Mosaic turner syndrome (45,X/46,XY) presenting as delayed puberty and ambiguous genitalia in an adolescent

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SUMMARY

Mosaic Turner Syndrome (45,X/46,XY) is a rare chromosomal condition that may present with varying clinical features. When classical dysmorphic features are absent, the condition may escape early recognition, as prenatal genetic screening is generally not indicated without specific antenatal findings. We describe a 13-year-old girl, raised as female, who presented with delayed puberty and ambiguous genitalia. Despite clitoromegaly noted at birth, the finding was overlooked until adolescence. Hormonal evaluation revealed hypergonadotropic hypogonadism, and karyotyping confirmed mosaic 45,X/46,XY. The absence of classical phenotypic features, along with caregiving challenges and limited follow-up during early childhood, may have contributed to delayed diagnosis. Multidisciplinary evaluation prompted timely surgical intervention, with gonadectomy confirming gonadoblastoma and highlighting the associated malignancy risk. Nevertheless, the mother's ongoing emotional support and open communication, contributed to the child's psychological well-being development and stable gender identity. In addition, this case highlights missed early clinical signs, gaps in early assessment, and positive psychosocial adaptation despite delayed diagnosis. It emphasises the importance of enhancing provider training and public awareness of meticulous pubertal assessment, early genital evaluation, and integration of psychosocial context into clinical care, particularly in families facing socioeconomic and caregiving burdens.

INTRODUCTION

Turner Syndrome (TS) is a chromosomal condition typically characterised by a 45,X karyotype, often presenting in early childhood with features like short stature and lymphoedema. However, mosaic variants such as 45,X/46,XY exist. This rare chromosomal pattern poses significant diagnostic challenges owing to its broad and often subtle phenotypic spectrum, which may range from a typical female presentation to ambiguous genitalia, or even a phenotypic male.[1]

Unlike classic Turner syndrome, which is often diagnosed in early life, mosaic forms may be substantially more difficult to recognise. The phenotypic variability means that associated features — including genital atypia — may be subtle at birth and therefore overlooked or considered clinically insignificant.[1] Consequently, diagnosis may not be established until adolescence, when the patient presents with primary amenorrhoea or delayed puberty. Such delayed recognition carries significant implications, particularly in individuals with 45,X/46,XY mosaicism, given the elevated risk of gonadal malignancy associated with Y chromosome material, as well as the considerable psychosocial impact during this critical developmental period.[2,5]

Importantly, delayed diagnosis has implications that go beyond medical management. Adolescents diagnosed with disorders of sex development (DSDs) may experience psychosocial stress, gender uncertainty, and stigma in the absence of adequate support. Without timely diagnosis, they are often left without the opportunity for gradual psychosocial adaptation or access to multidisciplinary support.[3,11-12] Social, economic, and healthcare system factors may further compound diagnostic delays. This is particularly relevant in resource-limited settings where access to routine genetic testing is limited.

In this report, we describe a 13-year-old phenotypic female who presented with primary amenorrhoea and ambiguous genitalia is described and ambiguous genitalia and was subsequently diagnosed with mosaic Turner syndrome (45,X/46,XY). In resource-limited settings, early features of genital ambiguity may be overlooked, resulting in delayed access to genetic testing and specialist referral. This case underscores the complexities within the clinical care pathway, where delays in diagnosis despite early observable signs, may reflect gaps in clinical awareness, documentation, and continuity of follow-up.

These findings point to the value of enhancing medical education on disorders of sex development (DSDs), particularly in recognizing subtle genital differences and supporting timely adolescent surveillance. The early childhood period offers a key window for medical assessment as well as family-centred guidance on developmental, psychological, and ethical aspects.

CASE PRESENTATION

Case History

A 13-year-old girl of Malay ethnicity, assigned female at birth, was referred for evaluation of primary amenorrhoea and ambiguous genitalia. She was born full-term via vacuum-assisted delivery to a 27-year-old healthy mother, with non-consanguineous parents and no known family history of genetic disorders. Her early developmental milestones were within normal limits, and she had no prior surgical interventions or significant medical history.

This article was accepted: 09 June 2026
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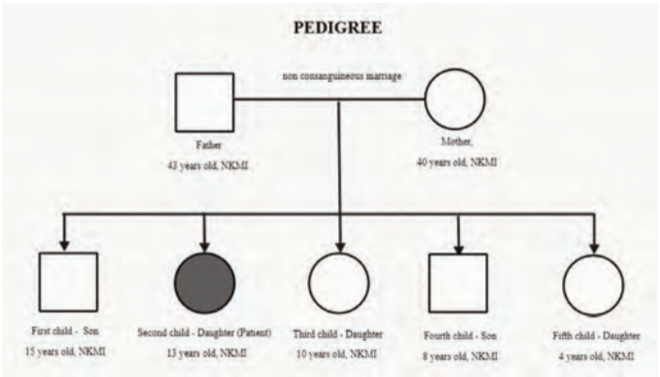
Although clitoromegaly resembling a penis was noted by the mother at birth, the finding was initially reassured by healthcare providers as normal and not investigated further. No indication for prenatal genetic screening existed, and no other dysmorphic features were noted at birth. The patient was primarily cared for by her grandmother during her early childhood.

Concerns were raised again at age 13 owing to failure to attain menarche and persistent genital abnormalities. She had no history of secondary virilization characteristics, such as deepening of the voice, or changes in hair distribution. Gender identity remained congruent with female sex assignment at birth.

Her family demonstrated strong emotional resilience and a thoughtful understanding when informed of the diagnosis. Both parents acknowledged and accepted the implications, including infertility and the potential need for gender-affirming support. Following her father's accident, which left him unable to work, her mother assumed the primary caregiving role within the family. Despite the challenges of raising five children and coping with financial strain, she remained a steadfast source of emotional support for her daughter. The child continues to thrive in school and daily activities, likely supported by this nurturing environment.

Family pedigree



Physical Examination

Her height was 141.5 cm, weight 35 kg, with a BMI of 17.5 kg/m². Secondary sexual development was Tanner Stage II, with breast buds present but not enlarged and minimal pubic hair. Axillary and facial hair were absent. Examination of the external genitalia revealed clitoromegaly with a penile-like appearance, labial fusion, hyperpigmentation, a small vaginal orifice, and no palpable gonads or scrotum. No café-au-lait spots, webbed neck, cardiac murmur, or other stigmata of Turner syndrome were observed.

** Clinical photographs were not included as consent for publication of genital images was declined.*

Results of relevant tests or investigations:

- Hormonal profile:
  - FSH: 102.4 IU/L ↑
  - LH: 30.29 IU/L ↑
  - Progesterone: <0.67 nmol/L ↓
  - Testosterone: 7.20 nmol/L ↑ (male range)
  - 17-OHP: 2.46 nmol/L (normal)
- Pelvic MRI:
  - Anteverted atrophic uterus (2.7 x 1.7 x 2.8 cm), single endometrial cavity, preserved zonal anatomy
  - Non-visualisation of both ovaries
  - Perineal structure resembling penis (Clitoromegaly, with a phallic structure identified on axial view)
  - No urinary tract or other abdominal abnormalities (Normal bladder, kidneys, liver, spleen, vertebrae)
- Standard karyotyping using G-banding technique on peripheral blood:
  - 30 cells analyzed:
  - - 22 cells (73.3%): 46,XY
  - - 8 cells (26.7%): 45,X
  - Final karyotype: 45,X[8]/46,XY[22]
  - Interpretation → Mosaic Turner Syndrome

Diagnosis

- Mosaic Turner Syndrome (45,X/46,XY) with Disorder of Sex Development (DSD)
- Ambiguous genitalia and delayed puberty

Treatment Plan

She was subsequently referred to a tertiary centre for further management under a dedicated Paediatric Adolescent Gynaecology team. She remains under regular follow-up by a multidisciplinary team comprising paediatric adolescent gynaecology, paediatric surgery, and psychological services, guiding her long-term care. Management has focused on providing affirming, patient-centred care aligned with her expressed female gender identity and psychosocial development.

Following multidisciplinary discussion, a staged surgical approach was planned. Priority was given to examination under anaesthesia (EUA) with diagnostic laparoscopy and bilateral inguinal exploration with gonadectomy. The decision for gonadectomy was made through shared decision-making after detailed counselling, for risk reduction in view of the presence of Y-chromosome material and its associated malignancy risk, as well as to allow definitive evaluation of gonadal tissue.

She then underwent examination under anaesthesia (EUA) with diagnostic laparoscopy, bilateral inguinal exploration with gonadectomy. Histopathological examination revealed gonadoblastoma in the left gonad, while the right gonad demonstrated mixed gonadal elements without evidence of malignancy. A final diagnosis of mixed gonadal dysgenesis with gonadoblastoma was established on the basis of histopathological findings.

Following surgery, oral hormone replacement therapy (progynova 1mg once daily) with oral oestrogen (estradiol 1mg twice weekly) was initiated to support pubertal development and bone health, with plans for ongoing titration and future addition of progesterone as appropriate. Bone health surveillance, including planned bone mineral density assessment, and cardiovascular monitoring have been incorporated into her long-term follow-up plan.

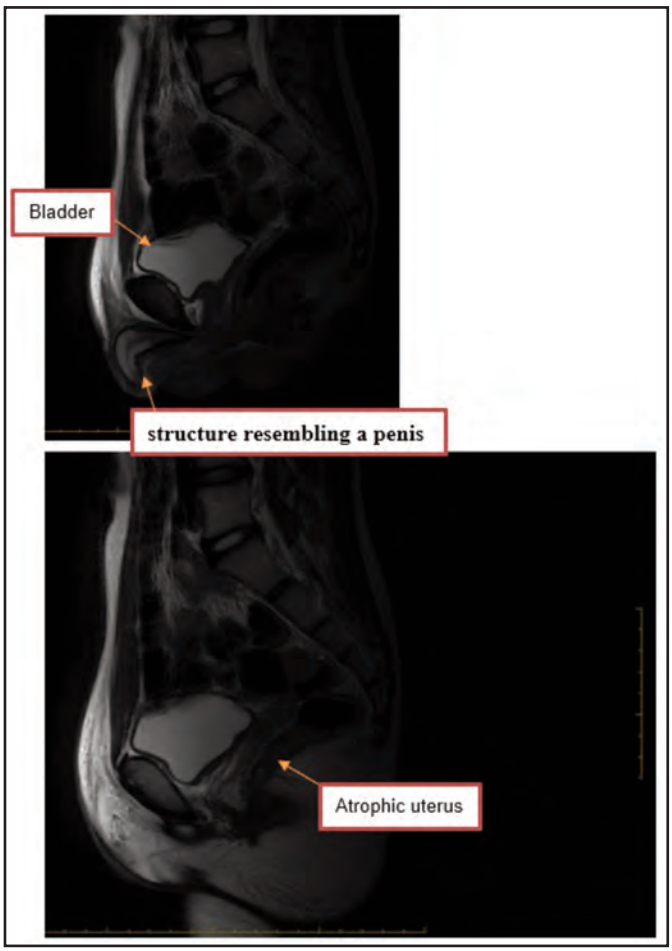


Fig. 1: Sagittal T2-weighted MRI: Shows the atrophic uterus (2.7 × 1.7 × 2.8 cm) with single endometrial cavity and preserved zonal anatomy

Surgical options for genital reconstruction, including reduction clitoroplasty and possible vaginoplasty, are being considered in a staged manner based on patient readiness and shared decision-making. Psychological support, including individual counselling and peer-based interventions, is being provided to facilitate emotional adjustment and strengthen resilience during adolescence and transition.

DISCUSSION

The absence of typical Turner syndrome features in this patient delayed recognition until primary amenorrhoea became apparent. Early genital ambiguity in the form of clitoromegaly was noted at birth but not further investigated, reflecting missed early clinical signs and gaps in initial assessment and follow-up. This case underscores the wide clinical variability associated with rare mosaic Turner syndrome and the diagnostic delays that arise when classical features are absent.[4]

The presence of Y-chromosome material in mosaic Turner syndrome confers an increased risk of gonadoblastoma or germ cell neoplasia in situ, reported in approximately 12–40% of patients.[5] In this case, the patient presented in early adolescence with delayed diagnosis and was subsequently found to have gonadoblastoma on histopathological examination following gonadectomy, highlighting the clinical relevance of this risk. Malignant transformation has most commonly been described during adolescence and early adulthood (approximately 13–24 years), although cases in younger children have also been reported. This supports consideration of early prophylactic gonadectomy, often at the time of diagnosis.[1,6] However, the optimal timing of gonadectomy should be individualized. In this case, early surgical intervention was undertaken based on the known malignancy risk associated with Y-chromosome material. Even in the absence of definitive imaging findings, surgical intervention may be warranted, given that imaging may fail to detect early neoplastic change in dysgenetic or intra-abdominal gonads.[7] Referral to a centre with expertise in the care of individuals with TS and Y chromosome material, along with a shared decision-making approach, is recommended, as demonstrated in this case.[8]

Hormonal analysis in this case revealed hypergonadotropic hypogonadism and elevated testosterone, consistent with primary gonadal failure with possible testicular tissue. Imaging confirmed an atrophic uterus and non-visualized ovaries, further supporting the diagnosis of mixed gonadal dysgenesis. Consistent with prior case descriptions, our patient's findings resemble those of a 22-year-old female with

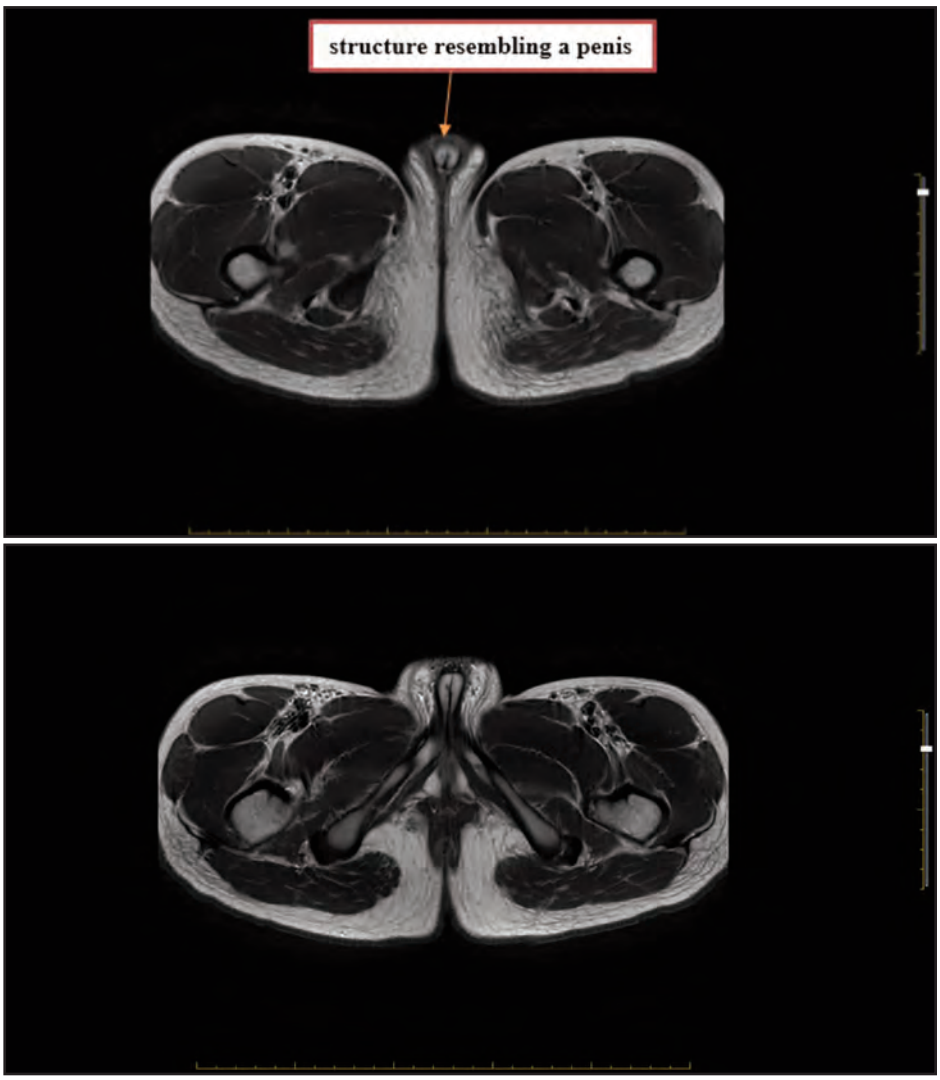


Fig. 2: Axial T2-weighted MRI: Demonstrates a structure resembling a penis and non-visualisation of both ovaries

45,X/46,XY mosaicism who presented with primary amenorrhea and demonstrated absent uterus and ovaries on imaging before prophylactic gonadectomy.[8]

In patients with hypergonadotropic hypogonadism, as in this case, hormone replacement therapy is recommended until the average age of natural menopause, initially to induce puberty and subsequently to maintain secondary sexual characteristics, optimise uterine development and support attainment of peak bone mass.[1] Hence, oestrogen therapy was initiated in our patient, with ongoing follow-up to optimise hormone replacement therapy, including the timing of progesterone addition for endometrial protection. In addition, baseline and periodic cardiac assessment is recommended to screen for structural cardiac anomalies, alongside bone health optimisation.[1]

Beyond medical implications, adolescents diagnosed with DSD often experience challenges related to identity, autonomy, and future reproductive potential.[10] These concerns are best addressed through multidisciplinary care — encompassing medical, surgical, psychosocial, and psychosexual support, alongside ethical and human rights considerations, and delivered via individualised counselling and shared decision-making in a developmentally appropriate manner.[11-12] Satisfaction with healthcare communication has been associated with improved psychosocial outcomes in adolescents with DSD.[13] The child continues to function well in school and daily activities, suggesting positive psychosocial adaptation. This highlights the protective role of supportive caregiving in adolescents with DSD, particularly in the context of delayed diagnosis and complex care needs.

Mosaic TS with 45,X/46,XY karyotype can present with subtle or ambiguous features that may not be recognised at birth. This case highlights the importance of early genital assessment and timely genetic evaluation, as missed early signs and gaps in follow-up may lead to delayed diagnosis. In addition, caregiving strain and social factors may further contribute to delays in diagnosis. Multidisciplinary involvement encompassing medical, surgical, psychological, and social support, plays a key role in addressing the needs of both patient and family.

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