An unusual case of undescended testis: type II persistent Müllerian duct syndrome

Sir,

We present an unusual case of undescended testis, type II persistent Müllerian duct syndrome (PMDS), and we identify a novel nonsense variant, c.64C>T (p.Arg22*), in *AMHR2* gene.

Our patient is a baby boy born full-term to non-consanguineous parents. He was noted to have bilateral undescended testes at birth with normal scrotum and penis. Re-examination at 2 months of age revealed descended left testis with inguinal hernia, whereas the right testis was not palpable; his scrotum and penis were otherwise normal looking. Diagnostic laparoscopy was performed at 14 months old and Müllerian remnants were noted (Fig. 1). Biopsy of the gonads confirmed the presence of normal testicular tissues with spermatogonia.

Karyotype analysis showed 46 XY, and blood tests at 1 year of age revealed normal electrolytes, cortisol, thyroid function and 17-hydroxyprogesterone (2.3 nmol/L). Testosterone (<0.5 nmol/L) and gonadotropins (LH 0.1 IU/L, FSH 0.37 IU/L) followed a prepubertal pattern. Urine steroid profile was essentially normal. HCG stimulation test showed appropriate increase in testosterone (19.6 nmol/L at 72 hours), indicating the presence of functioning testicular tissue. Serum anti-Müllerian hormone (AMH) level was 208.94 ng/mL and was within the age- and sex-matched reference interval (59.54−320.65 ng/mL; Quest Diagnostics Nichols Institute, USA).

In view of the findings of Müllerian remnants, together with detectable levels of AMH, type II PMDS was suspected. Genetic testing on *AMHR2* gene was performed with DNA extracted from peripheral blood of the patient and his parents. All coding exons and their exon/intron boundaries of at least 40 nucleotides were sequenced bi-directionally. Two heterozygous pathogenic *AMHR2* variants, a known pathogenic missense variant c.1499G>A. p.(Cys500Tyr), and a novel nonsense variant c.64C>T (p.Arg22*), were detected. Compound heterozygosity was confirmed by genetic testing on the patient's parents. His mother was confirmed to be an unaffected carrier of the former variant, p.(Cys500Tyr); while his father is an unaffected carrier of the latter variant, (p.Arg22*).

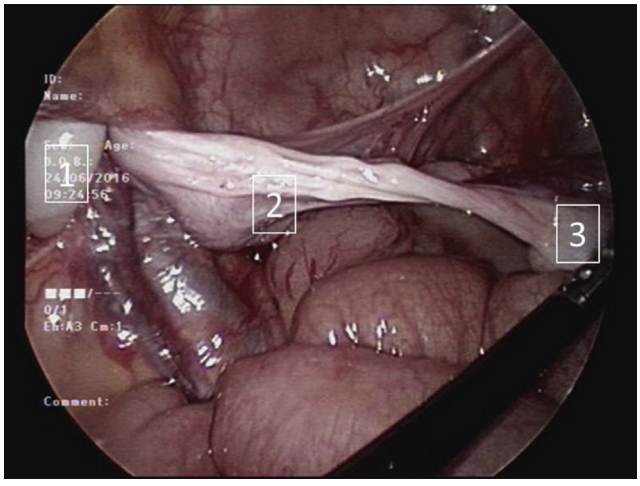

Fig. 1 Intraoperative finding of diagnostic laparoscopy at 14 months old. (1) Left descended testis; (2) Müllerian remnant; (3) undescended right testis.

The patient received robot-assisted excision of Müllerian remnant and bilateral orchidopexy at 19 months old. The excised tubular specimen was sent for histology and was morphologically reminiscent of female genital tract structure. Further immunohistochemical staining confirmed the strong expression of PAX-8, a marker for Müllerian differentiation, consistent with the clinical and genetic diagnosis of type II PMDS.

AMH secretion from Sertoli cells in male fetuses begins at around 6 weeks of gestation, and leads to regression of Müllerian ducts, whereas testosterone secretion from Leydig cells starts from around 8 weeks of gestation, causing stabilisation of the Wolffian duct and subsequent differentiation into vas deferens, epididymis and seminal vesicles. Testosterone is converted by 5α-reductase to dihydrotestosterone (DHT) and causes virilisation of the external genitalia. In the absence of AMH, as in female fetuses, the Müllerian duct will differentiate into the fallopian tube, uterus and upper one-third of the vagina.[1,2]

PMDS is caused by abnormal AMH secretion or action resulting in the persistence of Müllerian duct products in the male fetus. It is a rare disorder of sex development (DSD), inherited in an autosomal recessive manner, but manifesting only in a 46XY individual. It is commonly diagnosed as an incidental finding during surgical repair for inguinal hernia, or cryptorchidism.

There are three classical phenotypes (Fig. 2): (1) hernia uteri inguinalis (unilateral cryptorchidism and contralateral inguinal hernia with testis and Müllerian remnants in the sac); (2) transverse testicular ectopic (unilateral inguinal hernia with both testes and Müllerian remnants in the sac); and (3) bilateral cryptorchidism.[1] Our patient presented with hernia uteri inguinalis which is the most common presenting phenotype of PMDS. Surgical excision of Müllerian remnants and bringing down intra-abdominal viable testes to the scrotum are warranted, because there is a high risk of malignant transformation if left untreated. Alternatively, orchiectomy should be considered. Still, infertility and azoospermia are common in these patients despite normal testosterone levels and normal pubertal development. The causes are multifactorial, such as germ cell degeneration due to delayed orchidopexy, vascular damage to testes and vas deferens during surgery, or other congenital anatomical anomalies.[2,3]

Pathogenic variants, homozygous or compound heterozygous, were found in 85% of patient suffering from PMDS, approximately equally distributed in the genes coding either for AMH (*AMH*, type I PMDS) or its type II receptor (*AMHR2*, type II PMDS); in the remaining 15%, no pathogenic variants in either gene could be identified.[2] Serum AMH level may help in diagnosis of PMDS and in differentiating the two types of PMDS and thus guiding genetic testing. A very low/undetectable serum AMH level would be expected in type I PMDS, as the genetic defect in *AMH* gene would impair the biosynthesis of this hormone, while a normal or high serum AMH level would be expected in type II PMDS due to resistance of mutated AMH receptor to AMH action. In the present case, which is probably the first reported case for Hong Kong Chinese, a high normal AMH level is consistent with the diagnosis of type II PMDS.[1,3,4]

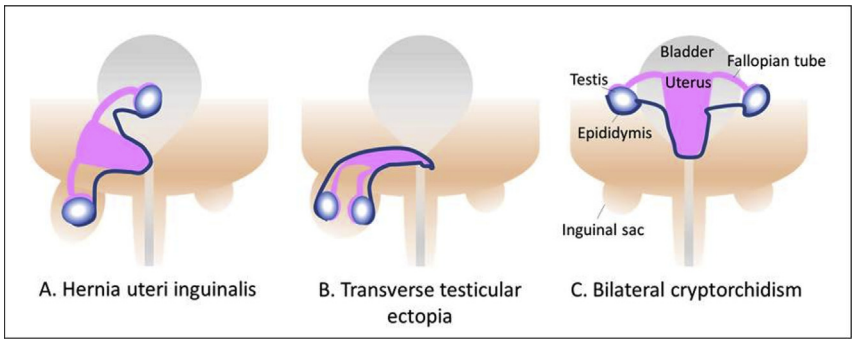

Fig. 2 The three different phenotypes of PMDS. (A) Hernia uteri inguinalis (unilateral cryptorchidism and inguinal hernia): unilateral undescended testis. The contralateral descended testis drags the Müllerian remnant down as inguinal hernia. (B) Transverse testicular ectopia: the descended testis drags down the Müllerian remnants together with the other testis on the same side. (C) Bilateral cryptorchidism: uterus in the pelvis, with bilateral testes embedded in the broad ligament.

The known pathogenic missense variant *AMHR2* c.1499G>A. p.(Cys500Tyr) causes substitution of cysteine to tyrosine at amino acid position 500 which is located at the intracellular domain of the AMH receptor and is frequently reported in PMDS patients.[1,2] The other nonsense variant *AMHR2* c.64C>T is a novel variant located in exon 2; the substitution of C to T nucleotide creates a premature stop codon at amino acid position 22 (p.Arg22*). This variant is extremely rare in normal controls (Exome Aggregation Consortium) and this is compatible with disease with autosomal recessive inheritance. *In silico* analysis by Mutation Taster and SIFT also predicts p.Arg22* as pathogenic.

In conclusion, an intra-operative finding of Müllerian duct remnants is diagnostic of PMDS, whereas serum AMH level is useful in differentiating the two types, and drives the genetic testing to either *AMH* gene or *AMHR2* gene. We present a case of type II PMDS with a novel nonsense variant (p.Arg22*) identified in *AMHR2*. Early surgical management is preferred to minimise the risk of malignant transformation of the intra-abdominal testes and Müllerian duct remnants, as well as to maximise the chance of preserving fertility.

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Concurrent anti-GBM disease and IgA glomerulonephritis

Sir,

A 22-year-old Caucasian male with a four pack-year history of smoking presented due to one month of recurrent, moderate volume haemoptysis and some dyspnoea. There was no history of recent flu-like illness or other infection. He had no other occupational or recreational exposures relevant to these respiratory symptoms. There was no other significant medical history, including no history of previously detected haematuria or proteinuria. At initial work-up haemoglobin was 90 g/L, serum creatinine 77 μmol/L and eGFR >90 mL/min. ESR was raised at 35 mm/hr. Chest X-ray showed bilateral lower lobe patchy heterogeneous parenchymal opacities. There were 250 dysmorphic erythrocytes in urine and 0.5 g per day of proteinuria.

Renal biopsy contained eleven glomeruli with one segmental necrotising lesion and two cellular crescents observed. The remaining glomeruli showed a mild and focal increase in mesangial cellularity. The tubules contained some luminal erythrocyte casts and no extraglomerular vasculitis was apparent. There was no interstitial fibrosis. Immunofluorescence demonstrated linear staining with IgG (Fig. 1A) and C3 along the glomerular basement membrane as well as prominent glomerular mesangial staining with IgA (Fig. 1B). Electron microscopy showed only the typical glomerular mesangial electron-dense deposits of IgA nephropathy.

At this point anti-GBM serology (ELISA for IgG autoantibodies against the NC1 domain of alpha-3 collagen chain) returned as positive. In addition, ANA and dsDNA antibodies were not elevated. Both an ENA screen and ANCA antibodies were also negative.

A final diagnosis of concurrent anti-GBM disease and IgA glomerulonephritis was made.

Treatment consisted of a fixed course of 21 sessions of plasma exchange. In addition, oral prednisolone was commenced at 75 mg daily, tapering to 10 mg daily at 4 months and with intention to cease at 6 months. Oral cyclophosphamide was also commenced at 150 mg daily. It was ceased at 2 months and replaced with oral azathioprine at 100 mg daily. The patient had resolution of clinical symptoms, with normalisation of haemoglobin and negative anti-GBM serology at 4-month follow-up. Serum creatinine remained within the normal range, however there had been a slight increase in proteinuria to 0.7 g per day.