Brief Communication

A rare case report of 46XY mixed gonadal dysgenesis

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ABSTRACT

A 16-year-old person, reared as female presented with complaints of genital ambiguity and primary amenorrhoea along with lack of secondary sexual characters, but without short stature and Turner's stigmata. She was taking steroids after being misdiagnosed as congenital adrenal hyperplasia (CAH). Karyotype analysis revealed 46XY karyotype. There was no evidence of hypocortisolemia (cortisol 9.08 μg/dl, adrenocorticotropic hormone [ACTH] 82.5 pg/ml) or elevated level of 17-OH-progesterone (0.16 ng/ml). Pooled luteinizing hormone (LH) was 11.79 mIU/ml and follicle-stimulating hormone (FSH) was 66.37 mIU/ml. Serum estradiol level was 25 pg/ml (21-251). Basal and 72 h post beta-human chorionic gonadotropin (hCG) levels of androstenedione and testosterone levels were done (basal testosterone of 652 ng/dl and basal androstenedione of 1.17 ng/ml; 72 h post hCG testosterone of 896 ng/dl and androstenedione of 1.34 ng/ml). Magnetic resonance imaging (MRI) pelvis (with ultrasonogrphy [USG] correlation) revealed uterus didelphys with obstructed right moiety and bilateral ovarian-like structures. Right sided gonads and adjacent tubal structures were visualized laparoscopically and removed. Left sided gonads were not visualized and Mullerian remnants were adhered to sigmoid colon. Histopathological examination revealed presence of testicular tissue showing atrophic seminiferous tubules with hyperplasia of Leydig cells. No ovarian tissue was seen. Based on these results a diagnosis of 46XY mixed gonadal dysgenesis (MGD) was made, which is rare and is difficult to distinguish from 46XY ovotesticular disorder of sexual differentiation (OT-DSD). The patient was managed with a multidisciplinary approach and fertility issues discussed with the patient's caregivers.

Key words: 46XY, disorders of sexual differentiation, mixed gonadal dysgenesis

Introduction

Mixed gonadal dysgenesis is a condition of unusual and asymmetrical gonadal development leading to an unassigned sex differentiation. A number of differences have been reported in the karyotype, most commonly a mosaicism 45,X/ 46, XY. We herein report an interesting case of mixed gonadal dysgenesis.

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Case Report

A 16-year-old person, reared as female, born out of nonconsanguineous marriage, presented to our clinic with complaints of genital ambiguity and primary amenorrhoea along with lack of secondary sexual characters. She underwent reduction clitoroplasty and vaginoplasty on 22/03/2000. There was no h/s/o crisis or cyclical abdominal pain in the past. However, the patient was taking 5 mg of prednisolone after being labeled as a case of congenital adrenal hyperplasia (CAH). No history of recent onset change in sexual identity. Other past history, family history, antenatal history, perinatal history, and developmental history were noncontributory. On earlier evaluations, a small uterus was found on ultrasonogrphy (USG) studies but no gonads were visualized.

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On examination, anthropometric measurements were appropriate for her age. She was normotensive for her age group. General and systemic examinations were unremarkable. No Turner's stigmata were visualized. Genital examination revealed a single perineal opening, phallic length of 5 cm, with a well-formed glans and a well-formed scrotal sac. Prader staging was 3/5. Sexual maturity rating was A0P1B2. The mucosa above the perineal opening was pink in color.

Investigations

Routine biochemical and hematological investigations were normal. A karyotype analysis revealed 46XY karyotype. There was no evidence of hypocortisolemia (cortisol 9.08 μg/dl, adrenocorticotropic hormone [ACTH] 82.5 pg/ml) or elevated level of 17-OH- progesterone (0.16 ng/ml). Basal testosterone level was 588 ng/dl with basal androstenedione level of 1.83 ng/ml (male: 0.7-3.6, female: 0.3-3.5). Pooled luteinizing hormone (LH) was 11.79 mIU/ml and follicle-stimulating hormone (FSH) was 66.37 mIU/ml. Serum estradiol level was 25 pg/ml (21-251). Basal and 72 h post beta-human chorionic gonadotropin (hCG) levels of androstenedione and testosterone levels were done (basal testosterone of 652 ng/dl and basal androstenedione of 1.17 ng/ml; 72 h post hCG testosterone of 896 ng/dl and androstenedione of 1.34 ng/ml).

MRI pelvis [Figure 1] revealed uterus didelphys with obstructed right moiety and bilateral ovarian-like structures.

Management

The patient was managed in collaboration with Department of Gynecology and Obstetrics and discussions with patient party and a decision was taken to remove the gonads and Mullerian structures laparoscopically. However at the time of surgery, only right sided gonads and adjacent tubal structures were visualized and removed. However, left sided Mullerian remnants could not be removed due to adhesion to sigmoid colon.

Histopathological examination [Figure 2] revealed presence of testicular tissue showing atrophic seminiferous tubules with hyperplasia of Leydig cells. Epididymal tissue and an epididymal cyst are also present. However, no ovarian tissue was seen.

The patient is still admitted with us as on the day of writing this manuscript and is being managed with oral estrogens.

Discussion

This 16-year-old normotensive person reared as a girl came with a labeled diagnosis of 46XX disorder of sexual differentiation (DSD) (diagnosed to be 46XX on the basis of buccal smear examination done outside), thought to be due to CAH and started on prednisolone 5 mg once a day, even without a history suggestive of salt losing crisis. Before the karyotype report was available, since the patient could not produce documents or investigation reports favoring the diagnosis of CAH and thus justifying the use of prednisolone, we thought of reevaluating the patient completely. We stopped the corticosteroid for 3 days and then reevaluated the adrenal axis, which was normal. The patient is still off corticosteroids and doing fairly well. Since the basal testosterone level was high, aromatase deficiency and partial androgen insensitivity syndrome (PAIS) were next in the line of diagnostic possibilities. PAIS was ruled out due to presence of Mullerian structures visualized on MRI pelvis, as Mullerian-inhibiting substance (MIS) secretion is not hampered in PAIS. The patient had no clinical or hormonal features suggestive of aromatase deficiency in the

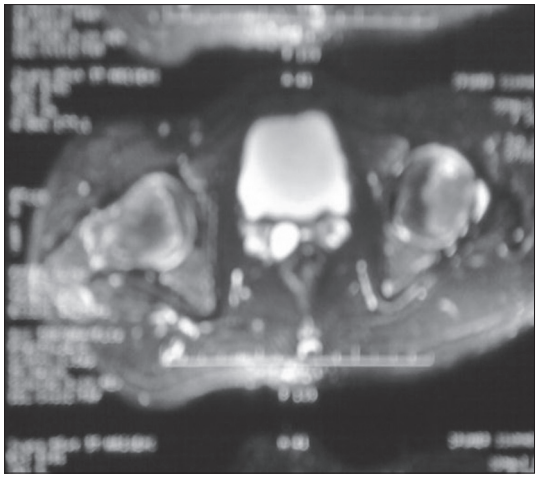

Figure 1: Magnetic resonance imaging (MRI) showing rudimentary uterus and bilateral ovarian-like structures

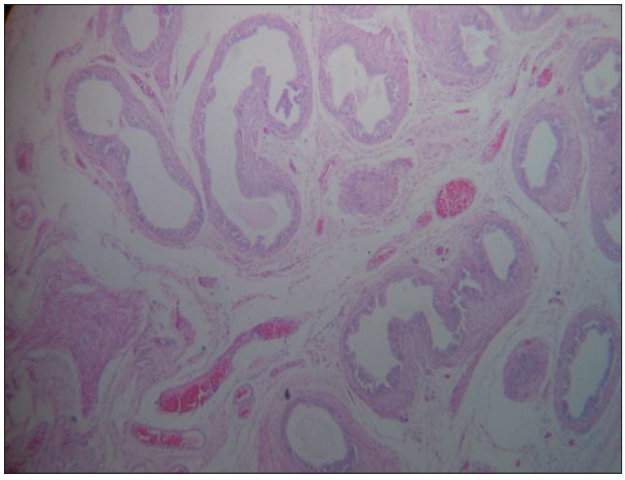

Figure 2: Histopathological examination (HPE) of resected gonads showing atrophic seminiferous tubules (×20)

form of absence of virilization of mother during pregnancy, presence of significant values of serum estradiol levels, low normal levels of serum androstenedione and an absence of a significant rise of serum androstenedione levels even after beta-hCG stimulation. Lastly, we were left with diagnostic considerations of ovotesticular DSD (OT-DSD) and MGD. The syndromic diagnoses associated with abnormal gonadal development were not suspected as patient did not reveal any of the known features of such defects (e.g., wild type [WT]-1, steroidogenic factor [SF]-4, DAX-1, etc.).

Since patient was reared as female with history of clitoroplasty and vaginoplasty in the past and functionality of the external genital organs was not expected, a combined decision involving the patient party, gynecologist, and our department was taken to remove the gonads and assign a female sex to the patient. On histopathological examination (HPE) of the gonadal tissue, only testicular tissue was seen, which favored the diagnosis of MGD over OT-DSD. Also a 46XX karyotype is more likely to be found in patients with OT-DSD. Although 46XO/46XY is the most common karyotype in patients with MGD, 46XY karyotype has also found in such patients. The only method of differentiating 46XY MGD from 46XY OT-DSD is by histopathological demonstration of testicular tissue. Another point favoring MGD over OT-DSD is the presence of Mullerian structures and testicular tissue on the same side, which is not seen in OT-DSD, as the testicular tissue is functional and secretes adequate amounts of MIS. However, in MGD, since the testicular tissue is dysgenetic, Mullerian structures may be preserved on the side of testicular tissue. The points that do not favor a diagnosis of MGD in our patient include an absence of short stature and Turner's stigmata.

MGD represents an intermediate between pure gonadal dysgenesis and OT-DSD.[1] The external genitalia, internal genitalia, and gonadal phenotype are highly variable.[2] The most common genotype in these patients is 46XO/XX, however 46XY genotype has also been described, which can be difficult to distinguish from 46XY OT-DSD. [3] The management of these patients can be difficult as phenotypically females may need multiple staged procedures for clitoroplasty, vaginoplasty, and gonadal biopsies/gonadectomies. Phenotypically male patients may need multiple procedures for hypospadias repair with limited gain in corporal tissue. These patients are at increased risk of cancer, so it is prudent to remove the nonfunctional gonadal tissues.[4] These patients usually need a multidisciplinary approach for management, but still long-term data on fertility and functional improvement of each approach of treatment is lacking.

References

1. Yamakita N, Yasuda K, Mori H, Kuriyama M, Kumamoto Y, Miura K. A case of mixed gonadal dysgenesis (MGD) – with a review of MGD patients reported in Japan. Jpn J Med 1989;28:744-52.
2. Zäh W, Kalderon AE, Tucci JR. Mixed gonadal dysgenesis. Acta Endocrinol Suppl (Copenh) 1975;197:1-39.
3. Crone J, Amann G, Gheradini R, Kirchlechner V, Fékété CN. Management of 46, XY partial gonadal dysgenesis – revisited. Wien Klin Wochenschr 2002;114:462-7.
4. Bulun SE. Aromatase deficiency and estrogen resistance: from molecular genetics to clinic. Semin Reprod Med. 2000;18:31-9.

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