Case Report

Polycystic ovarian syndrome co-existing in a patient of MRKH syndrome: A case report

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Abstract

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also referred to as Müllerian aplasia, is a congenital disorder characterized by aplasia of the uterus and upper part of the vagina in females with normal secondary sex characteristics and a normal female karyotype (46,XX).There is a known association between polycystic ovary syndrome and Mullerian developmental defects. A 27 year old unmarried girl presented with primary amenorrhoea due to complete Mullerian agenesis as documented sonographically by absence of the uterus. She presented with features of overt hirsutism, obesity Class 1 and biochemical evidence of hyperandrogenism as manifested by elevated LH to FSH ratio. She was found to be hypertensive and there was evidence of insulin resistance manifested as impaired glucose tolerance along with hypercholesterolemia. On physical examination, her BMI was found to be 32, no kyphoscoliosis, blood pressure was 150 / 95 mm of Hg and Ferriman-Gallwey score (F-G score) of 18. Internal examination revealed presence of a 3 centimetre deep vaginal dimple with complete absence of the cervix. Secondary sexual characteristics were normal in accordance with the age of the patient. However, she was not thoroughly evaluated by an IVU or MRI regarding concomitant urogenital dysplasia. Every case of MRKH syndrome is unique in the sense of management priorities, reproductive and sexual needs, co-morbidities. Addressing each of these issues is quite challenging to the clinician as these have significant long–term impacts on the quality of life in physical, sexual and mental health aspect. The prospect of having genetic and legal motherhood of MRKH patients through uterine transplantation has opened a new arena to be explored.

Keywords: Polycystic ovary symdrom, MRKH syndrome, Mullerian agenesis.

Introduction:

The ovarian development is separate from that of the uterus,cervix, vagina and fallopian tubes. Therefore normally formed and functioning ovaries are present even though there is a concomitant Mullerian defect. The ovaries differentiate from the undifferentiated gonad in thegonadal ridge, medial to the mesonephros induced by the migration of Primordial germ cells from the yolk sac under the influence of WNT4 gene (ovary-determining gene).[1]The oviducts, uterus, cervix, and upper two-thirds of the vagina origin from the paramesonephric (Müllerian) ducts (PMD), whereas the lower part of the vagina origins from the urogenital sinus. Formation of the PMD starts around 5th-6th gestational week as bilateral craniocaudal invaginations of the coelomic epithelium of the urogenital ridges (intermediate mesoderm) growing caudally guided by the mesonephric (Wolffian) ducts to reach the urogenital sinus (endoderm). The caudal part of the two PMDs fuses to form the uterus, cervix and upper vagina, whereas the upper parts of the PMDs form the twooviducts.[1] In MRKH syndrome which has a prevalence of 1 in 5000 live female births, there is aplasia or hypoplasia of the Mullerian ducts resulting in either complete absence or variable uterine remnants. Increasing reports of familial occurrence of MRKH syndrome and its associated anomalies support a monogenic genetic etiology.[2] Most pedigrees suggest autosomal dominant inheritance with incomplete penetrance. In contrast, most cases occurring sporadically, lacking recurrence in outcomes of surrogate pregnancies and several reports of discordant twin pairs support either polygenic/ multifactorial or non-genetic etiologies (e.g. teratogenic exposures in utero). [3,4]

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive age women. Although the diagnostic Rotterdam criteria include 2 of 3 features hyperandrogenism (HA), ovulatory dysfunction (OD), polycystic ovarian morphology (PCOM), PCOS women often display notable metabolic co-morbidities. These long-term metabolic consequences of PCOS cannot be denied in women with or without uterus as in Mullerianagensis. In the etiology of PCOS, hyper-androgenism at various developmental periods has been

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proposed as the major driver of associated reproductive and metabolic perturbations with long-term cardiovascular implications.[5]Therapeutic strategies need to be instituted to prevent and or manage the metabolic complications; starting from lifestyle modification, maintenance of an optimal BMI and appropriate medications for hypertension, glucose intolerance, hirsutism etc. However in patients with complete Mullerian agenesis with co-existing PCOS, the effect of unopposed oestrogen on the uterine endometrium is not applicable.

Case Presentation:

A 27 year- old unmarried Muslim working lady (self-employed) presentedas a known case of complete Mullerian agenesis detected at 16 years of age due to non–resumption of menstruation. She was diagnosedby the absence of the uterus and two ovaries on ultrasonography of lower abdomen and pelvis and presence of bilateral rudimentary uterine budson Pelvic MRI. She complained of excessive facial and body hair over the last 3 years and significant weight gain which was 17 kilograms over 9 months. On examination, blood pressure was 150 / 95 mm of Hg, weight: 79 kg, Height; 157 cm, BMI: 32.04. Ferriman - Gallwey score of 18 , Hair distribution was moderate hair under chin (FG score 3), upper abdomen(FG score 3), lower abdomen(FG score 3), upper back (FG score 4), thigh (FG score 3)and arms (FG score 2). Vaginal examination with consent revealed normal external genitalia and urethral orifice, presence of a 3 centimetre deep vaginal depression with absence of the cervix. Breast development was normal for age. Investigations revealed TSH and fT_4within normal limit, Serum FSH: 3.9 IU/l and serum LH 18.4 IU/l (evidence of HA), Fasting Blood sugar was 5.7 mmol/l , 2 hours Post prandial 8.7 mmol/l, HbA1c 6.9% reflecting impaired glucose tolerance , Fasting Lipid profile: Total cholesterol 315 mg/dl, HDL 28 mg/dl , LDL 132 mg/dl (suggesting atherogenic dyslipidemia). Ultrasonography of lower abdomen revealed bilaterally enlarged ovaries with 12-14 peripherally arranged follicles measuring 9-11 mm in diameter and absent uterus. Karyotype revealed 46XX. She was counselled regarding the long-term impact of chronic anovulation related to PCOS. Emphasis was placed on diet and life style modification. In collaboration with cardiologist, she was advised anti-hypertensive medication and lipid-lowering agents along with long-term cardiovascular surveillance. However, at the moment, she expressed no inclination towards sexual/reproductive needs. Moreover, she was not thoroughly evaluated regarding urogenital, cardiacand skeletal system.

Discussion:

The association of polycystic ovarian syndrome with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome has been studied and published in different articles.The polycystic ovary syndrome, whose etiopathogenesis is not clearly understood, has a wide spectrum of clinical presentations, and may co-exist with other pathologic conditions. In a study conducted by Mustafa Ugur, the prevalence of ultrasound-defined polycystic ovaries (PCO) in patients with müllerian anomalies (n =167, study group), and those without müllerian anomalies (n =3165, control group) from 1990 to 1994, in a population markedly composed of infertility patients was evaluated. PCOS were found in 50 (29.9%) patients in the study group, compared to 637 (20.1%) patients in controls ($P <$ 0.01).[5] Müllerian anomalies were further grouped according to the American Fertility Society (AFS) classification and it was found that patients with the septate uteri and bicornuate uteri malformations had a higher prevalence of PCOS (polycystic ovaries) than the controls ($P < 0.001$, $P < 0.05$, respectively). It was concluded in another study that PCOS was more prevalent in certain müllerian anomalies and an embryogenetic defect may also be involved in the etiopathogenesis of PCOS.[6]

MRKH is one of the most common causes of primary amenorrhea and affects at least 1 out of 4500 women. MRKH syndrome is caused by either complete agenesis or aplasia of the paramesonephric ducts to form the uterus and upper vagina. Its penetrance varies, as does the involvement of other organ systems. MRKH syndrome is classified as type I (isolated uterovaginal aplasia) (56-72%) or type II (associated with extra genital manifestations, 28-44%). Extra genital anomalies typically include renal, skeletal, ear, or cardiac malformations. MRKH syndrome Type II is associated in 40% of cases with kidney abnormalities (15% of these girls/women will be born with only one kidney), 10% will have hearing problems, and 10-12% will have vertebral anomalies, rib anomalies, hypoplastic or absent radii, abnormalities of the carpal bones and hypoplastic phalanges, bilateral femoral hypoplasia.[7,8,9] Duncan et al in 1979, in a review of 30 cases proposed the designation of the entity as "MURCS Association (Müllerian duct aplasia/hypoplasia, renal agenesis/ectopy, and cervicothoracic somite dysplasia (MURCS) association)". The four most common malformations specifically described in the association are: 1. uterine hypoplasia or aplasia, 2. renal agenesis or ectopia, 3. vertebral anomalies **(**e.g. Klippel-Feil syndrome/cervical vertebral fusion syndrome**)**, and 4. adult stature less than 152 cms. [10]

MRKH patients typically (95%) display bilateral uterine rudiments combined with a fibrous band and normally located ovaries on MRI. The uterine rudiments are generally small with only one-layer differentiation, a subset of which might be large and exhibited other atypical presentations, including two- or three-layer differentiation or even hematometra. Functional rudimentary uteri may present with endometriosis and related symptoms explained by retrograde menstruation. In MRKH syndrome, both ovaries are typically present and well-functioning. However, their anatomical position is usually more cranial than the normal position and they are often found lateral, rather than medial, to the external iliac arteries, probably due to the lack of Fallopian tube development. Ovarian anomalies are rare and only found in ~5-10% .[10,11]Inguinal ovary has also been reported as a rare diagnostic sign of Mayer-Rokitansky-Küster-Hauser

syndrome in a girl in attempt to operate on an inguinal hernia in a case of Type I MRKH syndrome.[12] However, in our case both ovaries were intra-abdominally located. Different ovarian anomalies previously reported include unilateral agenesis, ectopic ovaries, polycystic ovaries, streak ovaries, and rarely tumors.[14,15]

Detection of normal female karyotype (46,XX) on chromosomal analysis by G/Q-banding in this patient excludes the possibility of Complete androgen insensitivity syndrome (CAIS, also referred to as Morris syndrome) which is an X-linked disorder affecting genetically males (46,XY) caused by hemizygous mutations in the androgen receptor gene, AR (OMIM #300068) and 17-hydroxylase/17,20-lyase deficiency in 46,XY females caused by biallelic CYP17A1 mutations. These patients also have normal female appearance, blind-ending vagina and absent uterus and have breast development but sparse pubic hair at puberty.[16]

Relevant laboratory tests include FSH, LH, androgens and estradiol, which are generally considered to be normal in MRKH syndrome.[5,17,18] However, biochemical (non-clinical) hyperandrogenemia was recently reported in ~50% of patients. 85 In this case, the patient experienced excessive facial and body hair (F-G score of 18)over the last 3 years and 17 kilograms weight gain over 9 months with blood pressure 150 / 95 mm of Hg, BMI(Body Mass index): 32.04 .

After confirmation of the diagnosis of MRKH syndrome, management usually relates to the psychological and psychosexual issues, reproductive needs such as vaginoplasty and reconstructive surgery for hypoplastic /rudimentary uterus. Addressing concomitant issues are important in this case such as management of common co-morbidities such as insulin resistance, obesity and hypertension. MRKH syndrome may have profound psychological and/or psychosexual impact once the diagnosis is disclosed.[19] Receiving the diagnosis, many patients experience facing overwhelming issues regarding identity, sexuality and infertility, and the importance of good caring and counselling should not be underestimated. The diagnosis is often made during adolescence; a period of physical/emotional development and vulnerability, which further imposes the provider's caring and awareness towards the patients' emotions, reactions and coping strategies. Furthermore, it is important to be aware of potential cultural aspects and their influence on reactions to the diagnosis in patients and their families and peers.In our patient, mental adjustment was well and she was found to coping well with the condition.

Historically, in MRKH syndrome creation of a functional neovagina has been a hallmark in the treatment for those who are sexually active. Dilation therapy either by Frank's method or d'Alberton's method as first choice is supported by Callens et al.[20], which further suggest laparoscopic Vecchietti vaginoplasty as preferred second-line therapy. Most importantly, thorough counseling regarding expected outcome and possible complications should always precede any attempt for vaginal construction, and it is fundamental to ensure the full maturity and motivation of the patient undergoing such treatment. Importantly, the three latter methods, which are based on dilation of vaginal dimple, will provide the vagina with a normal mucosal lining. This may be advantageous in a uterus transplantation situation (UTx) since this will provide the vagina with a normal vaginal microbiota, which may be of importance for success at embryo transfer as well as for correctly grade rejection by cervical biopsy. Moreover, it is important to recognize the option of no treatment, which for some patients might be the right choice;[2,21] as currently applies to our case.

The current reproductive options for MRKH patients are adoption (non-genetic), gestational or host surrogacy (genetic) and uterine transplantation (UTx).Upto 2020, approximately 75 UTx procedures have been performed and all but two of these have been performed in MRKH patients (Brännström, personal communication). Around 25 babies have been born worldwide, with some of the MRKH patients having delivered healthy babies twice.[22,23]

Conclusion:

Every case of MRKH syndrome is unique in the sense of management priorities, reproductive and sexual needs, co-morbidities. Addressing each of these issues is quite challenging to the clinician as these have significant long –term impacts on the quality of life (QoL) in all aspects (physical, sexual, mental health). Approximately 30% of MRKH syndrome patients have concomitant urological, renal, skeletal or cardiac structural problems. Moreover, ovarian pathology such as Polycystic changes with or without clinical hyperandrogenism, endometriosis issues in case of functional uterine remnants in case of hypoplastic uteri are also to be kept in mind. Moreover, the prospect of having genetic and legal motherhood of MRKH patients through uterine transplantation has opened a new arena to be explored.

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