Late Histopathological Features of Testis Tissue in a Patient With Male Pseudohermaphroditism Due to Leydig Cell Aplasia

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Leydig cell aplasia is a rare form of male pseudohermaphroditism. We determined Leydig cell aplasia in a 39 yr old patient, grown up as a female, with female external genitalia and primary amenorrhea. Gonads were bilaterally palpable in the inguinal regions. Karyotype was 46, XY. Hormonal evaluation revealed markedly elevated gonadotropin levels with a low testosterone, which failed to increase after human chorionic gonadotropin stimulation. In Leydig cell aplasia, classically, testicular histology reveals seminiferous tubules, whereas Leydig cells are not present or appear only as immature forms. In addition to classical features of Leydig cell aplasia, we determined diffuse fibrosis, atrophy, interstitial edema and marked thickness in lamina propria of seminiferous tubules, and although Sertoli cells were seen, no germ cell was present. Very long duration of undescended testes (cryptorchidism) may be responsible for these additional histopathological changes. Because of a criptorchid testis is more likely to undergo malignant degeneration than normal testes, many urologists recommend orchiectomy for unilaterally undescended testicle.

Key Words: Leydig cell aplasia, male pseudohermaphroditism, cryptorchidism, diffuse fibrosis, atrophy and interstitial edema.

Introduction

Leydig cell aplasia or hypoplasia (LCH) is a rare form of male pseudohermaphroditism (46, XY) resulting from inadequate fetal testicular Leydig cell differentiation and estimated incidence of 1:1,000,000. The Leydig cells are unable to develop because of an inactivating mutation of the LH receptor that fails to provide the necessary stimulation of intracellular pathways (1). The underlying gene defect in Leydig cell hypoplasia was first described by Kremer et al (2) and various other defects have since been described (3-6,7). Elevated gonadotropins and low testosterone concentrations are found, and there is no rise in circulating testosterone after hCG injections. Although there is some Wolffian duct development, there is insufficient testosterone production to induce normal male differentiation of the external genitalia. Müllerian duct structures are absent because of normal Sertoli cell production of the Müllerian-inhibiting hormone. The phenotype is dependent on the extent of intrauterine testosterone secretion.

Two types of Leydig cell hypoplasia have been described. Type 1 is the most severe form, resulting in a female phenotype of the external genitalia with blind ending vagina, primary amenorrhea, and absence of secondary sex differentiation at puberty. It is caused by inactivating mutations in the LH receptor that completely prevent LH signal transduction and thus testosterone production. Leydig cell hypoplasia type 2 is characterized by milder signs of androgen deficiency with a predominantly male habitus but signs of hypogonadism with micropenis and/or hypospadias. This milder form is derived from mutations of the LH receptor, which only partially inactivate signal transduction and retain some responsiveness to LH (8). Histologic examination of the prepubertal testis...
demonstrates Sertoli cells with rare no spermatogonia and a marked paucity or absence of Leydig cells (9). The postpubertal testis may show spermatogonia but absence of germ cell maturation; the diameter of tubules is no greater than that of an 18-month-old infant (10). Epididymides and deferent ducts are usually present, whereas the uterus, tubes or upper vagina are not found. The histopathological hallmarks of cryptorchidism include; decreased numbers of Leydig cell, degeneration of Sertoli cells, failure of primary spermatocyte to develop and reduced total germ cells.

We aimed to report histopathological findings of testis tissue in a patient with Leydig cell aplasia and effect of long term cryptorchidism on testis tissue.

Materials and Methods
A 39 yr old female patient (GU) was referred to the Department of Endocrinology because of primary amenorrhea. The patient was born at the term after uncomplicated pregnancy from consanguineous parents, and was considered to be a female. The patient had been married but then she divorced after 3 years due to unsuccesfull sexual relationship. She presented with female external genitalia. A blind vaginal pouch (at the 10-15 mm deeping), and absence of Müllerian duct derivates were found in gynecological examination. Pubic and axillar hair and labium majus nearly were normal, labium minus was infantil and clitoromegali was absent. Breast development was at the infantil stage.

Results
Laboratory findings: While uterus and ovaries could not be found in ultrasonographic examination, 21x30x13 mm size testes were seen in the inguinal canal. Karyotype was 46,XY. Hormonal evaluation revealed markedly elevated gonadotropin levels with a low testosterone (LH: 27.61 mIU/ml, FSH:80.85 mIU/ml, progesterone: 0.174 ng/ml, total testosterone: 0. 066 ng/ml, E2:10.02 pg/ml, Prl:12.61 ng/ml). After hCG administration (intramuscular injection of 4000 IU of chorionic gonadotropin daily for 4 days) serum testosterone was 0.074 ng/ml. With these findings the patient was diagnosed as Leydig cell aplasia and both testes were removed with surgical intervention under general anesthesia.

Tissue preparation: Testis tissue specimens were fixed in Bouin's solution. The samples were dehydrated in graded alcohols, cleared in xylene and embedded in paraffin for light microscopic examination. The specimens were serially sectioned at 4 micrometer thickness, and they were picked up on a glass microscopic slide. In order to examine the general properties of the testes, the paraffin sectiones were stained with Hematoxylin-Eosin, anti-vimentin and Periodic Acid Schiff (PAS)-Hemalaun. We obtained normal human testis specimens from pathology department to compare Leydig cell aplasia at the light microscopical level.

Histological examination; Normal human testis specimens showed the seminiferous tubules and a population of interstitial cells that occur in small clusters and lie in the space between adjoining tubules. They consisted mostly of Leydig cells (LC). They were readily identified by virtue of their location and by small round nucleus and eosinophilic cytoplasm (Figure-1). In the histopathological examination of testis specimens of patient with Leydig cell aplasia, we determined diffuse fibrosis in interstitial area, atrophy and interstitial edema in seminiferous tubules. Although Sertoli cells were seen, no germ cell component related to spermatogenesis was present in seminiferous tubules. (Figure 2 and 3). In addition to differences in the dimensions of Seminiferous tubules, the histological figures showed very clearly the pathological thickening of the whole lamina propria of Seminiferous tubules (Figure-4). Histopathological appearance of testis of the patient demonstrated some differences from classical features of pure Leydig cell aplasia.
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Discussion

Our patient was Leydig cell aplasia type 1 because, she (he) had almost complete female phenotype of the external genitalia with blind ending vagina, primary amenorrhea, and absence of secondary sex differentiation at puberty. It is caused by inactivating recessive mutations in the LH receptor that completely prevent LH signal transduction and thus testosterone production (7).

In Leydig cell aplasia, classically, testicular histology reveals seminiferous tubules, whereas Leydig cells are not present or appear only as immature forms (10). Although epididymes and deferent ducts are usually present; the uterus, tubes or upper vagina are not found. Despite of the fact that seminiferous tubules were also determined, they were considerably atrophic and, although Sertoli cells were seen, no germ cell component related to spermatogenesis was present. Furthermore we found diffuse fibrosis, interstitial edema and a marked thickness in whole lamina propria of seminiferous tubules. These results showed some differences from classical features of Leydig cell aplasia. The patient remained as cryptorchid until 39 yr old. Indeed, ultrastructure of the cryptorchid testis begins to differ from the normally descended testis by the second and third year of life (11). The histopathologic hallmarks associated with cryptorchidism are evident between 1 and 2 years of age and include decreased numbers of Leydig cells, increased peritubular fibrosis, degeneration of Sertoli cells, delayed disappearance of gonocytes, delayed appearance of adult dark (Ad) spermatagonia, failure of primary spermatocytes to develop, and reduced total germ cell counts (11,12). Therefore, very long duration of cryptorchidism (39 years) may be responsible for these additional histopathological changes in testis tissue. A criptorchid testis is 20-30 times more likely to undergo malignant degeneration than normal testes. Becasue of the increased risk of neoplasia, many urologists recommend orchiectomy for unilaterally undescended testicle in a patient first seen during after puberty (13).

As a result; In addition to Leydig cell aplasia, very long duration of cryptorchidism may lead to atrophy in seminiferous tubule, marked thickness in lamina propria and diffuse fibrosis.
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References


