

CASE REPORT

ATYPICAL MAYER – ROKITANSKY – KUSTER – HAUSER SYNDROME, HYPERPROLACTINEMIA, HIRSUTISM AND MULTINODULAR GOITER WITH OBSTRUCTIVE SYMPTOMS

NASSER RAJALLAH AL-JUHANI,¹ EMAN BAROOM² AND MUHAMMAD AYYUB³

¹Departments of Endocrinology, ²Radiology and ³Gastroenterology,
King Abdulaziz Hospital and Oncology Center, Jeddah, Saudi Arabia

ABSTRACT

Mayer-von Rokitansky – Kuster – Hauser syndrome (MRKH), comprises of combined hypoplasia of the vagina and the uterus, in addition it may be associated with congenital anomalies of the urinary tract and the skeleton. Its main clinical presentation is primary amenorrhoea in the presence of normal secondary sexual characteristics. Multi nodular goiter (MNG) is one of the most prevalent thyroid disorders worldwide and sometimes impairs health and well being. We report a 33-year – old Saudi female with features of the atypical form of Mayer-von Rokitansky-Kuster – Hauser syndrome (MRKH) syndrome, large multinodular goiter with compression of trachea causing obstructive symptoms, hirsutism and hyperprolactinaemia. Although the concurrence of MRKHS and MNG appears to be coincidental, this association has not been previously reported and the association with endocrine abnormalities such as hyperprolactenaemia or hirsutism is rarely described.

Key words: Mayer – Rokitansky – Kuster – Hauser syndrome, Multinodular goiter, Hyperprolactinemia, Hirsutism

INTRODUCTION

Mullarian agenesis, commonly referred to as MRKH syndrome, is a rare disorder, which was first reported in the 1830s.¹ It is a congenital malformation of the female genital tract characterized by the absence of the vagina and a variety of Mullerian duct anomalies, with absence of the uterus being the most common. In addition it may be associated with congenital anomalies of the urinary tract and the skeleton or other abnormalities. The reported incidences of syndrome vary from 1:5000 to 1:10 000.

Women with MRKH syndrome have a normal female genotype (46, XX) and a normal female phenotype with spontaneous development of secondary sexual characteristics, as ovarian tissue is usually present and functions normally. Diagnosis of the MRKH patients is usually delayed until adolescence where primary amenorrhoea and / or difficulty in attempting sexual intercourse suggest diagnosis.

MNG are a relatively common clinical problem, especially in regions of frank or borderline iodine deficiency. Although most goiters are benign and asymptomatic, large goiters can cause dysphagia or difficulties in breathing due to local oesophageal or tracheal compression that requires thyroid surgery.²

The concurrence of MRKHS and MNG requiring thyroid surgery has not been previously reported and the association with endocrine abnormalities such as hyperprolactinaemia or hirsutism are occasionally described. Here we will review endocrinological abnormalities associated with MRKH syndrome with special emphasis on thyroid disorders.

CASE REPORT

A 33 – year – old, single, Saudi female referred to endocrinology unit in this hospital with history of multinodular goiter for the past 7 years which had increased in size the past month. She also complained of having chronic dry cough, dysnea on lying flat and on minimal exertion and occasional dysphagia for solid foods. There were no symptoms suggestive of hypo or hyperthyroidism. Past medical history revealed the presence of hirsutism starting at age of 18 years and primary amenorrhea. She was told that she had lower genital abnormalities, with-

MUHAMMAD AYYUB

Consultant Internist and Gastroenterologist
King Abdulaziz Hospital and Oncology Center
Jeddah, Saudi Arabia

Tel: 00966 2 6375555, Fax: 009662 6379442
E-mail: drayyub@hotmail.com



Figure 1: Shows goiter and mild hirsutism.

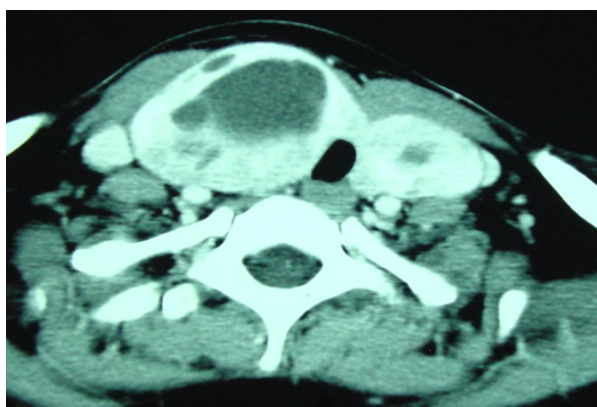


Figure 2: CT of neck: shows MNG with cystic degeneration mainly involving right thyroid Lobe with compression of trachea.

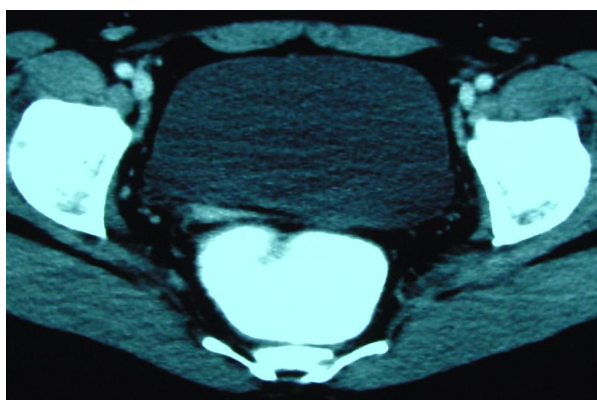


Figure 3: CT pelvis shows absent uterus, hypoplastic vagina, absent left ovary.

out specific diagnosis and no further investigation was performed since that time. Her father and mother are first degree relatives and she had 5 sisters and 2 brothers.

On physical Examination, she appeared to be well – developed and well – nourished with a body mass index (BMI) 25 kg/m². Her neck examination showed large multinodular goiter. Mild hirsutism over upper lip, chin side burn, areola and lower abdomen was noted (Figure 1). There was no acne. She had normal breast development (Tanner stage V) and axillary hair were present. Genital examination showed adult pubic hair (tanner stage V), and normal female external genitalia. Other systemic examinations were un-remarkable.

Fine needle aspiration biopsy (FNAB) of the right largest thyroid nodule revealed follicular lesion with cystic changes.

Because the patient had obstructive symptoms and follicular lesion on FNAB, right hemithyroidectomy and isthmectomy was done and histopathology findings were compatible with colloid goiter.

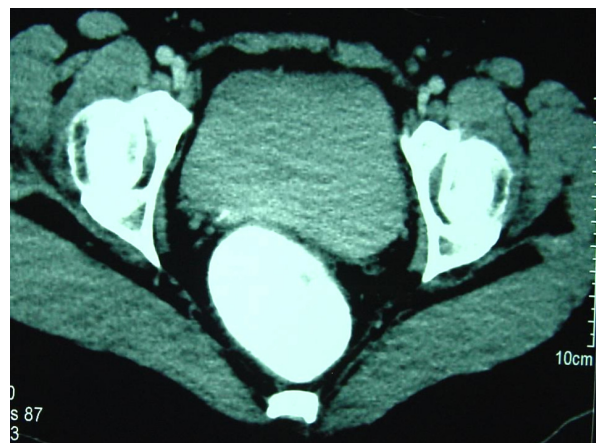


Figure 4: CT pelvis shows absent uterus, hypoplastic vagina, absent left ovary.

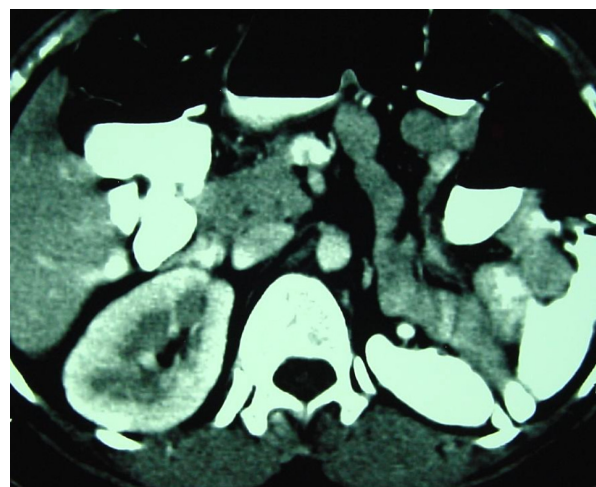


Figure 5: CT of abdomen shows absent left kidney with compensatory of right kidney.

Patient was offered laparoscopy but she declined the procedure.

Her laboratory tests showed that serum prolactin was 84.4 ng/ml (normal < 25), serum thyroid stimulating hormone (TSH) 0.7 (normal), free thyroxine (FT₄) 18.4, follicle stimulating hormone (FSH) 6.9, luteinizing hormone (LH) 9.60, total testosterone 0.45 (0.06 – 0.82) ng/ml and dehydroepiandrosterone sulphate (DHEAS) was 168 (99 – 340) micg/dl. Genetic study done by karyotype was normal female (46XX).

Ultrasonographic (US) examination of the thyroid showed bilateral multiple complex nodules, the largest nodule in right lobe measured 3.6 × 2 cm. Contrast CT of the neck and thyroid performed because of obstructive symptoms, showed MNG with cystic degeneration mainly involving right thyroid lobe with compression of trachea (*Figure 2*).



Figure 6: Plain x-ray of spine shows S-shaped thoracic spine scoliosis and spina bifida of lumbar spine.

"Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Ultrasonographic examination of pelvis and abdomen showed hypoplastic uterus 33 × 19 × 13 mm, aplastic left kidney and ovaries were not visualized (not shown). Contrast CT of the pelvis and abdomen showed absence of uterus, hypoplastic vagina, absence of left kidney with compensatory hypertrophy of right remaining kidney (*Figure 3, 4 and 5*).

Plain-x ray of cervical / thoracic / lumbar spine

showed S-shaped thoracic scoliosis and spina bifida of thoracic spine (*Figure 6*).

MRI of hypothalamic – pituitary area was normal (magnetic resonance imaging).

DISCUSSION

Primary amenorrhoea is defined as absence of menses by the age of 16 years in the presence of normal secondary sexual characteristics or 14 years in the absence of secondary sexual characteristics. There is a large spectrum of diseases known to cause primary amenorrhoea. However, Mullarian agenesis is the second commonest cause of primary amenorrhoea after gonadal dysgenesis, accounting for about 15% of cases.³

Most cases of MRKH syndrome are sporadic, however, familial cases have been described. Although MRKH syndrome results from agenesis or underdevelopment of the müllerian duct system, its exact aetiology is unknown. Several hypotheses have been postulated including environmental, genetic, hormonal or receptor factors. Deficiency of gestagen and / or oestrogen receptors may lead to an arrest in the further development of the embryonic Mullerian duct. An activating mutation of either the gene for the anti-müllerian hormone or its receptor and loss of function deletion in the WNT₄ gene has also been suggested.

The diagnosis of MRKHS can usually be made without the need for a laparoscopy. Ultrasound (US) is the first method of choice for the diagnosis.⁴ In the majority of patients US findings lead the correct diagnosis. MRI examination adds more information about uterovaginal anatomy and associated anomalies and may help in planning of the surgery.

There may be two subtypes of MRKH, the typical (also called type I or A) and the atypical form (type II or B) based on laparoscopic (or laprotomy), and radiological findings.⁵ The typical form (type I or A) (where only the caudal part of the Müllerian duct is affected, is characterised by vaginal atresia and symmetrical muscular buds (the Müllerian remnants) with an absent or rudimentary uterus and normal fallopian tubes, ovaries and renal system. The vaginal dimple can vary in length from just a slight depression between the labia up to 5 – 6 cm.

The atypical form (type II) represent a more severe form of the syndrome. It shows asymmetrical hypoplasia of one or two muscular buds with or without fallopian tubes developmental abnormalities, and often associated with renal and skeletal malformation.

Approximately one – third of patients with MRKH have renal anomalies including unilateral agenesis, hypoplasia, ectopic or horseshoe kidney and abnormal collecting ducts. Skeletal anomalies involving the spine (cervico – thoracic fused or wedged

vertebrae, scoliosis and Klippel – Feil anomaly) or ribs or upper limbs occurs in 10 – 15% of cases.⁶ Mullerian hypoplasia or aplasia – renal agenesis – cervicothoracic somite dysplasia known as the MURCS association (Mullerian duct aplasia; R: renal agenesis / ectopia; CS: cervical somite dysplasia) represent the most rare and severe form of the syndrome.⁷ Ovarian abnormalities such as ectopic or polycystic ovaries have been described. Other less common anomalies include deafness, congenital heart lesions, cleft palate, and inguinal or femoral hernias.

Treatment options focus on psychology and on the creation of a vagina comfortable for penetrative intercourse. Infertility, difficult or impossible vaginal intercourse represent a significant burden to women with MRKH syndrome, so psychological and social support are needed on diagnosis and continued for as long as necessary.

There are both surgical and nonsurgical approaches to vaginal agenesis depending on anatomy, motivation and age of the patient. It is usually delayed until the patient is ready to start sexual activity. Nonsurgical approach involve the use of vaginal dilators which provide excellent results. In cases where dilators are unsuccessful or where compliance is difficult, the laparoscopic creation of a neovagina by the modified Vecchietti or Davydov procedure or the use of other surgical procedures such as McIndoe procedure are effective, with good functional results. Many of the surgeries require the use of dilators postoperatively to maintain vaginal patency.

MNG is one of the most prevalent thyroid disorders worldwide and it is defined as structurally and functionally heterogeneous thyroid enlargement. Large goiters can cause dysphagia or breathing difficulties due to local oesophageal or tracheal compression. Thyroid function often becomes more autonomous with increasing age, and may eventually evolve into overt hyperthyroidism. The main indications for the treatment of patients with nontoxic multinodular goiter are compression of the trachea or oesophagus or growth of the goiter, especially where there is intrathoracic extension.

We conducted a search through Medline, Pubmed, focusing mainly on endocrinological abnormalities in MRKH syndrome (without specifying language) from 1966 through may 2009 using the combination search words (Mayer – Rokitansky – Kuster – Hauser syndrome or Mullerian agenesis or vaginal atresia or Rokitansky syndrome) and (goiter or prolactin or hirsutism or androgen) each time. A few studies addressed the endocrine abnormalities in MRKHS. The function of the hypothalamic – pituitary – ovarian axis in MRKH syndrome is classically normal.

Our reported case had some endocrinological

features not described or occasionally so in association with MRKH syndrome. She had the atypical form of MRKHS (absent uterus, hypoplastic vagina, absent left ovary, left renal agenesis with compensatory right kidney hypertrophy, scoliosis, mild spina bifida of thoracic spine). In addition to large MNG, she had clinical hirsutism and moderate hyperprolactinemia in the presence of normal thyroid function tests.

In our case both hyperprolactinaemia and MRKH syndrome can cause primary amenorrhea, although the later has high priority their association is occasionally reported. MNG is an unlikely cause of her high prolactin level which usually occurs in setting of hypothyroidism. In addition, MRI of hypothalamic – pituitary axis was normal making the possibility of prolactinoma unlikely. In a study of endocrine features involving 19 cases of MRKHS, hyperprolactinaemia was found in 3 patients. In 7 of 11 in whom progesterone was measured, it was ovulatory cycles, LH, FSH, oestradiol were normal.⁸

In a German study of hormonal status in 15 patients of MRKHS, 8 patients showed mild hyperprolactinaemia post thyrotropin – releasing hormone (TRH) stimulation tests and showed diminished FSH and LH response to gonadotropin-releasing hormone (GnRH) test.⁹ In the later study they used stimulation tests that are rarely used today except in special situations due to advance in basal hormonal assays performance.

In addition our patient also had mild – moderate hirsutism with normal total testosterone and DHEAS level with no features suggestive of cushing syndrome. Free or bioavailable testosterone and androstenedion level were not measured which could be high. Androgen excess has been reported in 2 out of 15 patients of MRKH syndrome. It has also been reported in 1 of 6 patients of Mullerian agenesis and was attributed to WNT₄ mutation.

Although the association of the MRHS and MNG with obstructive symptoms seems coincidental, it has not been previously described. Our patient required thyroid surgery and pathology showed colloid goiter. Thyroid abnormalities in association with MRKHS are very rarely reported. Primary hypothyroidism or subclinical primary hypothyroidism have been described in a few case reports.¹⁰

Hypergonadotropic hypogonadism (Primary ovarian failure) due to unilateral or bilateral gonadal dysgenesis or agenesis had been also described in a few case reports in association with MRKHS.

ACKNOWLEDGEMENTS

The authors are grateful to the administration of King Abdul Aziz Hospital and Oncology Center for providing the facility to investigate and treat this patient.

REFERENCES

1. Mayer CAJ. Über Verdoppelungen des Uterus und ihre Arten, nebst Bemerkungen über Harenscharte und Wolfsrachen. *Journal der Chirurgie und Augen-Heilkunde*. 1829; 13: 525-564.
2. Hegedus L, Bonnema SJ, Bennedbaek FN 2003 Management of simple nodular goiter: current status and future perspectives. *Endocr Rev* 24: 102-132.
3. Reindollar, RH, Byrd, JR, McDonough, PG. Delayed sexual development: A study of 252 patients. *Am J Obstet Gynecol* 1981; 140: 371.
4. Rosenberg HK, Sherman NH, Tarry WF, Duckett JW, Snyder HM. Mayer – Rokitansky – Kuster – Hauser syndrome: US aid to diagnosis. *Radiology* 1986; 161: 815-819.
5. Strubbe EH, Cremers CW, Willemsen WN, Rolland R, Thijn CJ: The Mayer – Rokitansky – Kuster – Hauser (MRKH) syndrome without and with associated features: two separate entities? *Clin Dysmorphol* 1994; 3: 192-199.
6. Fore SR, Hammond CB, Parker RT, Anderson EE. Urologic and genital anomalies in patients with congenital absence of the vagina. *Obstet Gynecol*. 1975; 46 (4): 410-416.
7. Duncan PA, Shapiro LR, Stangel JJ, Klein RM and Addonizio JC. The MURCS association: Mullerian duct aplasia, renal aplasia, and cervicothoracicsomite dysplasia. *J Pediatr* 1979; 95: 399-402.
8. Carranza – Lira S, Forbin K, Martinez – Chequer JC. Rokitansky syndrome and MURCS association – clinical features and basis for diagnosis *Int J Fertil Womens Med*. 1999 Sep – Oct; 44 (5): 250-5.
9. Egarter C, Schurz B, Fitz R, Grunberger W (Hormonal status in patients with Mayer – Rokitansky – Kuster syndrome) *Geburtshilfe Frauenheilkd*. 1988 Apr; 48 (4): 235-9.
10. Gorgojo JJ, Almodovar F, Lopez E, Donnay S. Gonadal agenesis 46, XX associated with the atypical form of Rokitansky syndrome *Fertil Steril*. 2002 Jan; 77 (1): 185-7.