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## Background

- Primary amenorrhea is a rare condition (0.3% of the general population) characterized by absent menarche.
- Serum levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) differentiate hypergonadotropic (gonadal failure) from hypogonadotropic hypogonadism (central defect).
- We present a case of primary amenorrhea with end stage renal disease.

## Case report

A 27-year-old female from Georgia presented for evaluation of primary amenorrhea and incomplete pubertal development, and continuous linear growth.

**Past medical history:** Positive for progressive glomerulopathy arising during adolescence resulting in end stage renal failure and hemodialysis starting at age 19.

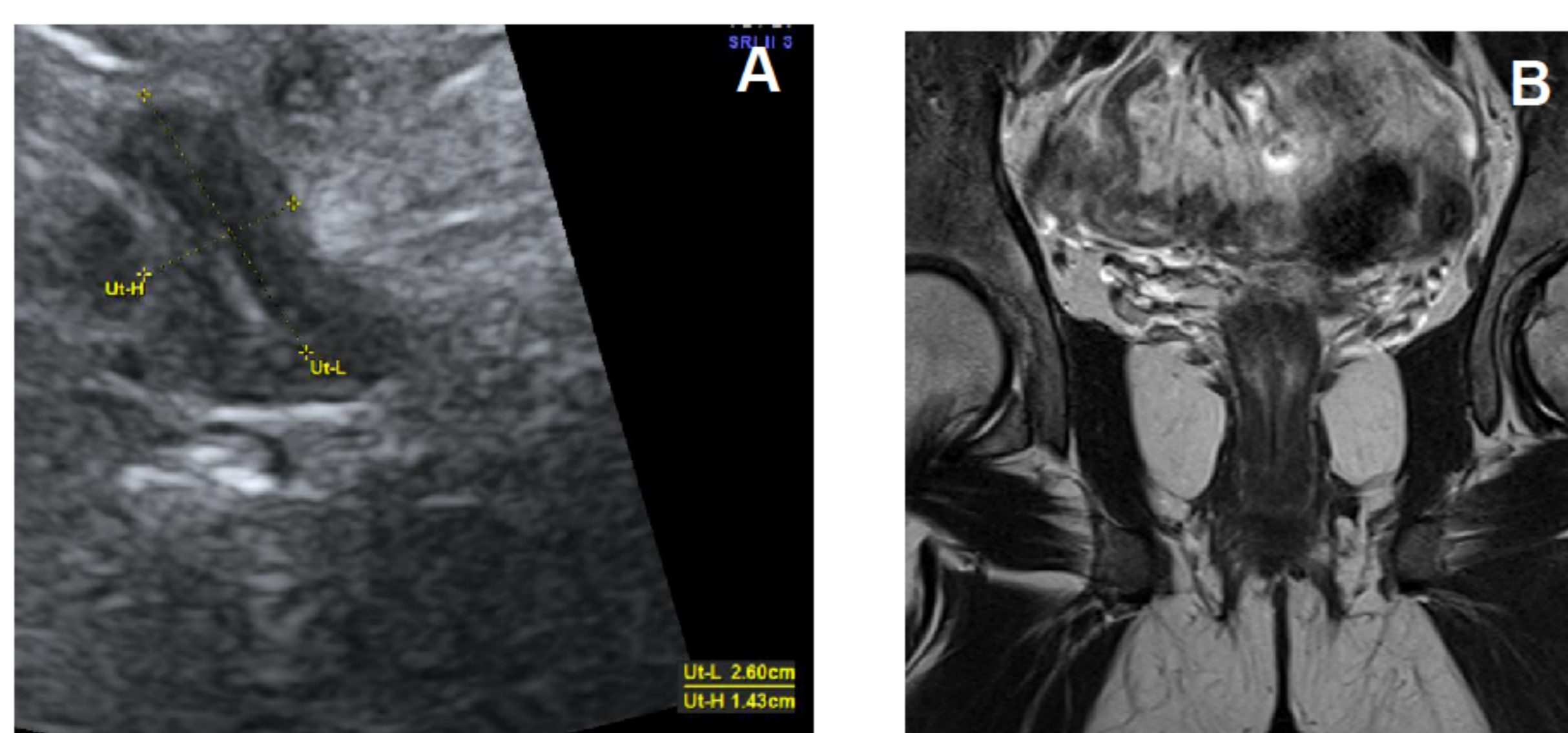
**Clinical examination:** Height 173 cm, arm span 179 cm, no acne, no hirsutism, normal BMI (22 kg/m<sup>2</sup>), Tanner III breasts, Tanner IV pubic hair, female external genitalia with pale vaginal mucosa and clitoromegaly (2,5 cm).

**Family history:** unremarkable.

## Evaluation

### 1. Clinical evaluation

Parameter	Value	Reference Range
LH	151,8 UI/L	(20-90)
FSH	179,4 UI/L	(4-22)
estradiol	0,07 nmol/L	(0.13-1.34)
inhibin B	23.2 pg/ml	(10-200)
anti Müllerian hormone (AMH)	undetectable	(4-105)
SHBG	50 nmol/l	(34-91)
testosterone	2 nmol/L	(0.4-2.0)



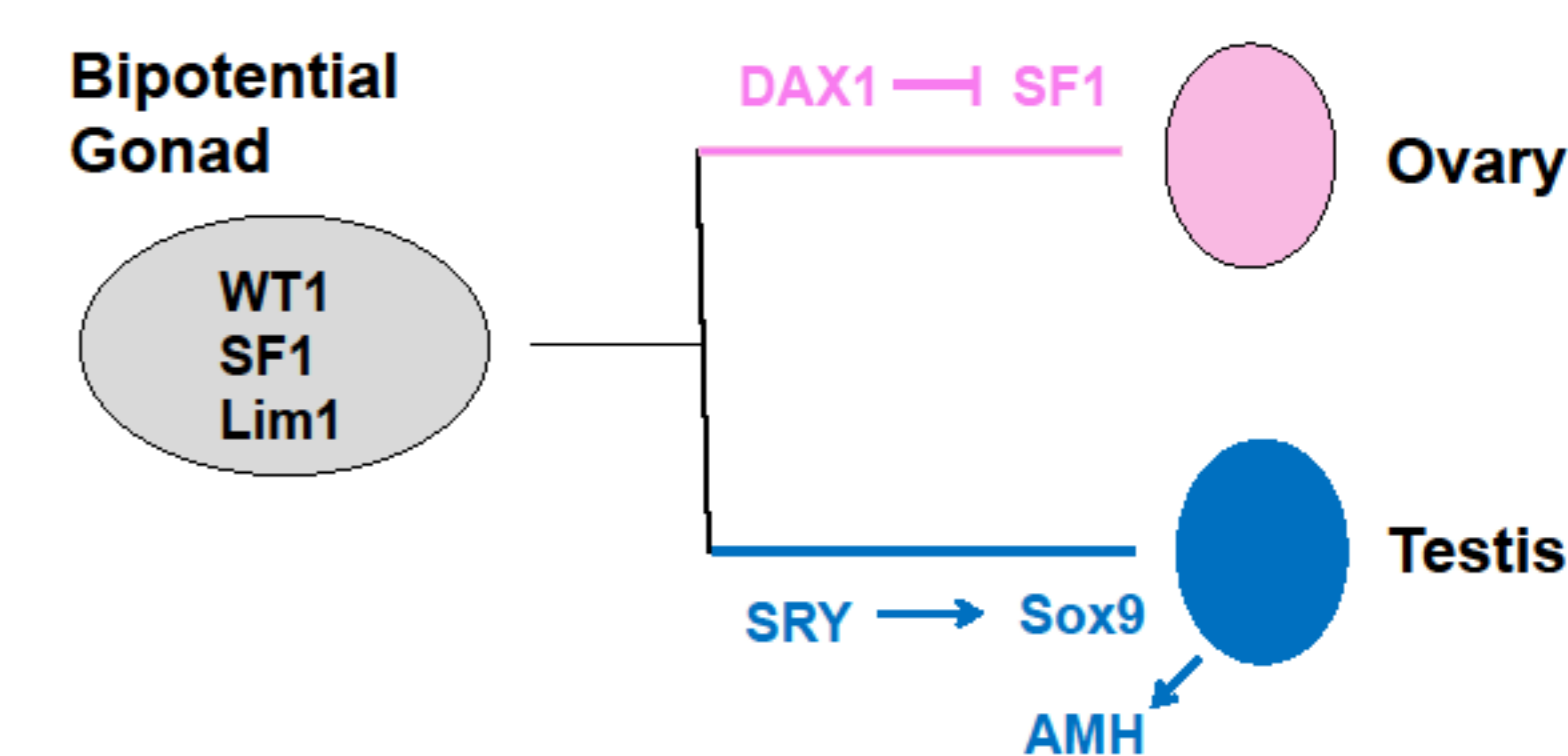
**Imaging studies** (A) Pelvic ultrasound showing a small uterus, gonads were not visualized. (B) MRI: normal vagina, hypotrophic, pre-pubertal uterus (consistent with absent AMH levels). No gonads were identified. Subsequent laparoscopy revealed fallopian tubes & gonads (1.5 X 1.0 cm). Densitometry (DEXA) showed severe osteoporosis (spine: T score -4.9, hip: -2.4).

### 2. Genetic analyses

Karyotype: 46,XY

Genetic screening:

- SRY no mutations
- WT1 heterozygous intronic mutation (c.1128+5G>A) previously reported to affect splicing *in vitro*.



**Schematic depicting sex determination**  
WT1 is involved in the formation of the bipotential gonad. SRY activates Sox9 and AMH, critical for the developing male gonad. In the absence of SRY, DAX1 suppresses SF1 resulting in the development of an ovarian gonad.

### 3. Diagnosis

The association of 46,XY disorder of sexual development (DSD), dysgenetic gonads and end stage renal disease in adolescence is reported in Frasier syndrome (FS) – a rare genetic disorder caused by mutations in Wilms tumor gene (WT1).

### 4. Intervention & treatment plan

Given the high risk of malignancy in Frasier syndrome, gonads were removed.

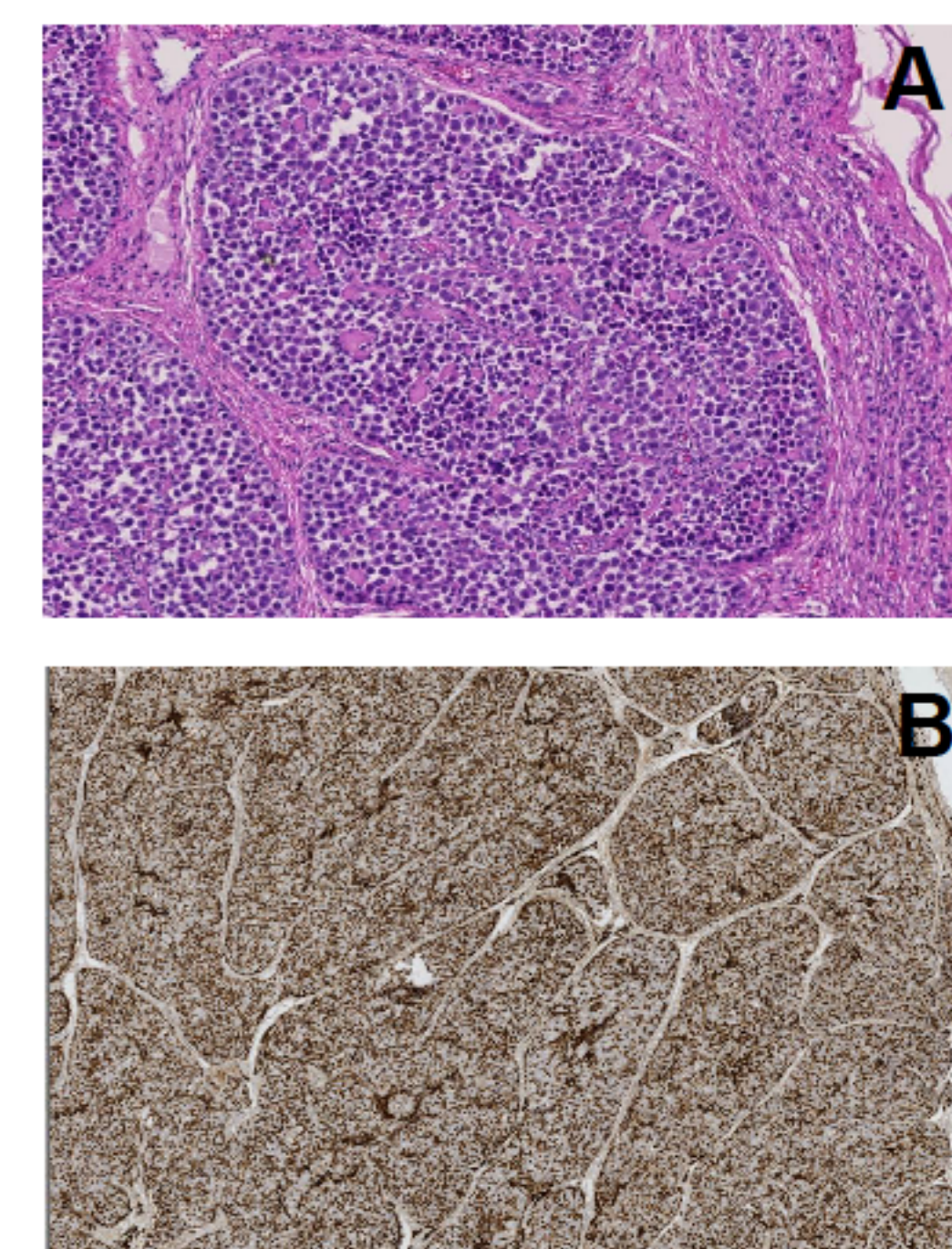
Pathology reported a **dysgerminoma (Fig. A) arising in a gonadoblastoma** in the left gonad (diameter 1 cm).

(Fig A) clusters of **Leydig cell hyperplasia** were evident in both gonads, consistent with elevated serum testosterone levels. (Fig B) immunostaining for Inhibin alpha demonstrated positivity in the sex cord cells of the gonadoblastoma suggesting that Inhibin B might have been produced by the dysgenetic gonads or alternatively by the gonadoblastoma.

Post-gonadectomy, serum testosterone normalized (2.0 → 0.5 nmol/L) and Inhibin B decreased (23 → <7 pg/mL).

The patient was started on estrogen replacement therapy (alone) to complete breast development, followed by long term estro-progestins for reproductive and bone health.

### Gonadal Histology



## Conclusions

- In cases of primary amenorrhea, and end stage renal disease, Frasier syndrome should be ruled out. The findings of gonadoblastoma and dysgerminoma in this patient highlights the importance of gonadectomy in Frasier syndrome.
- Screening for proteinuria in cases of 46,XY DSD can aid early detection of Frasier syndrome and timely intervention to minimize cancer risk (i.e. gonadectomy).
- In the setting of undetectable serum AMH levels and inconclusive imaging studies regarding the presence of gonads, serum Inhibin B levels may be a useful marker to indicate the presence of gonads.