Bilateral gonadoblastoma with extended calcification: Case report of a tumor developing on dysgenetic gonads

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Summary

Gonadoblastoma is a rare tumor occurring almost exclusively in phenotypic females with intersex disorders and dysgenetic gonads. We report a case of gonadoblastoma in an 18-year old female who was admitted to our hospital for the investigation of primary amenorrhea. The patient underwent bilateral gonadectomy. A histopathologic study revealed streak gonads with extended calcification and bilateral gonadoblastoma. We describe the histopathologic features of gonadoblastoma and the pattern of its potential malignant transformation. Difficulties in the histological diagnosis of this rare tumor are also discussed. The need for early prophylactic removal of dysgenetic gonads, especially in patients that carry the Y chromosome, is emphasized.

Key words: Gonadoblastoma; Dysgenetic gonads; Dysgerminoma; Germ cells; Calcification.

Introduction

Gonadoblastoma is a rare tumor, composed of two or more gonadal cell types, mainly germ cells and cells of sex cord derivation [1]. It occurs almost exclusively in phenotypic females with intersex disorders and dysgenetic gonads [2]. Although it has also been documented in chromosomically and phenotypically normal females, its prevalence in this minority of patients is unknown [3]. Pure gonadal dysgenesis (including Swyer's syndrome, 46 XY), mixed gonadal dysgenesis (45X/46XY) and male pseudohermaphroditism (46XY), are the most common abnormalities of sexual development associated with this form of tumor [4]. The risk of neoplasia in these dysgenetic gonads is estimated to be 25% [1]. Even though gonadoblastoma was first described by Scully in 1953 as an in situ germ-cell malignancy, its nature still remains a matter of debate: some authors describe it as an in situ cancer, while others as a benign tumor [4-6]. We describe the only case of gonadoblastoma among 40 cases of ovarian tumors (in women under 20 years of age) examined in our laboratory in the last decade.

Case presentation

An 18-year-old patient, phenotypically female, was admitted to our hospital for the investigation of primary amenorrhea. Hormone assays showed increased levels of FSH and LH (FSH: 74.6 mIU/ml, normal values: 1-8 mIU/ml and LH: 64.9 mIU/ml, normal values: 2-12 mIU/ml) while on X-ray examination of the pelvis foci of calcification were noted. Laparoscopic findings showed an hypoplastic uterus and fallopian tubes with small sized ovaries, measuring 1 x 0.5 x 0.3 cm. The patient underwent bilateral gonadectomy. Both gonads were sent immediately after surgery to our pathology laboratory, where frozen sections and formalin-fixed and paraffin-embedded tissues of the specimens were examined. Microscopic studies revealed streak gonads, composed mainly of fibrous tissue, with nests of epithelial-like tubular structures and extended calcification that almost entirely covered the stroma (Figure 1), clusters of large cells of germinal type (Figure 2) and tubules lined by Sertoli-like cells (Figure 3). These histologic features led to the diagnosis of bilateral gonadoblastoma on the grounds of dysgenetic streak gonads.

Discussion

Gonadoblastomas typically arise in dysgenetic gonads of indeterminate nature [6]. They are bilateral in about one-third (36-38%) of cases and extremely small in size, so that they may be easily missed in the gross examination [1]. They are mainly composed of nests containing a mixture of germ cells and sex cord derivatives resembling immature Sertoli and granulosa cells [6]. These sex cord derivatives may be recognized in three basic patterns: 1) surrounding round spaces filled with hyaline and eosinophilic material resembling Call-Exner bodies, 2) lining the periphery of nests of tubular structures, or 3) surrounding individual germ cells just like the follicular epithelium "embraces" the ovum [4, 6]. Besides the cellular nests, Leydig-type cells may be present in the stroma, and are to blame for steroid-hormone production and subsequent virilization of the patients [7]. Hyalinization and calcification are also commonly found [1]. Hyalinization has been described as the result of the coalescence of the hyaline Call-Exner bodies and of the basement-membrane-like band of similar material present around the nests. Calcification begins in the Call-Exner-like bodies in the form of laminated calcific spherules [6]. Gradualllly, the stroma may also undergo hyalinization and calcification. The aggregates of calcium may gradually replace tumor cells, leaving only sparse remnants of the lesion [6]. Therefore, it should be noted that the

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g. 1

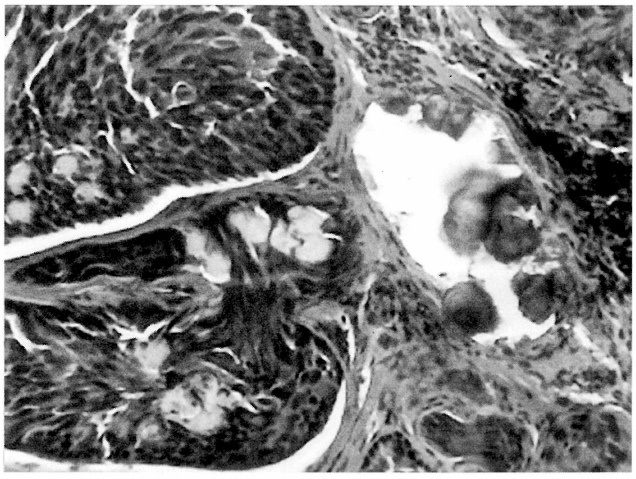
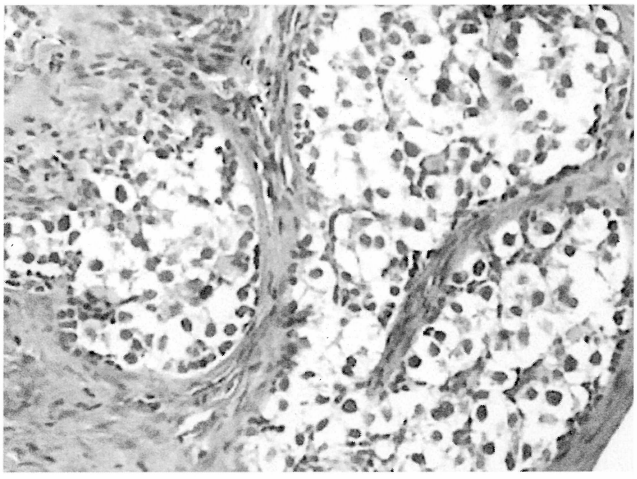


Fig. 2



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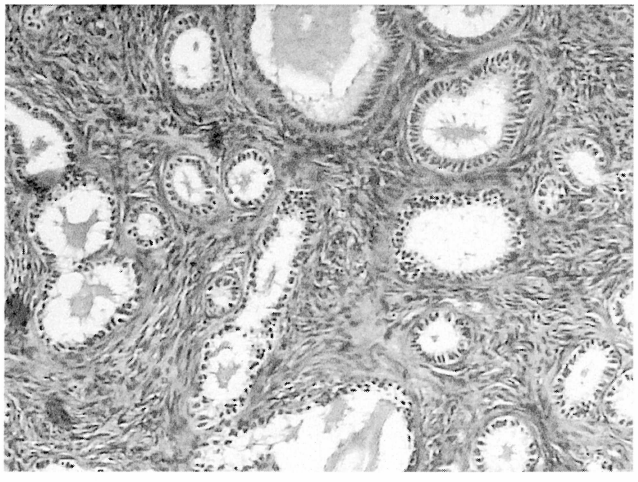

Figure 1. — Histological section of the right gonad showing nests of epithelial-like tubular structures with prominent calcification (hematoxylin and eosin x 250).

Figure 2. — Histological section of the right gonad showing clusters of large cells of germinal type (hematoxylin and eosin x 250).

Figure 3. — Histological section of the left gonad showing tubules lined by Sertoli-like cells (hematoxylin and eosin x 250).

histopathologic features of gonadoblastoma may be altered, especially in the presence of abundant calcification. In our case, the cellular components of gonadoblastoma lay mostly under calcific masses and were evaluated after decalcification of the specimen, but still with difffficulty. However, the significant association of gonadoblastoma with abnormalities of sexual development, especially Swyer syndrome, facilitates the pathologist in the diagnosis. The presence of streak gonads in a female with a clinical history indicative of Swyer syndrome or another intersex disorder is more than enough to "ring" the "alarm bell" for the existence of a gonadoblastoma.

The differential diagnosis of gonadoblastoma must be made from pure dysgerminoma and a sex-cord tumor with annular tubules [4, 8]. The diagnostic clue is the presence of calcification or the presence of a focus of typical gonadoblastoma. The sex-cord stromal tumor exhibits a pattern of growth that resembles gonadoblastoma but is easily recognized by the characteristic absence of germ cells [6, 9].

The relative overgrowth of the germinal component of gonadoblastoma in comparison with the stromal elements is indicative of a transition to dysgerminoma [4]. This malignant transformation of gonadoblastoma has been described histologically as a gradual progression to a locally infiltrating pattern predisposing to the metastatic spread of the lesion [6]. However, the histological pattern of gonadoblastoma itself has never been reported in a metastasis, and it seems that this tumor always remains confined to the gonads [4]. Still, there is no doubt that gonadoblastoma may progress to invasive cancer, as in 50% of cases reported transition to dysgerminoma has been described and an additional 10% of cases exhibit development of even more malignant germ cell neoplasms, such as embryonal teratoma, embryonal carcinoma, endodermal sinus tumor or choriocarcinoma [10].

The definition of gonadoblastoma either as a benign neoplasm or as an in-situ cancer is more of a theoretic dilemma than a choice of any clinical significance, as it does not affect the therapeutic management which consists of early prophylactic removal of dysgenetic gonads, especially in patients that carry the Y chromosome [5, 11].

Conclusion

Gonadoblastoma is a neoplasm affecting mostly patients with disorders of sexual development. The recognition of its histopathologic features can be a challenging task for the pathologist, especially in cases where abundant calcification is present. However, the diagnosis is usually facilitated by the information provided in the clinical history, chromosomal analysis and laparoscopic findings.

References

[1] Rosai J., Ackerman L.V.: "Female reproductive system". In: Rosai J. (ed.). Surgical Pathology. Edinburgh, Mosby, 2004, 1704.

[2] Bjersing L., Cajander S.: "Ultrastructure of gonadoblastoma and dysgerminoma (seminoma) in patient with XY gonadal dysgenesis". *Cancer,* 1977, *40,* 1127.

[3] Nakashima N., Nagasaka T., Fukata S., Oiwa N., Nara Y., Fukatsu T. *et al.*: "Ovarian gonadoblastoma with dysgerminoma in a woman with two normal children". *Hum. Pathol.*, 1989, *20,* 814.

[4] Talerman A.: "Germ cell tumors of the ovary". In: Kurman R.J. (ed.). Blaustein's Pathology of the Female Genital Tract. New York, Springer, 2002, 1017.

[5] Casenave F., Saurel J., Boutet G., Parneix I., Brun G.: "Gonadoblastoma. Review of the literature. A propos of a case". *J. Gynecol. Obstet. Biol. Reprod.* (Paris), 1986, *15,* 757.

[6] Scully R.E.: "Gonadoblastoma. A review of 74 cases". *Cancer,* 1970, *25,* 1340.

[7] Mackay A.M., Pettigrew N., Symington T., Neville A.M.: "Tumors of dysgenetic gonads (gonadoblastoma). Ultrastructural and steroidogenic aspects". *Cancer,* 1974, *34,* 1108.

[8] Scully R.E.: "Sex cord tumor with annular tubules. A distinctive ovarian tumor of the Peutz-Jeghers syndrome". *Cancer,* 1970, *25,* 1107.

[9] Ikarashi T., Sudo N., Arakawa O., Furuya M., Kato M., Hirashawa H. *et al.*: "46, XY pure gonadal dysgenesis with gonadoblastoma". *Nippon Sanka Fujinka Gakkai Zasshi,* 1989, *41,* 1831.

[10] Kariminejad M.H., Movlavi M.A., Nassergodssi M.A., Ghafoorzadin D., Behjatnia Y.: "Gonadoblastoma associated with mixed gonadal dysgenesis". *Am. J. Obstet. Gynecol.*, 1972, *113,* 410.

[11] Berg F.D., Kurzl R., Hinrichsen M.J., Zander J.: "Familial 46, XY pure gonadal dysgenesis and gonadoblastoma/dysgserminoma: case report". *Gynecol. Oncol.,* 1989, *32,* 261.

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