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

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Gonadoblastoma is a neoplasm containing an intimate mixture of germ cells and elements resembling immature granulosa or Sertoli cells. It has been considered as an in situ germ cell malignancy that can be associated with malignant components. The tumor has been reported to almost exclusively develop in various types of gonadal gene mutation syndromes, such as in pure or mixed gonadal dysgenesis and among females carrying Y chromosome material. However, it can be rarely present in normal women with 46, XX karyotype. Ovarian gonadoblastoma presenting with signs of contrasexual puberty in a young female child with normal 46, XX karyotype is an extremely rare clinical entity and seldom reported in the literature. We report a case of a nine-year-old girl child who presented with signs 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.

1. Introduction

Various inherited and acquired causes can lead to hyper-androgenism 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 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 contrasexual pubertal development which was subsequently attributed to right ovarian gonadoblastoma with dysgerminoma. We describe her clinical presentation and management outcome along with a review of the literature describing cases of gonadoblastoma arising in individuals with normal 46, XX karyotype.

2. Case Report

A nine-year-old girl presented for evaluation of progressively increased hair growth over androgen-dependent areas,
diagnosis of virilizing ovarian tumor leading to contrasting clinical, biochemical, and supportive radiological findings, a not reveal any Y chromosome material. Based on the above sample revealed a normal female 46, XX pattern. Fluorescent normal range. Karyotype analysis from peripheral blood drostenedione sulphate (DHEAS) levels were within a (30 pg/ml, normal: [20–200 ng/ml]). Serum dehydroepiandrosterone sulphate level of more (70–1100 ng/ml) is characteristic of virilizing ovarian and

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 tumors associated with burned out gonadoblastoma. 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 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.
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

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**Figure 1:** A large lobulated solid heterogeneously enhancing mass (solid black arrows) arising from the right ovary of size 11.9 cm × 6.5 cm × 9.4 cm with punctuate internal calcification and ascites.

**Figure 2:** Resected specimen showing cut opened the right ovary with an attached fallopian tube. The right ovary measures around 15 cm × 10 cm with a bosselated outer surface. The ovary is entirely replaced by a solid mass which greyish-yellow with focal areas of myxoid changes and haemorrhage with an intact capsule. The fallopian tube appears normal.

**Figure 3:** Histological findings showing nests of germ cells separated by fibrous septa infiltrated by lymphoid cells. Tumor cells are large, high N:C ratio with prominent nucleoli. (hematoxylin and eosin (H&E), 200x).

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| Author                  | Year | Clinical presentation | Age in years | Precocity | Karyotyping | Laterality | Management | Additional findings in histopathology (in addition to gonadoblastoma) | Adjuvant therapy                      |
|-------------------------|------|-----------------------|--------------|-----------|-------------|------------|------------|-------------------------------------------------------------------|---------------------------------------|
| Erhan et al. [14]       | 1992 | Abdominal mass        | 26           | No        | 46, XX      | Right      | TAH + BSO  | Dysgerminoma                                                      | Combination chemotherapy               |
| Obata et al. [15]       | 1995 | Abdominal pain        | 10           | No        | 46, XX      | Bilateral  | B/L oophorectomy        | Left with dysgerminoma, right with yolk sac tumour Choriocarcinoma, embryonal carcinoma, yolk sac tumor, immature teratoma, and dysgerminoma | Combination chemotherapy               |
| Zhao et al. [16]        | 2000 | Abdominal mass        | 27           | No        | 46, XX      | Unilateral | USO + chemotherapy + later TAH + USO + LND + omentectomy         | Chemotherapy                           |
| Erdemoglu & Ozen [17]   | 2007 | Abdominal mass        | 19           | No        | 46, XX      | Unilateral | Left oophorectomy       | Endodermal sinus tumor                                               | Chemotherapy                           |
| Gorosito et al. [10]    | 2010 | Pregnancy with ovarian mass | 17         | No        | 46, XX      | Left       | Left oophorectomy       | Dysgerminoma                                                        | Chemotherapy                           |
| Yilmaz et al. [11]      | 2010 | Abdominal distention with mass | 20         | No        | 46, XX      | Bilateral  | BSO        | Chemotherapy (bleomycin, etoposide, and cisplatin) and radiation | Chemotherapy                           |
| Esin et al. [3]         | 2011 | Irregular vaginal bleeding Pelvic pain | 15         | No        | 46, XX      | Left       | Left oophorectomy with right ovary wedge biopsy | Dysgerminoma                                                      | Combination chemotherapy               |
| Kanagal et al. [8]      | 2013 | Abdominal distention and mass | 14         | No        | 46, XX      | Left       | USO + cytoreductive surgery + right ovarian wedge biopsy | Mixed germ cell and sex cord cell derivatives                       | Combination chemotherapy               |
| Kulkarni et al. [4]     | 2016 | Abdominal pain        | 20           | No        | 46, XX      | Left       | USO + omental biopsy    | Dysgerminoma                                                        | —                                     |
| McCuaig et al. [6]      | 2017 | Oligomenorrhea and menorrhagia | 20         | No        | 46, XX      | Left       | USO        | Dysgerminoma with syncytiotrophoblastic differentiation          | Observation                           |
| Roth et al. [5]         | 2019 | Abdominal pain and mass | 9            | No        | 46, XX      | Right      | USO        | Malignant mixed germ cell tumour                                 | Cisplatin based combination chemotherapy |
| Rafeey et al. [1]       | 2020 | Abdominal pain and mass | 10           | No        | 46, XX      | Bilateral  | USO with cytoreduction with right ovarian biopsy, para-aortic LN sampling with Partial Omentectomy | Dysgerminoma (Bleomycin, Etoposide and Cisplatin) |
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.

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