Case Report

Indian Journal of Pathology: Research and Practice
Volume 6 Number 3, July - September 2017 (Part-II)
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.6317.55

A Case of Mixed Gonadal Dysgenesis with 46, XY Karyotype, A Rare Anomaly

Shenbagam J.M.*, K. Rama**

*Postgraduate, Institute of Pathology, Madras Medical College, Chennai, Tamil Nadu 600003, India. **Professor, Department of Pathology, Kasturba Gandhi Hospital, Madras Medical College, Chennai, Tamil Nadu 600003, India.

Abstract

Mixed gonadal dysgenesis represents a genetically, phenotypically and clinically heterogenous entity. It is defined by the presence of dysgenetic testis or streak gonads on one side and differentiated testis on the other side. The exact incidence of MGD is unknown. They can present in childhood with abnormal or ambiguous external genitalia or in an adult with history of primary amenorrhea in female and infertility in male. This discussion briefs about a case of mixed gonadal dysgenesis which is presented here for its rarity. A 22 year old female presented with history of primary amenorrhea. A complete clinical, hormonal, radiological and karyotypic analysis followed by exploratory laparatomy with histological examination of the gonadectomy specimens revealed a diagnosis of mixed gonadal dysgenesis. An important differential diagnosis for MGD includes true hermaphroditism. Histopathological examination of the gonads helps in confirming the diagnosis of MGD.

Keywords: Mixed Gonadal Dysgenesis; True Hermaphroditism; Persistent Mullerian Duct Syndrome.

Introduction

Mixed gonadal dysgenesis forms one of the most important intersex disorders. The exact incidence of MGD is unknown, but is found to occur at a frequency of 1 in 10,000 live births [1]. It refers to those individuals with a karyotype of 45,X;46,XY having differentiated testis on one side and streak gonad on the other side or bilateral streak testis or bilateral dysgenetic testis [2]. Here with presenting a case of mixed gonadal dysgenesis in a 22 year old phenotypic female. This is the second case of mixed gonadal dysgenesis reported in our institute in the period of past fifteen years.

Case Summary

A 22 year old female patient came to the out patient department with complaints of not attained menarche. She was normal at birth and all milestones were attained at the stipulated time. Her external genitalia was normal at birth. She started to develop breast, sparse amounts of pubic and axillary hair at 18 years of age.

On Examination

Patients build, body weight and height was normal. Breast development was in tanner stage 2. There was underdevelopment of axillary and pubic hair.

Examination of External Genitalia

Revealed moderately developed labia majora and underdeveloped labia minora, clitoris and vagina orifice were normal. Per vaginal examination showed vagina to be 5 cm deep and felt as a blind ended pouch without attached cervix.

Imaging Studies

Radiological imaging analysis by ultrasound and computer tomography scan of abdomen revealed

Corresponding Author: Shenbagam J.M., Plot No. 117,118, P.U.Chinnapa Nagar, Pudukottai. Pincode-622001, Tamilnadu, India.
E-mail: shenbajm9@gmail.com

(Received on 23.06.2017, **Accepted on** 11.07.2017)

mullerian anomaly with infantile uterus and presence of a left adnexal cyst measuring 5x2.5 cm.

Hormonal Evaluation

her free testosterone levels were found to be normal at 1.66 ng/dL, anti mullerian hormone levels were elevated at 50.50 ng/ml and serum follicular stimulating hormone was normal at 1.60 mIU/ml.

Karyotyping: Chromosomal analysis by routine G banding karyotyping revealed male type 46 XY karyotype.

Diagnostic Laparoscopy: Showed rudimentary uterus with two horns. Bilateral ovaries and tubes were normal with an attached fimbrial cyst measuring 4 cm on the left side. Bilateral gonadectomy was done. The fimbrial cyst, portion of the tubes and rudimentary uterus were also removed and sent for histopathological examination.

At the histopathology laboratory bilateral gonadectomy specimens were received with Right gonad measuring 3x2x1cm and left gonad measuring 3.5x2.5x1 cm with an attached cyst measuring 3x3cm. Cut surface of both the gonads revealed yellow tan

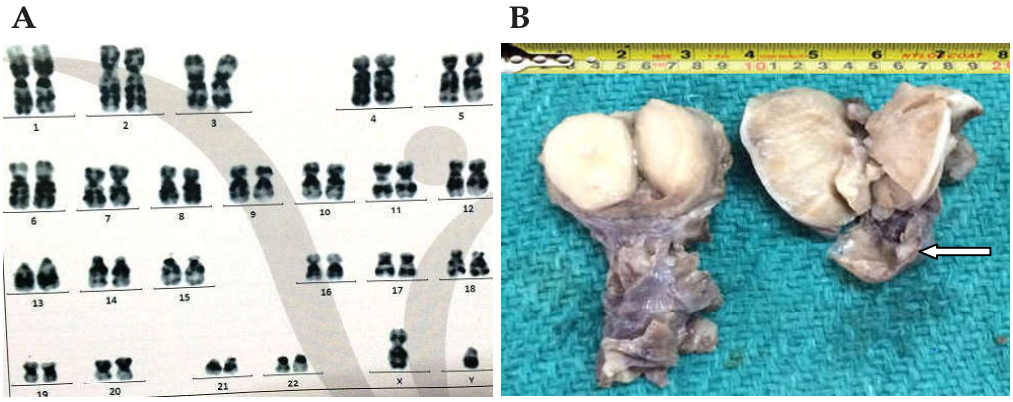

Fig. 1A: Cytogenetic study shows karyogram with 46 XY karyotype. **B.** shows bilateral gonadectomy specimens with one gonad showing attached cyst (arrow) measuring 3x3cm. Cut surface of both the gonads revealed yellow tan testicular parenchyma. Cut surface is the cyst revealed few solid papillary excrescences

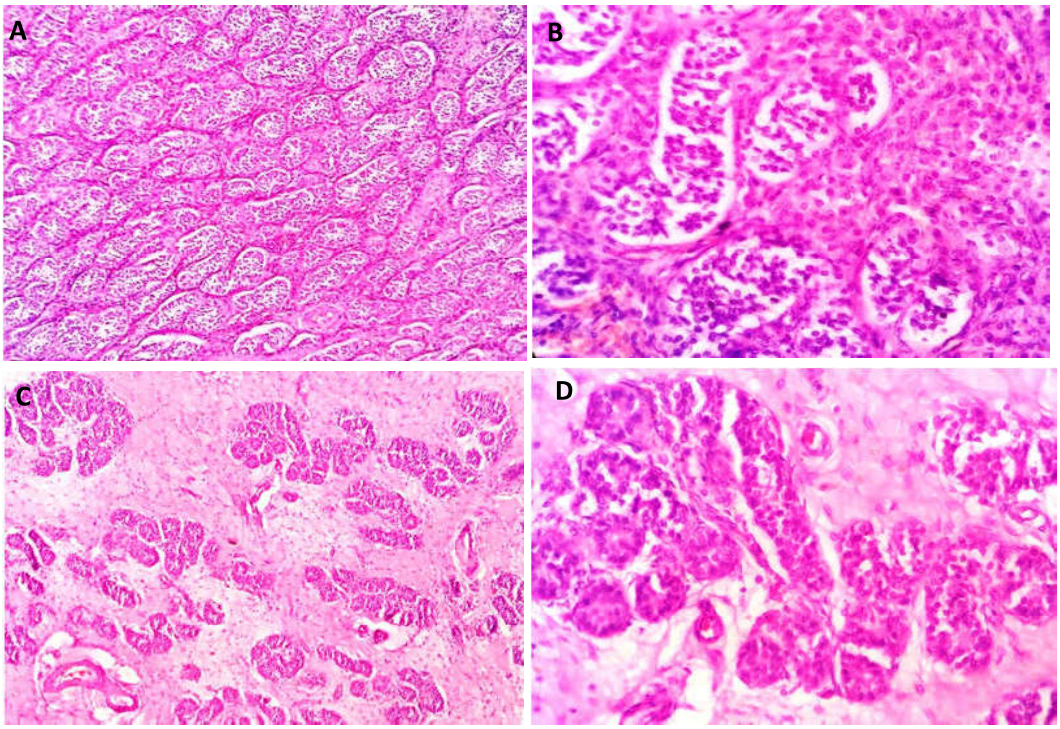

Fig. 2A: (H&E,100X) and B(H&E,400X) shows one gonad having closely packed solid atrophic seminiferous tubules showing only immature Sertoli cells. **B.** also shows Leydig cell hyperplasia. **C.** (H&E,40X) and **D.** (H&E,400X) includes sections from other gonad showing testicular parenchyma having atrophic seminiferous tubules with intervening abundant stromal fibrosis

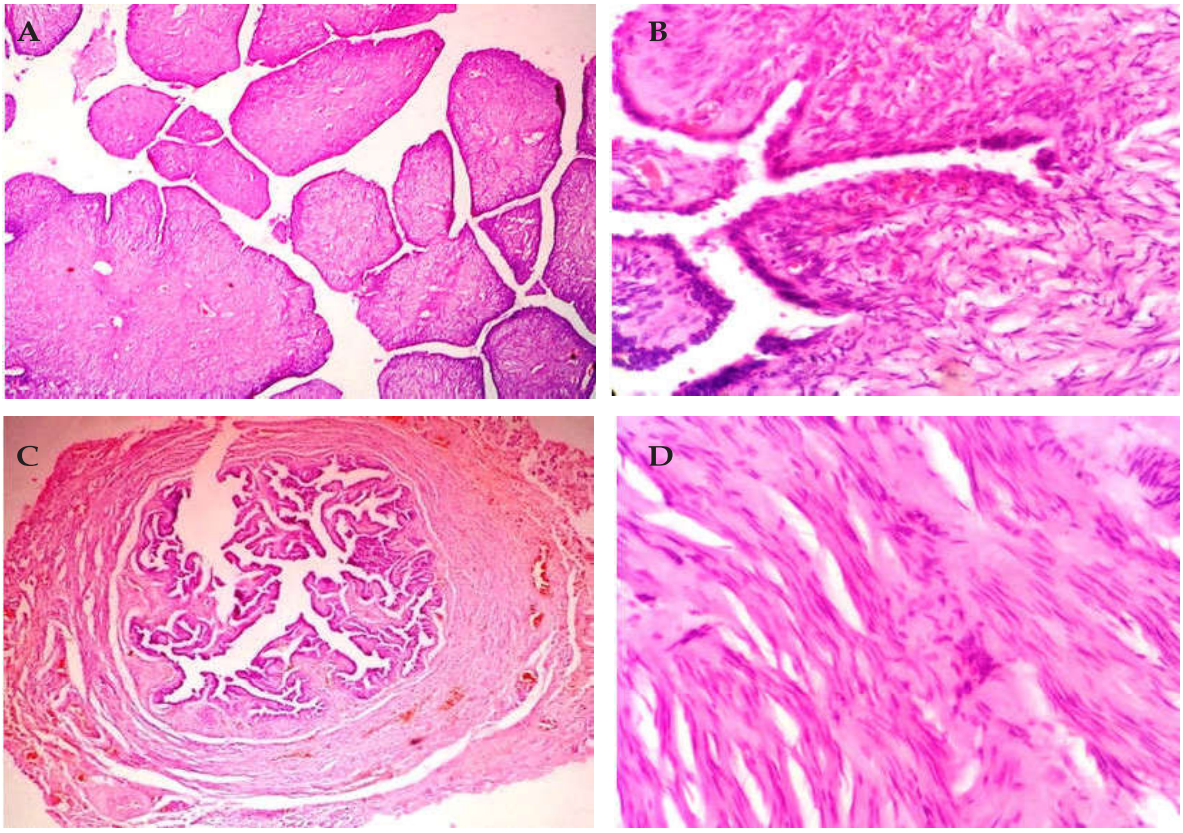

Fig. 3A: (H&E,40X) and **B.** (H&E,400X) shows features of serous cystadenofibroma with the cyst wall showing ovarian parenchyma. **C.** (H&E,40X) shows histology of normal fallopian tube. **D.** (H&E,400X) section from rudimentary uterus shows fascicles and bundles of smooth muscle fibres resembling myometrium

testicular parenchyma. Cut surface is the cyst revealed multiloculated cyst filled with serous fluid having few solid papillary excrescences largest measuring 0.5 cm. Both the gonads had attached tube like structure measuring 0.5 cm in length. Microscopic examination of the left gonad showed closely packed solid seminiferous tubules most of which are atrophic showing only immature sertoli cells and some of them show spermatogonia. No spermatids or spermatozoa made out. Intervening stroma shows leydig cell hyperplasia. The attached cyst shows features of serous cystadenofibroma with the cyst wall showing ovarian parenchyma without ovarian follicles. The other gonad also showed testicular parenchyma having atrophic seminiferous tubules with intervening stromal fibrosis and focal leydig cells. Sections from the rudimentary uterus showed smooth muscle bundles resembling myometrium and no endometrial tissue was made out. The tubes showed normal fallopian tube histology.

With this an impression of mixed gonadal dysgenesis was arrived at. Following bilateral gonadectomy, the patient was started on hormonal therapy with oral estradiol and was planned to be kept under long term follow up with ultrasound since patients with MGD have increased risk of developing germ cell tumours.

Discussion

Mixed gonadal dysgenesis was first described in 1963 by sohval [3]. Mixed gonadal dysgenesis represents a genetically, phenotypically and clinically heterogenous entity [2]. They can present either in adulthood or childhood. Gantt et al in his study had said that those patients with bilateral streak ovaries presented as sexually infantile female, those with intraabdominal testis and contralateral streak gonad presented as female patients with primary amenorrhea and clitoromegaly, those with bilateral descended testis presented as males with infertility [4].

MGD is associated with incomplete structural differentiation of mesonephric duct derivatives and incomplete inhibition of mullerian structure development leading to development of dysgenetic testis and streak gonads/testis [5]. Streak gonad refers to the presence of ovarian stroma but without any evidence of differentiated gonad such as primordial

or primary ovarian follicles. Streak testis refers to the presence of streak tissue at the peripheral portion of a differentiated testis [6]. In addition to classical histopathological features described in this case, patients with MGD can also have sex cord stromal tumour and gonadoblastoma like areas [6]. Persistent mullerian duct syndrome (PMDS) refers to the existence of both wolffian and müllerian duct derivatives due to absence or lack of response to mullerian inhibiting substance [2]. There are 2 clinical presentations of PMDS- type 1 and type 2. Type 1 is the most common type accounting for about 80 to 90% of cases.

In type 1, the patient present phenotypically as males with herniation or descend of testis along with uterus and fallopian tubes in to the inguinal canal. In type 2, the patient will be a female by phenotype with bilateral undescended testis which will be attached to the round ligament at the anatomic position of the ovaries [7].

This particular case of MGD had type 2 PMDS. The presence of mullerian derivatives in this phenotypic female with 46,XY karyotype can be explained on the basis of the following:- During normal embryogenesis, the immature Sertoli cells of the male embryo releases antimullerian hormone (AMH) by 8 th to 10 th week of gestation which inhibits the development of the mullerian duct derivatives. AMH along with gubernaculum also plays role in the descent of testis through the inguinal ring in to the scrotum. In patients with MGD either AMH is secreted in insufficient levels or the paramesonephric or the mullerian tissue is insensitive to AMH leading to development of mullerian derivatives such as uterus and fallopian tubes [6].

Patients with MGD can have variable karyotypic abnormalities such as 46,XY; 45,X/46,XY ; 45,X/ 47,XYY [8]. This was found to be due to chromosomal rearrangements and mitotic anaphase lag occurring during early embryogenesis[5].Those patients with Y chromosome must undergo gonadectomy as one third of these patients are at increased risk of developing gonadoblastomas and other malignant germ cell tumours such as embryonal carcinoma, yolk sac tumour, choriocarcinoma and immature teratoma [9].

It is essential to distinguish between MGD and true hermaphroditism as the treatment and prognosis of both the conditions are different. True hermaphroditism refers to presence of both well developed testis and also ovary in the same individual [6]. Patients with true hermaphroditism requires removal of only that gonad which is opposite to the gender of the patient and a biopsy from the rest left over gonad. On the other hand treatment of patients with MGD requires a multidisciplinary approach. It includes bilateral gonadectomy followed by hormonal therapy and long term follow up with ultrasound since they have increased risk of developing tumours [10].

Conclusion

Histopathological examination of the gonadectomy or biopsied specimens forms the important diagnostic tool in distinguishing MGD from true hermaphroditism as rest all features such as hormonal levels, karyotyping, appearance of external genitalia and presence or absence of mullerian derivatives may support but not takes one to definitive diagnosis which is very important in the management of these patients.

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