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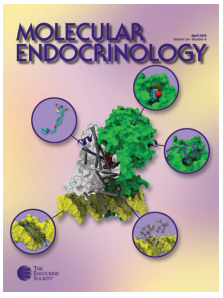

Testicular Effects of Isolated Luteinizing Hormone Deficiency and Reversal by Long-Term Human Chorionic Gonadotropin Treatment

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Isolated gonadotropin deficiency due to inactivating mutations of β-subunits of LH or FSH are rare. Isolated LH inactivation was identified in 1992, although the patient's clinical characteristics had been reported earlier (1, 2). Males with inactivating LHβ mutations (five adults have been reported) present with clinical features of hypogonadism and oligo/azoospermia (1–5). In 2004, we reported the case of a 30-yr-old man with this clinical presentation (3). The patient gave informed consent for a testicular biopsy (Fig. 1, A and B), which showed arrested spermatogenesis and fetal-type Leydig cells (3). A homozygous missense mutation (G36D) in the LH β-subunit gene was identified that abrogated $\alpha\beta$-subunit dimerization and rendered LH biologically and immunologically inactive (3). We initiated treatment with intramuscular human chorionic gonadotropin (hCG) (1500 IU three times a week for 1 month, then 5000 IU weekly). Tanner staging was 5 after 3 months. After 24 months treatment, FSH decreased to 2.3 mIU/ml (normal range, 1–8 mIU/ml) and testosterone increased to 7 μg/liter (normal range, 2.5–10.0 μg/liter). There was near normalization of testicular structure, which was likely related to Leydig cell maturation and subsequent increases in intratesticular testosterone, leading to a sperm count of 1000 spermatozoids/ml. (Fig. 1, C and D). The patient and his wife conceived a child by intracytoplasmic sperm injection from ejaculated sperm. The male child was heterozygotic for the G36D LHβ mutation and was phenotypically normal with normal LH, FSH, and testosterone levels at the age of 4 wk.

Although rare, isolated LH deficiency due to inactivating mutations of LH β-subunit gene is a useful illustration of the precise role of LH in testicular maturation and function in humans. Furthermore, it also provides a good example of the clinical efficacy of LH receptor stimulation using hCG.

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Abbreviation: hCG, Human chorionic gonadotropin.

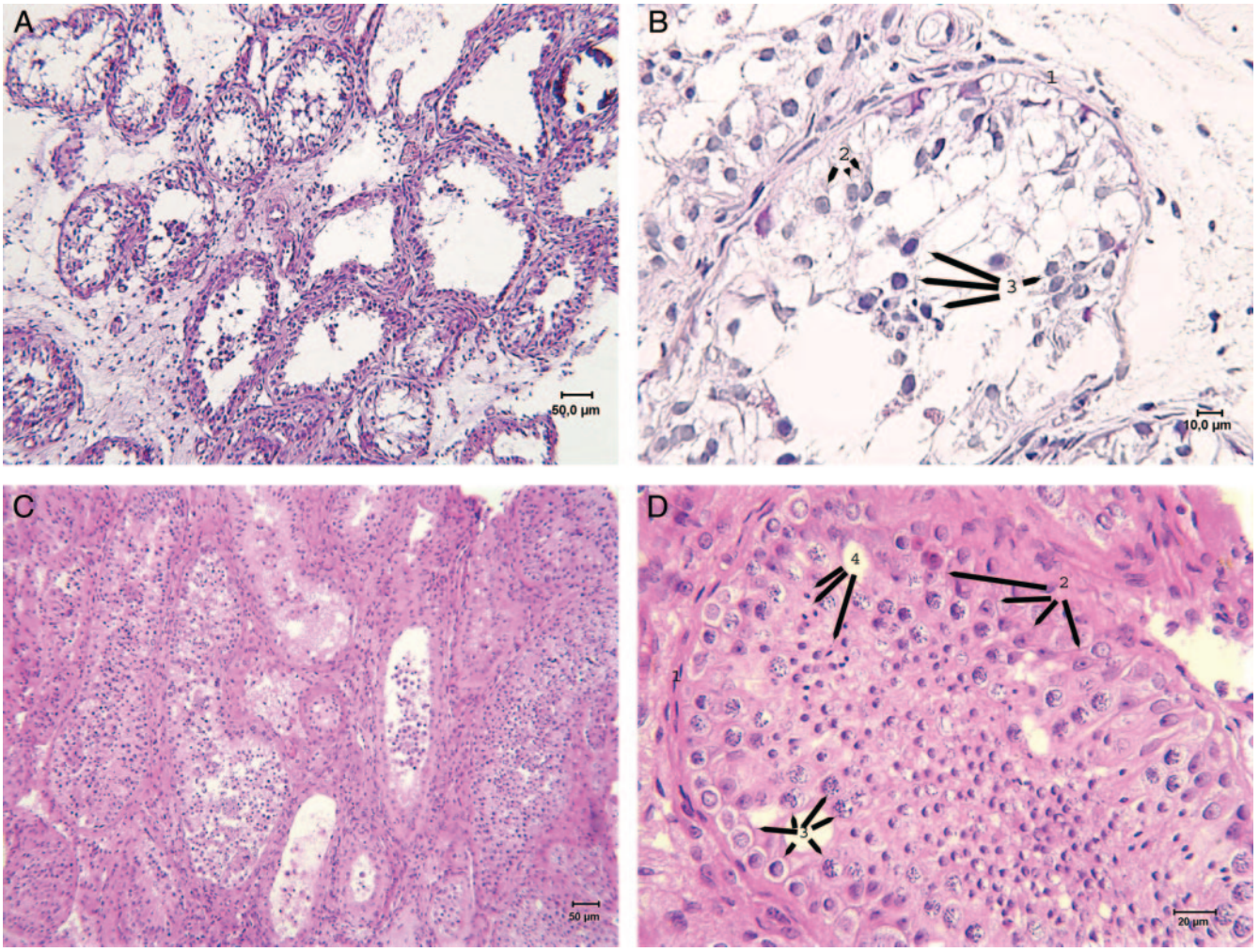

FIG. 1. Testicular biopsy from a patient with isolated LH deficiency due to an inactivating G36D mutation in the LH β-subunit gene before hCG administration. A and B, Before treatment. The testicular volume was 8 ml. Hypocellular tubules with greatly decreased spermatozoid numbers, arrested spermatogenesis, and absent mature forms were seen. B, 1, Tunica propria; 2, normal Sertoli cells; 3, and primary immature spermatocytes. A, Hematoxylin and eosin stain; magnification, ×100; B, hematoxylin and eosin stain; magnification, ×400. C and D, After treatment with 5000 IU hCG im once weekly for 24 months. The volume of the testis increased to 14 ml. Large hypercellular tubules with increased spermatogenesis and complete maturation forms are seen. D, 1, Tunica propria; 2, normal Sertoli cells; 3, primary immature spermatocytes; 4, with the addition of spermatids. C, Hematoxylin and eosin stain; magnification, ×100; D, hematoxylin and eosin stain; magnification, ×400.