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BRIEF REPORT

GONADOBLASTOMA: A BRIEF REPORT

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ABSTRACT

Gonadoblastoma typically occurs in dysgenetic gonads, but may rarely also involve a normal ovary or testis. Approximately 40% of such tumors are bilateral. Among affected individuals, up to 80% are phenotypic females and the rest are phenotypic males. Most patients with gonadoblastoma have 46,XY karyotype or various forms of mosaicism. The gonads are usually abnormal, with hypospadias, cryptorchidism and internal female secondary sex organs, which are either in the inguinal region or intra-abdominally. Gonadoblastomas are considered to be clinically benign neoplasms, but up to 50% are accompanied by foci of malignant germ cell tumor, mostly seminoma, and occasionally yolk sac tumor, embryonal carcinoma, choriocarcinoma or teratoma. This paper presents a brief literature review based on a case of an XY female reared as male, with development of a gonadoblastoma in the left ovary.

KEY WORDS

Gonadoblastoma; rare tumor; disorder of sex development; ovary; testis.

IMPACT STATEMENT

Gonadoblastomas are rare gonadal tumours, which are usually benign but they may sometimes become malignant if not treated. This paper presents a case report of gonadoblastoma in a case of intersex followed by a brief literature review.

INTRODUCTION

Gonadoblastoma is a rare tumor which consists of more than one type of cell (germ, stromal and granulosa cells) normally found in the gonads (ovaries and testes) (1). Although gonadoblastomas tend to be benign, they may occasionally turn malignant if left untreated. In up to 60% of cases, gonadoblastomas are associated with malignant germ cell tumours: typically, pure dysgerminoma or less frequently as yolk sac tumour, immature teratoma, embryonal carcinoma or choriocarcinoma (2). The majority of patients with gonadoblastoma present in infancy and young adulthood with abnormal gonads and have certain chromosome mutations. Here, we present a case of a gonadoblastoma in an individual with intersex, followed by a brief literature review.

CASE REPORT

At birth, a baby was noted to have ambiguous genitalia with no gonads palbable externally. Karyotyping was done and was reported as 46,XY. A diagnosis of severe hypospadias with undescended testis was made. In his teens, at the age of 16 years, he was investigated for marked gynaecomastia and hypogonadism. Hormone profiling revealed a follicle stimulating hormone (FSH) level of 99.4 U/L (males < 25 U/L; LH of 79.2 U/L (males < 25 U/L); and testosterone level of 1.5 nmol/L (males 12.5-34.3nmol/L). Being genotypically male, his parents consented that he could undergo a bilateral inguinal hernia repair, correction of hypospadias and bilateral subcutaneous mastectomies. The gonads were assumed to be intraabdominally placed. At the age of 19 years, he presented with abdominal pain with signs of peritonitis. On examination, he was found to be febrile and tachycardic at 128 bpm. He had an acute abdomen and blood investigations revealed a high white cell count (maximum 11.6 x 10^9 per cmm). A diagnosis of appendicitis was made and an open appendectomy was carried out via an incision over McBurney point. Histology confirmed a necrotic appendicitis. Additionally, a tube-like structure was identified and excised during surgery was reported to be a pyosalpinx with secondary peritonitis. At the age of 25 years, the patient presented as an emergency with anpther episode of acute abdominal pain and signs of peritonism (febrile with a pulse rate of 120bpm). Blood investigations revealed a high white cell count (maximum 19.2 x 10^9 per cmm). He gave a long history of having had monthly episodes of recurrent 'haematuria'. An intravenous pylogram had revealed no abnormality in the urinary tract.

A laparotomy was performed. At operation, a torted left-tubo-ovarian mass, with normal uterus and right ovary-looking gonad were found. Both gonads were removed at surgery. Histology revealed a gonadoblastoma in the left ovary and left pyosalpinx. The right ovary contained follicular cysts and degenerating corpus luteum. The patient was prescribed long-term testosterone supplementation.

In summary, this is a case of an intersexual disorder with incomplete virilization of the external genitalia requiring multiple corrections for what appeared to be hypospadias; and normal female internal genitalia which were functional as evident by monthly "haematuria" and surgical and histological findings. Karyotype was 46,XY, probably with absence of HY antigen – mullerian inhibiting factor.

BRIEF REVIEW ON GONADOBLASTOMA

The origin of gonadoblastoma and related entities

Gonadoblastoma was first described by Scully in 1953 (3), who then went on to report a case series

of 74 patients over a time frame of 17 years (4). Classical gonadoblastoma arises from undifferentiated gonadal tissue within the dysgenetic gonads of a person having a Y chromosome (or part thereof) and a disorder of sex development (5-9).

The precursor of classical gonadoblastoma has been proposed to be undifferentiated gonadal tissue in dysgenetic gonads, which has been identified in 67% of cases (5). The germ cells in both classical gonadoblastoma and undifferentiated gonadal tissue are heterogeneous and can express octamer-binding transcription factor 4 (OCT4), testis-specific protein, Y-linked 1 (TSPY1) or both (10). The expression of OCT4 in undifferentiated gonadal tissue can determine the delay in maturation of germ cells and, consequently, the risk of carcinogenesis in dysgenetic gonads (11). The last step in the transition to classical gonadoblastoma may be the clonal expansion of germ cells and final organization in undifferentiated gonadal tissue (12). The cellular gonadal stroma, which is typical of undifferentiated gonadal tissue, can sometimes form a small part of classical gonadoblastoma (13).

A different model has been proposed where classical gonadoblastoma was hypothesized as arising from 'dissecting gonadoblastoma' (14). The "dissecting" variant is believed to be a significant intermediate step in between the development of classical gonadoblastoma and germinoma. The latter is the likely precursor of other more malignant germ cell tumors including embryonal carcinoma, immature teratoma, yolk sac tumor and choriocarcinoma. Expression of SF1 or α-inhibin in the "dissecting" variant has been investigated to identify residual sex cord elements and differentiate it from germinoma (13).

There is far less known about those cases of gonadoblastoma that occur in females with a normal 46,XX karyotype or in males with a normal 46,XY karyotype and no evidence of a sex development disorder. Rarely, gonadoblastoma occurs in normal females with a 46,XX peripheral karyotype and no evidence of a disorder of sex development (15-19). Although the underlying cause is still unknown, it is very likely that these tumors arise through a completely different molecular pathway than the classical gonadoblastoma occurring in individuals with a disorder of sex development.

Clinical and histological features

Gonadoblastoma is a rare tumor that is more likely to occur in individuals with a sex development disorder, especially in phenotypic females (80% in phenotypic females versus 20% phenotypic males) (20). The commonest predisposing mutations are 46,XY complete gonadal dysgenesis; 46,XY disorder of sex development; and 45,XO/46,XY partial gonadal dysgenesis (5). Affected individuals usually have abnormal gonads with hypospadias, cryptorchidism, and internal female secondary sex organs located in the inguinal or intra-abdominal region. Although by definition, in individuals who have a disorder of sex development have at least one gonad which is developmentally abnormal; however, this abnormality may not be detected histologically if the gonad is completely replaced by the tumour. To date, only one case of gonadoblastoma has been reported in a 46,XY phenotypic female with androgen insufficiency syndrome and an associated germinoma (21).

Histologically, gonadoblastoma is a noninvasive neoplasm which consists of rounded islands or nests of cells surrounded by a variably cellular stroma. The rounded islands are composed of germ cells that are intimately mixed with immature sex cord derivatives, commonly surrounding hyaline basement membrane deposits or, rarely, calcifications. The germ cells present in individual cases of gonadoblastoma are heterogeneous, consisting of both mature and immature forms (6). Very often, gonadoblastoma undergoes involutional changes, leading to calcification and the formation of deposits of hyalinized basement membrane material. Occasionally, the involutional changes are extensive, resulting in a calcified mass without any viable neoplastic cells. This is referred to as involuted or "burnt out" gonadoblastoma (22, 4).

Classical gonadoblastoma contains 2 types of germ cells: the mature and immature. The germinoma-like cells have been shown to be the precursor of the malignant germ cells leading to gonadoblastoma. However, other germ cells resemble spermatogonia, but vary in nuclear size (23, 13). The mature germ cells express TSPY1, whereas the immature germ cells express OCT4. There is a small subpopulation of germ cells which coexpresses both proteins (10). The sex cord cells demonstrate cytoplasmic expression of α-inhibin and nuclear expression of steroidogenic factor 1 (SF1).

In individuals with a disorder of sex development, the differentiation of testis in dysgenetic gonads can be analysed using the transcription factors SRY-box 9 (SOX9), while ovarian differentiation can be visualized using forkhead box L2 (FOXL2) (24). The sex cord element of gonadoblastoma has been shown to express only FOXL2, and not SOX9.

Cases of ovarian mixed germ cell–sex cord stromal tumor can be mistaken for gonadoblastoma, especially in normal females. Criteria have been developed for distinguishing these from gonadoblastoma in females with a 46, XX peripheral karyotype and no evidence of a disorder of sex development (22). Ovarian mixed germ cell–sex cord stromal tumor characteristically has a diffuse growth pattern and lacks the numerous rounded islands of tumor nests surrounded by a basement membrane or the degenerative changes of hyalinization, which are typical of classical gonadoblastoma. Moreover, ovarian mixed germ cell–sex cord stromal tumor normally lacks basement membrane, basement membrane material, or calcifications (25). Furthermore, gonadoblastoma contains both benign and premalignant germ cells. In contrast, ovarian mixed germ cell–sex cord stromal tumor contains germ cells of only one type that is typically benign in those neoplasms occurring in the testis, and malignant in those tumors present in the ovary.

Management of gonadoblastoma

Upon diagnosis, individuals with gonadoblastoma undergo surgery, and in cases with malignant germ cell component, this can be followed by chemotherapy. Prognosis depends on the characteristics of the malignant germ cell component. However, excellent outcome has also been reported in cases of dysgerminoma (18, 26).

It is important to take into consideration the preferences of the individuals involved when planning the management of individuals with gonadoblastoma and a concomitant disorder of sex development. The ultimate functionality of the gonad is very relevant to this decision. In order to reduce the risk of sex dysphoria, patients' advocacy groups tend to be in favor of a more conservative approach whenever medically feasible, with the aim of avoiding possible gonadectomy, or at least delay it in those children till they are capable of giving their own informed consent (22). The individual described in this case had been identified to be chromosomally an XY individual and had his external genitalia altered to function as a male. When emergency surgery revealed the patient to have a gonadal tumour and an ovarian-looking gonad on the contralateral side, a decision was made to remove both gonads. Such a decision should ideally be carried out electively after a full chromosomal, anatomical, and psychological profiling is carried out to identify the true gender orientation of the individual. If an informed decision is made to remove the intra-abdominal gonads, then these can be removed through a laparoscopic approach, possibly also including the removal of existing Mullerian tube structures.

Following gonadotectomy, the patient was supplemented with long-term testosterone replacement therapy to prevent the symptoms of reproductive hormones withdrawal and to increase virilization features. Several testosterone supplement preparations are available these being administered orally (testosterone undecanoate 237 mg twice daily), transdermally (testosterone 40.5 mg per day), as subcutaneous pellets (crystallized testosterone every six months), or by intramuscular injection (testosterone enantate 250 mg every 3-6 weeks or testosterone undecanoate 1000 mg every 10-14 weeks). The choice of supplementation form is dependent of patient preference but the use of long-term supplementary testosterone should be monitored to screen for any significant increase in haematocrit that may place the individual at increased risk of thrombotic episodes. Individuals with a prostate should be monitored with regular prostate specific antigen (PSA) screening since the supplementation may increase the risk of prostatic cancer development (27).

CONCLUSIONS

Since the first case of gonadoblastoma was described, advances have been made in our understanding of the pathophysiology of this rare neoplasm. The majority of cases of gonadoblastoma occur in individuals with a disorder of sex development and an abnormal karyotype. However, some cases have been reported in normal individuals with no evidence of a disorder of sex development. Although there is a risk of occasional errors in diagnosis, criteria have now been established for distinguishing gonadoblastoma from ovarian mixed germ cell-sex cord stromal tumor in individuals who have a normal karyotype and no evidence of a disorder of sex development.

ETHICS

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Conflict of interests

The authors have declared no conflict of interests.

Availability of data and materials

All the data supporting the findings of this study are available within the article and can be shared upon request to the corresponding author.

Authors' contribution

Writing including the original draft, review, and editing was performed by RDF, AA, CC, SS. Writing including review and editing was performed by all the authors. This work was supervised by JC-A and CS-V. All authors have read and agreed to the published version of the manuscript.

Ethical approval

Ethics approval has been obtained from the Faculty Research Ethics Committee at the Faculty of Medicine and Surgery, University of Malta (FREC ID: MED-2022-18).

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