CASE REPORT

Unusual association between cardiac, skeletal, urogenital and renal abnormalities

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SUMMARY

We present a 33-year-old woman with an array of congenital abnormalities. She has been diagnosed with polycystic kidney disease (PCKD) with no detectable mutations in PKD1 or PKD2, spina bifida occulta, thoracic skeletal abnormalities, a uterus didelphys and a patent foramen ovale (PFO). There are several associations reported in the literature that include abnormalities similar to the patient's, but none describe her presentation in its entirety. The MURCS association is characterised by (M)ullerian duct aplasia, (R)enal dysplasia and (C)ervical (S)omite anomalies and goes some way in explaining these conditions. Patients with both MURCS and PCKD have not been described in current literature. Through this report, we hope to bring a potential diagnosis to light and provide the patient with an improved understanding of her health.

BACKGROUND

The patient is naturally curious as to why she has developed numerous medical problems and wishes to understand the aetiology of her condition. By presenting this case we hope to improve awareness of the associations between renal, skeletal and genital abnormalities and, ultimately, provide her with a deeper understanding of her conditions.

These medical issues are rare when considered in isolation. The incidence of Mullerian duct aberration has been estimated at ~0.4%,¹ whereas polycystic kidney disease (PCKD) occurs in ~0.0013% live births.^{2,3} The statistical probability that all of the patient's anomalies arose independently is low. We question whether this is a new association, or

the first reported case of (M)ullerian duct aplasia, (R)enal dysplasia and (C)ervical (S)omite anomalies (MURCS) alongside other specific multisystem abnormalities.

Although her health conditions do not impact on her everyday life, she is concerned what effect these may have on her well-being in the long-term. Abnormalities of the genital tract may significantly impact fertility and obstetric performance.⁴ Early diagnosis allows effective management and improved outcomes.⁵ This is important in this case, as the patient is concerned about starting a family.

CASE PRESENTATION

The patient's mother suffered a previous miscarriage prior to delivery of her. Her antenatal period was also complicated by heavy bleeding during pregnancy.

During childhood, the patient was diagnosed with spina bifida occulta, scoliosis of the thoracic spine and fused ribs. Conservative management has been successful in maintaining normal functional status.

In 2004, she underwent a routine cervical smear. She was found to have two cervices; subsequent ultrasound scanning confirmed a complete uterine didelphys with a double endocervical canal, double cervix and two normal ovaries (as illustrated in figure 1). Uterine didelphy occurs due to failure of Mullerian duct fusion during embryogenesis. She is currently awaiting a gynaecological review to discuss her options with regards to conception and pregnancy.

The patient was also diagnosed with PCKD. As both her father and sister are affected, she

Figure 1 Diagrammatic representation of a didelphys uterus alongside a normal uterus. Diagram courtesy of a Professor Frank Gaillard, Radiopaedia.org, rID: 11115.

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requested an USS (ultrasound scan) of her kidneys in addition to the pelvic USS to assess her uterus. The scan identified renal cysts prompting referral to a nephrologist, who diagnosed the PKD. Genetic analysis failed to identify a mutation in either PKD1 or PKD2 genes. However, linkage studies suggest that the patient, her sister and father all have the same copy of the PKD1 gene despite no mutation being picked up on genetic testing. It is known that up to 10% of patients with PKD do not have a detectable mutation on PKD1.⁶ Further biochemical and genetic tests excluded a mutation on the HNF1 β gene.

In addition to the uterine didelphys and renal cysts it was noted that the patient had low set ears and a webbed neck, suggestive of Turner's syndrome. Genetic defects in chromosome 1 have also been reported to cause similar abnormalities to those described here.⁷ Karyotyping showed a normal 46, XX genotype and further genetic investigation demonstrated a normal chromosome 1. A genetic microarray test was carried out, but failed to reveal any abnormalities that may account for the patient's presentation. There is no one within the patient's family with any known genetic condition other than PKD and nobody within the family is known to have a similar association of conditions. Moreover, there is no history of consanguinity within the family.

At 23 years she presented with exertional dyspnoea. She denied chest pain, palpitations and syncope; ECG and chest radiograph were unremarkable. An echocardiogram revealed a small pericardial effusion, mild tricuspid valve regurgitation and demonstrated a left-to-right shunt. Subsequent cardiac imaging confirmed the presence of a PFO with a left atrial opening of 8 mm and a right atrial opening of 7 mm.

OUTCOME AND FOLLOW-UP

At age 28 her PFO was successfully repaired. Her blood pressure and renal function are currently within normal ranges, and are regularly monitored by her general practitioner.

Having uterine didelphys is likely to make pregnancy more difficult, with an increased risk of spontaneous abortion, preterm delivery and stillbirth.⁸ Despite the high-risk nature of these pregnancies, with appropriate antenatal care pregnancy outcomes are known to be good. Importantly, the patient has not yet encountered any fertility concerns.

She has raised concerns about the heritability of her abnormalities as she is planning to start a family, and is currently undergoing genetic counselling. Considering no clear disease-causing mutation on either PKD genes or chromosome 1 was identified, further linkage studies are necessary to understand the aetiology of her PKD and whether it is independent of, or associated with her other abnormalities. Her geneticists felt that the patient and her family may benefit from taking part in the Genomics England 100 000 Genome Project—as of now, she has not confirmed her participation.

Although her father and sister both have PKD, she is the only one presenting with other congenital abnormalities. The genetics team concluded, therefore, that the patient's other problems are unlikely to be related to her PKD and may well not have a genetic aetiology. It is not clear whether these additional problems will affect her future children.

These concerns further motivated the presentation of her case to establish any association that may help to explain her medical history and provide the answers she desires.

DISCUSSION

Owing to a lack of a unifying diagnosis that would account for all the patient's congenital abnormalities, several of her

conditions were not diagnosed until adulthood. Congenital abnormalities are not uncommonly discovered until symptomatic in later life.⁹ Mullerian duct abnormalities are often only diagnosed when amenorrhoea, miscarriage or infertility become apparent.^{1 10} Additionally, atrial septal defects such as a PFO may be silent until a patient presents with a unexplained dyspnoea or a cerebral vascular event.¹¹ Undetected, abnormalities such as these can have both physical and psychological impacts on quality of life, illustrating the importance of early diagnoses.

A number of cases have been described identifying renal abnormalities alongside uterine didelphys.^{12 13} It was not possible to find any associations that fully characterise the combination of abnormalities we present here. There are several possible explanations for this:

- The numerous conditions may have arisen independently, though the probability of this is small.
- This combination of conditions could be a novel presentation of a previously described syndrome or condition. Literature search identified the MURCS association as a potential candidate.
- These abnormalities could represent a yet undescribed association.

There have been numerous associations described in the literature that link development abnormalities similar to those seen in the patient. Most well-known is the VACTERAL association which often involves vertebral, renal and heart malformations.¹⁴ Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is characterised by congenital aplasia of the uterus and upper two-thirds of the vagina in women showing normal development of secondary sexual characteristics and a normal 46, XX karyotype.¹⁰ MRKH associated with renal and skeletal abnormalities defines the MURCS association. In rare cases, patients with MURCS have also had cardiac abnormalities.¹⁵

A recent report identified 25 patients with MURCS association, of these 20% had scoliosis and 16% had non-vertebral skeletal abnormalities. One of the patients within the study was reported to have a PFO with mild left-to-right shunting.¹⁶ However, there are important differences between the cases in the literature and the presentation described above. The renal abnormalities expected in MURCS association include agenesis, ectopic or horseshoe kidneys;¹⁰ it was not possible to find a case of MURCS association where the patient had PKD. In MURCS there is usually aplasia of the uterus and upper two-thirds of the vagina.¹⁰ Our patient demonstrated uterus didelphys alongside a short but normal vagina.

This case highlights a rare combination of multisystem abnormalities. A review of the literature suggests the MURCS association could be a possible diagnosis; however the totality of the

Patient's perspective

- I am fortunate that none of my myriad medical issues currently impacts my day-to-day living. However, I am concerned this will change as I grow older and I worry what impact a pregnancy may have on my health and vice versa.
- With each condition, I received fairly intensive input shortly after diagnosis but was subsequently discharged and am not undergoing any active follow-up or monitoring. I feel very alone. I would really benefit from more joined-up care between the specialists and my general practitioner so I can be monitored effectively and treated/referred as necessary.

patient's condition is beyond the scope of the MURCS definition. There is a distinct possibility that the patient is affected by a number of individual conditions, the association of which has never been reported.

Learning points

- ▶ We hope to promote awareness of uterine abnormalities and their presentation. This should be considered as an important differential for women seeking guidance on fertility problems.
- ▶ Uterine and renal abnormalities are often linked.¹⁷ Healthcare professionals should be mindful of these associations when investigating women for gynaecological or renal problems.
- ▶ Genital tract abnormalities can have adverse physical and psychological effects. Earlier detection will enable prompt referral to necessary specialists to minimise adverse outcomes. General practitioners must be vigilant as first contacts to detect and investigate for genital tract malformations.
- ▶ The MURCS association captures parts of the patient's condition, however classification and diagnosis is made difficult due to variability in the reported cases. In sharing this case we aim to promote further awareness and discussion her presentation and similar developmental conditions.

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REFERENCES

- 1 Byrne J, Nussbaum-Blask A, Taylor WS, *et al.* Prevalence of Müllerian duct anomalies detected at ultrasound. *Am J Med Genet* 2000;94:9–12.
- 2 Chapman AB, Devuyst O, Eckardt K-U, *et al.* Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2015;88:17–27.
- 3 Wilson PD. Polycystic kidney disease. *N Engl J Med* 2004;350:151–64.
- 4 Chan YY, Jayaprakasan K, Tan A, *et al.* Reproductive outcomes in women with congenital uterine anomalies: a systematic review. *Ultrasound Obstet Gynecol* 2011;38:371–82.
- 5 Parmar M, Tomar S. Bicornuate uterus: infertility treatment and pregnancy continuation without cerclage: an unusual case. *Open J Obstet Gynecol* 2014;4:981–5.
- 6 Rossetti S, Consugar MB, Chapman AB, *et al.* Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2007;18:2143–60.
- 7 Weber S, Landwehr C, Renkert M, *et al.* Mapping candidate regions and genes for congenital anomalies of the kidneys and urinary tract (CAKUT) by array-based comparative genomic hybridization. *Nephrol Dial Transplant* 2011;26:136–43.
- 8 Grimbizis GF, Camus M, Tarlatzis BC, *et al.* Clinical implications of uterine malformations and hysteroscopic treatment results. *Hum Reprod Update* 2001;7:161–74.
- 9 Mazouni C, Girard G, Deter R, *et al.* Diagnosis of Müllerian anomalies in adults: evaluation of practice. *Fertil Steril* 2008;89:219–22.
- 10 Morcel K, Camborieux L, Guerrier D, Programme de Recherches sur les Aplasies Müllériennes. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. *Orphanet J Rare Dis* 2007;2:13. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1832178/>
- 11 Pinto FJ. When and how to diagnose patent foramen ovale. *Heart* 2005;91:438–40. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1768819/>
- 12 Wu TH, Wu TT, Ng YY, *et al.* Herlyn-Werner-Wunderlich syndrome consisting of uterine didelphys, obstructed hemivagina and ipsilateral renal agenesis in a newborn. *Pediatr Neonatol* 2012;53:68–71.
- 13 Prada AM, Muguerza VR, Montero SM, *et al.* Uterus didelphys with obstructed hemivagina and multicystic dysplastic kidney. *Eur J Pediatr Surg* 2005;15:441–5.
- 14 Solomon BD. VACTERL/VATER Association. *Orphanet J Rare Dis* 2011;6:56.
- 15 Duncan PA, Shapiro LR, Stangel JJ, *et al.* The MURCS association: Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia. *J Pediatr* 1979;95:399–402.
- 16 Pittcock ST, Babovic-Vuksanovic D, Lteif A. Mayer-Rokitansky-Kuster-Hauser anomaly and its associated malformations. *Am J Med Genet A* 2005;135:314–16.
- 17 Li S, Qayyum A, Coakley F V, *et al.* Association of renal agenesis and müllerian duct anomalies. *J Comput Assist Tomogr* 2000;24. http://journals.lww.com/jcat/Fulltext/2000/11000/Association_of_Renal_Agenesis_and_Mullerian_Duct.1.aspx

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