Section: Miscellaneous

Case Report

INTERESTING CASE OF PRIMARY AMENORRHOEA WITH MIXED GONADAL DYSGENESIS

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ABSTRACT

Background: Disorders of sexual development (DSD) are characterized by discordance between chromosomal, gonadal, and phenotypic sex. Mixed gonadal dysgenesis is a rare form of 46, XY DSD that commonly presents with primary amenorrhoea and delayed secondary sexual characteristics. Early diagnosis is important due to the increased risk of gonadal malignancy and the need for appropriate hormonal therapy.

Case Presentation: A 17-year-old phenotypic female presented with primary amenorrhoea and absence of breast development. Clinical examination revealed Tanner stage I breast development with sparse pubic and axillary hair.Local examination revealed normal female external genitalia with an intact hymen. Hormonal evaluation showed elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels with low anti-Müllerian hormone (AMH) and testosterone levels. Karyotyping revealed 46, XY genotype. Pelvic ultrasonography and magnetic resonance imaging demonstrated hypoplastic uterus with non-visualization of ovaries or testicular tissue. Diagnostic laparoscopy revealed infantile uterus with bilateral thin fallopian tubes and streak gonads. Bilateral gonadectomy with salpingectomy was performed. Histopathological examination showed ovarian stromal tissue with Sertoli cells on one side and tubular structures resembling epididymal tissue on the contralateral side, confirming mixed gonadal dysgenesis.

Conclusion: Mixed gonadal dysgenesis is an uncommon but important cause of primary amenorrhoea in phenotypic females with a 46,XY karyotype. Early diagnosis through hormonal, genetic, and imaging evaluation followed by prophylactic gonadectomy is essential due to the risk of gonadal malignancy. Hormone replacement therapy is necessary for the development of secondary sexual characteristics and long-term health.

Keywords: Primary amenorrhoea; mixed gonadal dysgenesis; 46,XY female; disorders of sexual development; streak gonads.

INTRODUCTION

Sex determination and differentiation in humans is a complex process involving coordinated interaction between genetic, gonadal, and phenotypic factors. Genetic sex is determined by the sex chromosomes (46, XX or 46, XY), while gonadal sex depends on the differentiation of the primordial gonads into ovaries or testes. Phenotypic sex is determined by the development of internal and external genitalia and the appearance of secondary sexual characteristics during puberty.[1-5]

The presence of the sex-determining region of the Y chromosome (SRY) plays a crucial role in testicular differentiation. Activation of this gene leads to development of testes from the primordial gonads. Several other genes such as SOX9, FGF9, and WT1 contribute to testicular differentiation, whereas WNT4, RSPO1, DAX1, and FOXL2 promote ovarian development. Mutations or abnormalities in these genes can lead to disorders of sexual development (DSD).[6-10]

DSD are broadly classified into three categories:

1. 46,XX DSD

2. 46,XY DSD
3. Sex chromosome DSD

Individuals with 46, XY DSD have a male karyotype but may present with female or ambiguous phenotypic characteristics due to abnormal testicular development or impaired androgen action. Conditions in this category include pure gonadal dysgenesis (Swyer syndrome), mixed gonadal dysgenesis, partial gonadal dysgenesis, and androgen insensitivity syndrome.

Primary amenorrhoea is defined as the absence of menarche by 13 years of age in the absence of secondary sexual characteristics or by 15 years in the presence of normal secondary sexual characteristics. Evaluation of primary amenorrhoea requires careful clinical assessment along with hormonal evaluation, imaging studies, and chromosomal analysis.

Mixed gonadal dysgenesis is a rare condition characterized by asymmetrical gonadal differentiation, often presenting with streak gonads and variable internal genital structures. Early diagnosis is essential because the presence of Y chromosome material carries a significant risk of gonadal malignancy, necessitating timely surgical management and hormonal therapy.

Here, we report a case of primary amenorrhoea in a 17-year-old phenotypic female with a 46,XY karyotype, where laparoscopic evaluation and histopathological findings confirmed mixed gonadal dysgenesis.

CASE REPORT

A 17-year-old girl presented to the gynecology outpatient department with complaints of primary amenorrhoea and absence of breast development. There was no history of cyclic abdominal pain. She had no past history of chronic medical illness, previous surgery, hormonal therapy, radiation exposure, or chemotherapy.

She is the second child of a non-consanguineous marriage and has one elder brother who had normal pubertal development. There was no significant family history of delayed puberty or disorders of sexual development.

On general examination, the patient was 155 cm in height with a body mass index of 19.1 kg/m². Secondary sexual characteristics were poorly developed. Breast development corresponded to Tanner stage I, with sparse pubic and axillary hair. Systemic examination was unremarkable.

Local examination revealed normal female external genitalia with an intact hymen. There were no signs of virilization or genital ambiguity.

Investigations

The patient underwent detailed endocrine, genetic, and radiological evaluation to determine the cause of primary amenorrhoea.

Hormonal analysis revealed elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels with low anti-Müllerian hormone (AMH) and low testosterone, suggesting hypergonadotropic hypogonadism and impaired gonadal function.

Karyotype analysis demonstrated a 46, XY chromosomal pattern, indicating a discrepancy between the patient's chromosomal sex and phenotypic female appearance.

Pelvic ultrasonography showed a hypoplastic uterus, while both ovaries were not visualized in the adnexal regions.

For further evaluation, magnetic resonance imaging (MRI) of the pelvis was performed, which confirmed the presence of a small hypoplastic uterus with poorly developed myometrium and thin endometrium. No ovarian tissue was identified in the adnexa, inguinal canal, or labial regions. There was also no evidence of testicular tissue or ovotestis.

Based on these findings, the patient was planned for diagnostic laparoscopy to evaluate the internal genital structures and to identify the gonads**.**

Operative Findings: Diagnostic laparoscopy was performed to evaluate the internal genital organs and gonadal structures. On entering the pelvis, a small infantile uterus was identified in the midline. Bilateral fallopian tubes were present and appeared morphologically normal.

Adjacent to the fallopian tubes, bilateral streak gonads were visualized, suggestive of dysgenetic gonadal tissue. No well-formed ovaries or testicular structures were identified within the pelvis.

Both inguinal canals were explored intraoperatively, and no evidence of testis or ovotesticular tissue was found.

Considering the presence of dysgenetic gonads and the associated risk of gonadoblastoma in patients with Y-chromosome material, a bilateral gonadectomy with salpingectomy was performed. The excised gonadal tissues were sent for histopathological examination to confirm the diagnosis.

Histopathology: Histopathological examination of the excised gonadal tissues revealed bilateral streak gonads composed predominantly of fibrous stromal tissue.

Microscopic examination of one gonad demonstrated ovarian stromal tissue containing scattered Sertoli cells, suggesting dysgenetic gonadal differentiation. The contralateral gonad showed tubular structures resembling epididymal tissue, indicating the presence of Wolffian duct derivatives.

No evidence of malignant transformation or gonadoblastoma was identified in the examined sections.

These histopathological findings were consistent with mixed gonadal dysgenesis, correlating with the patient's clinical presentation, hormonal profile, and karyotype of 46, XY.

Management and Follow-up: Following confirmation of mixed gonadal dysgenesis with 46, XY karyotype, the patient underwent bilateral

gonadectomy with salpingectomy to eliminate the risk of gonadal malignancy, particularly gonadoblastoma, which is known to occur in dysgenetic gonads containing Y-chromosome material.

The postoperative period was uneventful, and the patient recovered well from surgery. After histopathological confirmation of the diagnosis, she was started on hormone replacement therapy (HRT). Estrogen therapy was initiated to promote the development of secondary sexual characteristics, including breast development and maintenance of bone health. Gradual hormonal therapy was planned under endocrinological supervision.

The patient and her parents were extensively counseled regarding the diagnosis, long-term management, and prognosis. They were informed about the necessity of lifelong hormonal therapy and the importance of regular medical follow-up.

During follow-up visits, the patient will be monitored for:

- Development of secondary sexual characteristics
- Hormonal balance and response to HRT
- Bone health and metabolic status
- Psychological support and counseling when required

The patient was also counseled regarding future fertility options, including assisted reproductive techniques using donor oocytes, as spontaneous fertility is not possible due to the absence of functional gonadal tissue.

Regular gynecological and endocrinological follow-up was advised to ensure optimal long-term health and quality of life.

RESULTS

The patient presented with primary amenorrhoea and absence of secondary sexual characteristics. Clinical examination revealed Tanner stage I breast development with sparse pubic and axillary hair, while the external genitalia appeared normal female.

Hormonal evaluation demonstrated elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) with low anti-Müllerian hormone (AMH) and testosterone levels, indicating hypergonadotropic hypogonadism. Karyotype analysis showed a 46, XY chromosomal pattern, confirming discordance between genetic and phenotypic sex.

Radiological evaluation with pelvic ultrasonography and MRI revealed a hypoplastic uterus with poorly developed myometrium and thin endometrium, and absence of identifiable ovarian tissue or testicular structures.

Diagnostic laparoscopy revealed an infantile uterus with bilateral fallopian tubes and bilateral streak gonads. Bilateral gonadectomy with salpingectomy was performed. Histopathological examination confirmed bilateral streak gonads with ovarian stromal tissue containing Sertoli cells on one side and epididymal-like tubular structures on the other, consistent with mixed gonadal dysgenesis.

The patient had an uneventful postoperative recovery and was initiated on hormone replacement therapy for development of secondary sexual characteristics.

Table 1: Clinical and Investigative Findings of the Patient

Parameter	Findings
Age	17 years
Presenting complaint	Primary amenorrhoea
Height	155 cm
BMI	19.1 kg/m²
Breast development	Tanner stage I
Pubic hair	Sparse
External genitalia	Normal female
FSH	Elevated
LH	Elevated
AMH	Low
Testosterone	Low
Karyotype	46,XY
Ultrasound pelvis	Hypoplastic uterus, ovaries not visualized
MRI pelvis	Hypoplastic uterus, no gonadal tissue identified
Laparoscopy findings	Infantile uterus, bilateral streak gonads
Surgical procedure	Bilateral gonadectomy with salpingectomy
Histopathology	Mixed gonadal dysgenesis
Postoperative management	Hormone replacement therapy

Table Notes: BMI = Body mass index; FSH = Follicle-stimulating hormone; LH = Luteinizing hormone; AMH = Anti-Müllerian hormone; MRI = Magnetic resonance imaging; HRT = Hormone replacement therapy. Hormonal profile suggested hypergonadotropic hypogonadism, and karyotype revealed 46, XY genotype indicating chromosomal–phenotypic discordance.

Table 2: Timeline of Clinical Events

Timeline	Clinical Event
Age 17 years	Patient presented with primary amenorrhoea and absence of breast development
Initial clinical evaluation	Physical examination showed Tanner stage I breast development with sparse pubic and axillary hair

Hormonal assessment	Elevated FSH and LH with low AMH and testosterone, suggestive of hypergonadotropic hypogonadism
Genetic evaluation	Karyotype analysis revealed 46,XY genotype
Imaging studies	Ultrasound and MRI pelvis showed hypoplastic uterus with non-visualization of ovaries
Surgical evaluation	Diagnostic laparoscopy performed to assess internal genital organs
Operative findings	Infantile uterus with bilateral fallopian tubes and bilateral streak gonads identified
Surgical management	Bilateral gonadectomy with salpingectomy performed
Histopathological diagnosis	Findings consistent with mixed gonadal dysgenesis
Postoperative care	Hormone replacement therapy initiated
Follow-up	Regular gynecological and endocrinological follow-up advised

Notes: Table Notes: FSH = Follicle-stimulating hormone; LH = Luteinizing hormone; AMH = Anti-Müllerian hormone; MRI = Magnetic resonance imaging. Timeline summarizes the key diagnostic, surgical, and therapeutic events in the management of the patient.

Table 3: Differential Diagnosis of 46, XY Disorders of Sexual Development

Condition	Karyotype	Gonads	Internal Genitalia	External Genitalia / Clinical Features
Swyer syndrome (Pure gonadal dysgenesis)	46,XY	Streak gonads	Presence of uterus and fallopian tubes	Female phenotype, primary amenorrhoea, absent puberty
Mixed gonadal dysgenesis	Usually 45,X/46,XY or 46,XY	One streak gonad with dysgenetic testis	Variable Müllerian structures	Ambiguous or female genitalia, delayed puberty
Androgen insensitivity syndrome (AIS)	46,XY	Testes present	Müllerian structures absent	Female external genitalia, normal breast development, absent uterus
5-alpha reductase deficiency	46,XY	Testes present	Wolffian structures present	Ambiguous genitalia at birth, virilization at puberty

Table Notes: DSD = Disorders of sexual development; AIS = Androgen insensitivity syndrome. This table summarizes the important differential diagnoses to consider in patients with a 46, XY karyotype presenting with primary amenorrhoea or atypical sexual development

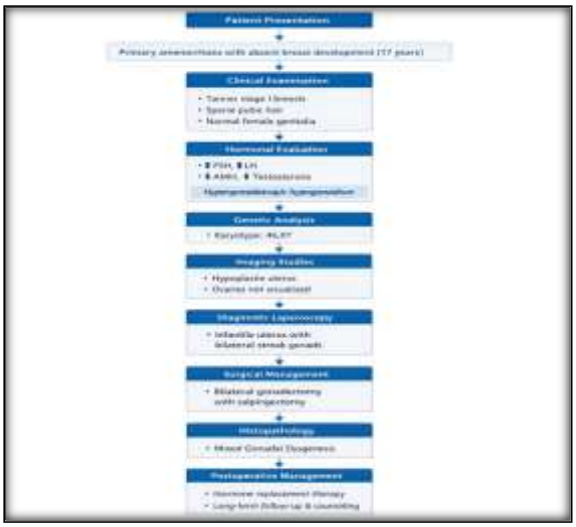

Figure 1: Diagnostic and Management Flowchart of a Patient with Primary Amenorrhoea and Mixed Gonadal Dysgenesis

Figure Notes: FSH = Follicle-stimulating hormone; LH = Luteinizing hormone; AMH = Anti-Müllerian hormone; MRI = Magnetic resonance imaging; HRT = Hormone replacement therapy. The flowchart illustrates the stepwise diagnostic evaluation and management pathway of the patient presenting with primary amenorrhoea.

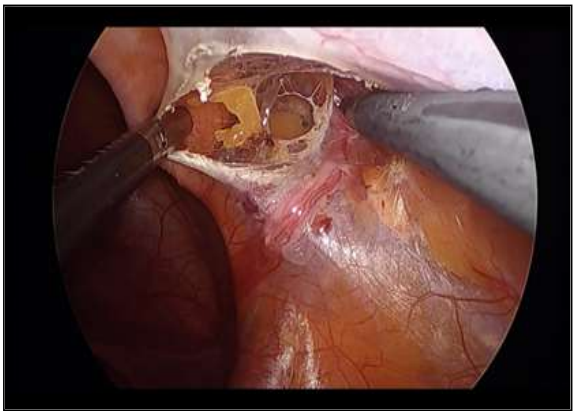

Figure 2: Laparoscopic view of dysgenetic streak gonad during surgical dissection

This image shows dysgenetic streak gonadal tissue being dissected during laparoscopic surgery.

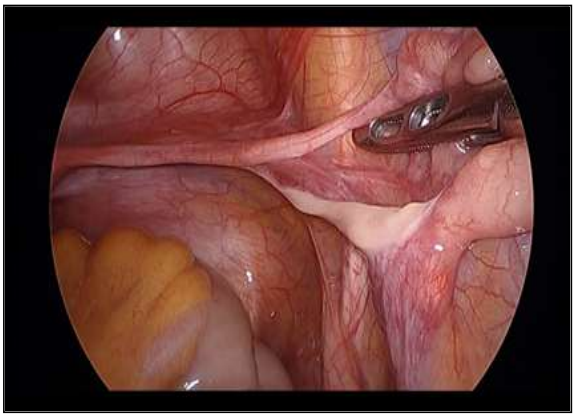

Figure 3: Laparoscopic image showing infantile uterus with fallopian tube

The image demonstrates a small hypoplastic uterus with fallopian tube, consistent with Müllerian structures in gonadal dysgenesis.

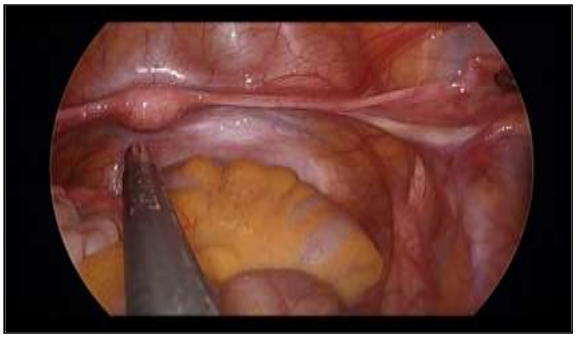

Figure 4: Laparoscopic image demonstrating streak gonad adjacent to fallopian tube

This image shows streak gonadal tissue located near the fallopian tube before gonadectomy.

DISCUSSION

Mixed gonadal dysgenesis (MGD) is a rare disorder of sexual development characterized by asymmetric gonadal differentiation and discordance between chromosomal, gonadal, and phenotypic sex. It commonly occurs in individuals with the presence of Y chromosome material, most frequently associated with mosaic karyotypes such as 45,X/46,XY, although cases with 46,XY karyotype have also been reported.

The development of normal male sexual differentiation depends on the presence of the sex-determining region of the Y chromosome (SRY), which initiates testicular development from the primordial gonads. The developing testes produce anti-Müllerian hormone (AMH) from Sertoli cells, leading to regression of Müllerian structures, and testosterone from Leydig cells, which promotes development of Wolffian duct derivatives. Any disruption in these processes may result in abnormal gonadal differentiation and disorders of sexual development.

Patients with mixed gonadal dysgenesis may present with a wide spectrum of clinical manifestations ranging from ambiguous genitalia at birth to delayed puberty or primary amenorrhoea during adolescence. In phenotypic females, the most common presentation is primary amenorrhoea with poorly developed secondary sexual characteristics, as seen in the present case.

Evaluation of primary amenorrhoea requires a systematic approach including clinical examination, hormonal evaluation, imaging studies, and chromosomal analysis. Elevated FSH and LH levels with low sex steroid levels typically indicate hypergonadotropic hypogonadism, suggesting gonadal failure. Karyotyping plays a crucial role in identifying underlying chromosomal abnormalities and guiding further management.

Imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) help assess the presence and morphology of internal genital organs and gonads. However, dysgenetic gonads may be difficult to visualize radiologically, and diagnostic laparoscopy remains the gold standard for definitive evaluation.

One of the most important considerations in patients with gonadal dysgenesis containing Y chromosome material is the increased risk of gonadal malignancy, particularly gonadoblastoma and dysgerminoma. The reported risk of malignancy in such cases ranges from 15% to 35%, which justifies the recommendation for prophylactic gonadectomy once the diagnosis is established.

In the present case, laparoscopy revealed bilateral streak gonads associated with an infantile uterus and fallopian tubes, and histopathological examination confirmed features consistent with mixed gonadal dysgenesis. Early surgical removal of dysgenetic gonads was performed to prevent potential malignant transformation.

Following gonadectomy, hormone replacement therapy (HRT) is essential to induce the development of secondary sexual characteristics, maintain bone density, and support overall metabolic health. In addition to medical management, psychological counseling and long-term follow-up are important aspects of care for individuals with disorders of sexual development.

This case highlights the importance of early evaluation of primary amenorrhoea and a multidisciplinary approach involving gynecologists, endocrinologists, and pathologists to ensure accurate diagnosis and optimal management.

CONCLUSION

Mixed gonadal dysgenesis is a rare disorder of sexual development that may present with primary amenorrhoea and delayed secondary sexual characteristics in phenotypic females with a 46, XY karyotype. A systematic evaluation including clinical examination, hormonal profile, imaging studies and chromosomal analysis is essential for accurate diagnosis. Diagnostic laparoscopy plays an important role in identifying dysgenetic gonads when imaging findings are inconclusive. Early prophylactic gonadectomy is recommended because of the increased risk of gonadal malignancy in patients with Y-chromosome material. Timely initiation of hormone replacement therapy and multidisciplinary follow-up are crucial for the development of secondary sexual characteristics and long-term health outcomes.

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