovarian biopsy, para-aortic LN sampling with Partial Omentectomy</td>
<td>Dysgerminoma</td>
<td>Chemotherapy (Bleomycin, Etoposide and Cisplatin)</td>
</tr>
</tbody>
</table>

similar presentation is extremely rarer in children less than ten years and only one such case has been reported earlier [5]. Cases of dysgerminoma presenting with precocious puberty in children have also been described rarely in children [9, 18]. The presentation of 46, XY complete gonadal dysgenesis as pubertal virilizing disorder in adolescent due to underlying virilizing ovarian tumor (presence of concomitant gonadoblastoma and dysgerminoma) has been well described in the literature [19].

Surgery remains the main modality of treatment. The extent of surgery includes oophorectomy accompanied by salpingectomy, hysterectomy, omentectomy, and lymph node dissection depending on the disease status [3, 8, 11]. Germ line and tumoral Y chromosome analysis are helpful in deciding regarding contralateral oophorectomy in young patients keeping in mind fertility issues. The coexistence of invasive malignancy in gonadoblastoma requires adjuvant chemotherapy [2, 9, 11].

4. Conclusion
The presence of virilizing features in a young girl should be thoroughly evaluated. Gonadoblastoma is a rare virilizing ovarian tumor that usually arises in dysgenetic gonads. Although frequently associated with presence of Y chromosome, these tumors can rarely be seen in individuals with normal 46, XX karyotype. The presence of concomitant malignancy associated with gonadoblastoma should be always ruled out due to important therapeutic and prognostic implications.

Data Availability
Data are available on reasonable request to the corresponding author.

Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure
All authors have no financial relationship related to this article to disclose.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

References
