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46,XY PURE GONADAL DYSGENESIS WITH GONADOBLASTOMA

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Synopsis A case of gonadoblastoma on one side in streak gonads in a phenotypic female with a chromosomal 46,XY pattern is described. The histopathological resemblance between ganadoblastoma and sex cord tumor with annular tubules is discussed. The high serum testosterone level, being unrelated to the administration of human chorionic gonadotropin is valuable for the diagnosis of gonadoblastoma in an individual with dysgenetic gonads. Gonadoblastoma is frequently very small in size and is located in ectopic regions, so that laparotomy with biopsy has been stressed. The hormonal supplement for a postgonadectomied girl is also discussed.

Key words: 46,XY • Pure gonadal dysgenesis • Gonadoblastoma • Testosterone

Introduction

In 1955, Swyer described 46,XY karyotype pure gonadal dysgenesis (XY-PGD, so-called Swyer's syndrome), characterized by the tall eunucoid phenotypic female, absence of the somatic stigmata of Turner's syndrome, normal female type external genitalia, the underdeveloped mullerian structures, and bilateral streak gonads[5)7)8)11)]. The familial XY-PGD was inherited as either X-linked recessive trait or male-limited autosomal dominant trait. The XY-PGD was speculated as late embryonic testicular regression according to the critical regression time. The gonadal atresia in XY-PGD was attributed to abnormalities of either the structural genes of H-Y (Histocompatibility Y) antigen, regarded as the testis-determining factor or the gonad-specific H-Y receptors[2)]. Furthermore, the prophylactic gonadectomy was indicated as soon as the confirmation of diagnosis was made, because gonadoblastoma (GBL) and dysgerminoma (or seminoma) developed frequently after puberty, especially in XY-PGD with H-Y antigen[6)~9)11)13)]. The report addressed a patient of XY-PGD with GBL and discussed the hormonal activity, the significance of laparotomy and the histopathological characteristics[7)11)].

A Case Report

A 16-year-old girl was referred for the investigation of primary amenorrhea. Prenatal and family histories were noncontributory. Her maternal parents were cousins in the marital relationship and their siblings (2 brothers and her mother) appeared normal phenotypes. Her paternal 6 cousins (4 brothers and 2 sisters) were also supposed to be normal ones.

The physical examination revealed a tall girl, 167-cm height, 55-kg weight, small breasts remained in Tanner Stage II after estrogen-progestogen supplementation during one year, poorly developed pubic hair of Tanner Stage II, absence of Turner's stigmata and low-tone voice. The pelvic examination demonstrated moderate-degreed clitoromegaly, normal external genitalia of female type, a normal vagina, small anteverted uterus with erosion and no pelvic tumor (Photo. 1). The skeretal roentogenogram in 18-year-old revealed the correspondance for her legal age.

Preoperative hormonal analyses showed: prolactin 10.3~20.8 (normal range: 2~20ng/ml), follicle stimulating hormone (FSH) 144.2~184.7 (5~20mIU/ml), lutenizing hormone (LH) 144.2~159.9 (5~20mIU/ml), dehydroepiandroster-

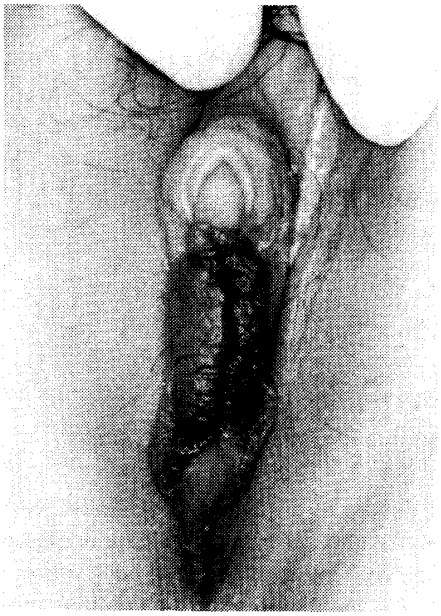

Photo. 1. External genitalia of female type and clitolomegaly.

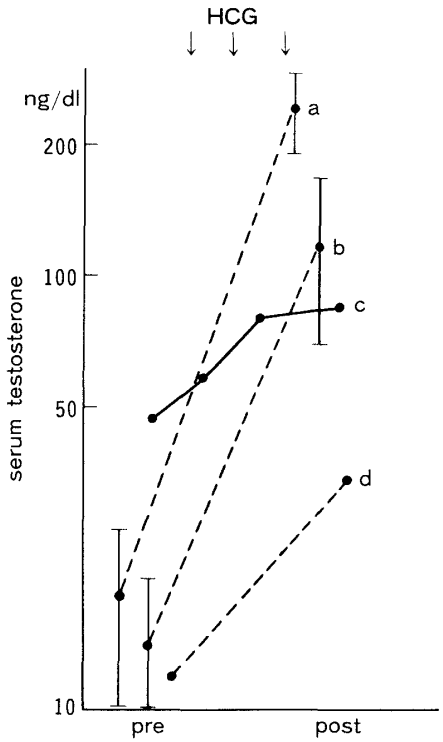

Fig. 1. Serum testosterone level in the HCG test (HCG 3,000 IU/m²/day by 3 days im.): This case (c), normal boys (a), ones of retentio testes (b), other case of XY-PGD without GBL (d).

one 6.37 (1.2～7.5ng/ml), androstenedione 0.52 (0.5～1.5ng/ml), testosterone 45～69 (20～60ng/dl) and 0.6 in pre- and post-operative state, respectively, estradiol 10 (34～223pg/ml), 17-OH-corticosteroid 4.7 (2～4mg/day), and 17-ketosteroid 9.1 (4～8mg/day). The reaction curve of serum testosterone after HCG injection[10)12)] placed between those of retentio testes and XY-PGD without the evidence of GBL (Fig. 1). The maturation index of vaginal smear revealed 30/69/1.

The karyotype of peripheral blood lymphocytes was 46,XY. There were no abnomalities of chromosomes in members of her family.

The laparotomy was performed in her 18 of age because of both the existence of a Y chromosome and the gradual increment of serum testosterone level. The uterus was atrophic and tubes appeared normal. The right gonad consisted of two parts; one, placed on the outer side of fimbria, up to 1cm in diameter, showed a lobulated soft mass, and the other, located at the side of isthmus, showed an uneven hard mass, measured 1.0 by 0.5cm. The left gonad appeared streak. The first one was extirpated for the histopathological examination. After the confirmation of GBL, the bilateral salpingo-oophorectomy was performed.

At the post-operative histopathological analyses the right gonad revealed findings of the typical GBL. The tumor was separated in lobulations by connective tissue and consisted of both the large round cells and the medium-sized oval cells, which corresponded to germ cells and cells of a sex-cord type, respectively. The germ cells were lined by the flattened sex-cord cells, which resembled primary follicles (Photo. 2, Left). The tumor nests contained hyalinized materials surrounded by cleave-nucleated sex-cord cells (Photo. 2, Right). These materials were continuous to surrounding hyalinized basement membranes, which separated the tumor nests into small fragments (Photo. 3). Furthermore, there were several buds of GBL and compact spindle cells similar to ovarian stroma (Photo. 4). The left gonad revealed streak gonad with several stromal cells.

The hormonal supplementation had started to achieve the cyclic hormonal dynamics with conjugated estrogen 3.75mg and medroxyprogesterone acetate 10mg per day during 6 years from 17-year-old and the artificial menstrual cycles were established. After the normalization of serum testosterone levels by the gonadectomy in 18-year-old, the breasts development was remained minimal in Tanner Stage II. Patient underwent

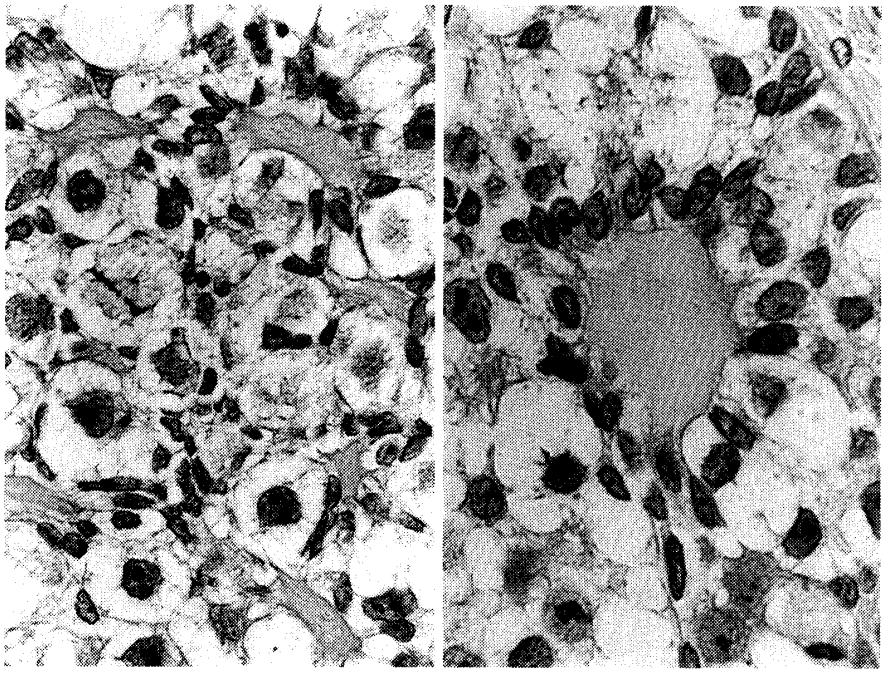

Photo. 2. Left : Germ cells lined by sex-cord cells and hyalinized foci (H-E, ×200). Right : Hyaline bodies, surrounded by cleave-nucleated cells (×400).

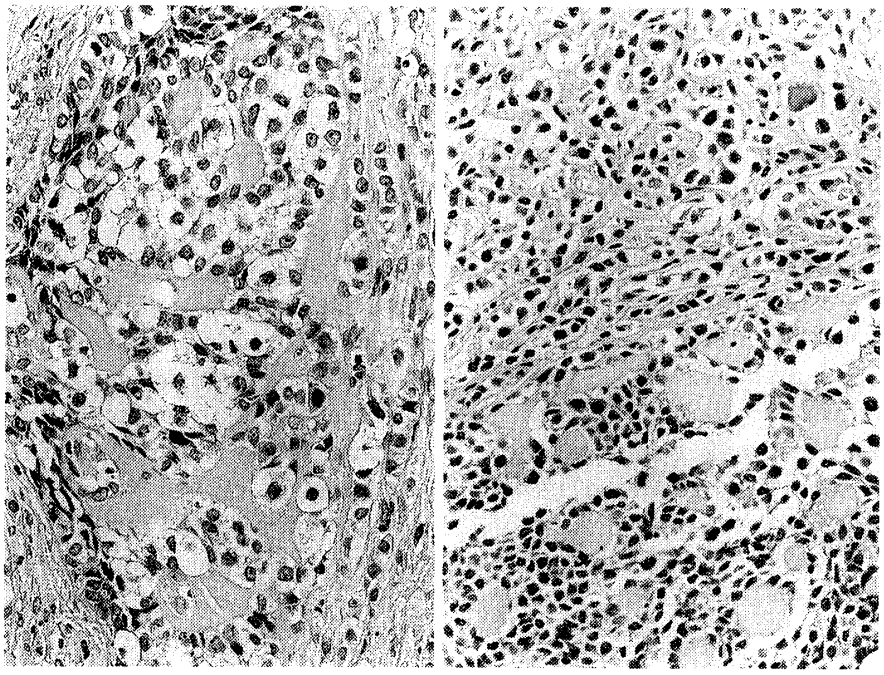

Photo. 3. Left : Hyaline materials, spilled out around tumor nests (×100). Right : Bands of hyaline material mixing with sex-cord-stromal cells and the resultant ill-definition of germ cells (×50).

cosmetic mastoplasty in 23-year-old. At present there is no recurrence of GBL. The continuation of hormonal supplement is argued because the side effects of hormones have exhibited as hyperlipemia and hypertension (132/92mmHg).

Discussion

Gonadal tumors were found at least 30% in individuals with XY-PGD and were particularly frequent (55%) in H-Y antigen-positive patients.

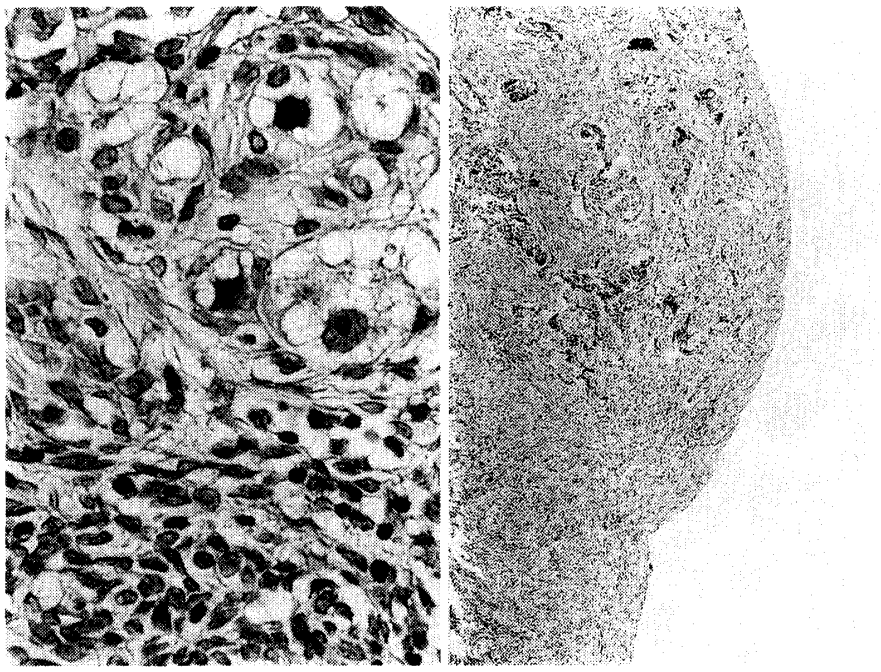

Photo. 4. Left: Buds of GBL in ovarian stroma, similar to primary follicles (×200). Right: GBL in ovarian stroma (×10).

These tumors were almost always GBLs or dysgerminomas[6)~9)11)13)]. The GBL is the tumor which histologically shows solid alveolar patterns and consist of germ cells and sex-cord-stromal cells. These sex-cord cells are speculated as Sertoli cells because of spermatogenetic remnants in vivo and their production of basement membrane in vitro[12)]. In the present case, however, these sex-cord cells were speculated to granulosa cells on the ground that these cells accompanied with ovarian stroma, surrounded the germ cells, which were similar to those of follicles and contained cleaved nuclei (coffee-bean appearance). Furthermore, the characteristics of hyaline bodies in GBL resembled closely those in sex-cord tumor with annular tubules (SCTAT) in the following respects: These materials were continuous to hyalinized basement membranes along the edges of tumor nests and consisted of basal lamina[1)3)8)]. Therefore, GBL could show the histopathological spectrum from pure dysgerminoma on one side to dysgerminoma with SCTAT on the other side. The careful detection of GBL was insisted in laparotomy since there were microscopic-sized GBL.

Primary amenorrhea, abnormal pubescent development and urinary signs (Dash or Frasier syndrome) are the first clue for the diagnosis of XY-PGD and the GBL is usually identified in puberty or downward, even in 15-month-old[6)~8)11)]. A hormonal analysis is often valuable for the diagnosis of XY-PGD. Patients with XY-PGD shows elevated FSH and LH levels, however, the patients with testicular feminization syndrome has FSH and LH within the normal range[7)]. Therefore, in the female-phenotyped patients with a Y chromosome and elevated FSH level, the laparotomy and the gonadal biopsy might be mandatory to avoid the confusion of clinical diagnosis[7)]. It is generally accepted in XY-PGD that the gonadectomy is performed as soon as possible because there are an early development and an increased prevalence of GBL in XY-PGD[6)7)11)].

Tumor cells or associated stromal cells in GBL produces dehydroepiandrosterone, testosterone, prolactin, estrogen and progesterone. Based on these findings, the high serum testosterone value without normal response after HCG injection[10)12)] was regarded as the hormanal marker of the development of GBL in cases of XY-PGD as in this present case.

The therapeutically castrated juvenile cases had to be rescued hormonally soon after operation and

maintained long-term to reduce cardiovascular disease, osteoporosis and target organ atrophy[4]. The periodical assessment of the serum lipoprotein profile was worthwhile to detect any adverse effects and essential to decide the favorable hormonal regimens[4]. Though the serum testosterone value of this case dropped to the normal female range after bilateral gonadectomy, the supplemental hormonal therapy with conjugated estrogen and medroxy-progesterone acetate could not sufficiently develop her secondary sexual characteristics. Regarding to the hormonal supplements, further studies concerning the period of administration and the side effects are necessary for these cases[4].

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概要 Gonadoblastomaを合併した，46,XY純粋型性腺形成不全症例について報告した．症例は，16歳で，高テストステロン血症，女性型表現型，女性型内性器，線状性腺を示し，右性腺には，1cm.，1×0.5 cm.大の2個のGonadoblastomaが認められた．

また，Gonadoblastomaにおける，Sex-cord tumor with annular tubules（SCTAT）との病理組織学的類似性，および，高テストステロン血症症例のHCG負荷テストの診断的意義について考察した．さらに，若年者における性腺摘出後の性ホルモン補充療法の問題点についても考察した．