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METASTATIC MIXED GERM CELL TUMOUR IN A PATIENT WITH CRYPTORCHIDISM AND PERSISTENT MÜLLERIAN DUCT SYNDROME

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ABSTRACT

Introduction: Persistent Müllerian duct syndrome (PMDS) is a rare disorder of sexual development characterized by the persistence of Müllerian structures, such as the uterus and fallopian tubes, in phenotypically and genotypically normal males. It is usually identified during surgical interventions for cryptorchidism or inguinal hernias, and rarely during cancer of the ectopic testis.

Case description: We present the case of a 32-year-old male with a history of right cryptorchidism and hypospadias who presented with a metastatic germ cell tumour of the testis. Following systemic chemotherapy, the patient underwent midline laparotomy to remove all residual tumours. During the surgery, PMDS was unexpectedly diagnosed. Postoperative karyotyping confirmed a 46, XY genotype with a pathogenic defect in the anti-Müllerian hormone type II receptor (AMHR-II).

Discussion: Interestingly, germ cell tumours have been reported in up to 33% of patients with PMDS, suggesting that the syndrome may confer an elevated risk of malignant transformation beyond that attributable to cryptorchidism alone. This case highlights the significant clinical association between PMDS and testicular germ cell tumours.

Conclusion: This case emphasizes that clinicians should consider underlying PMDS when cryptorchidism is accompanied by additional anomalies, such as hypospadias, particularly in adults presenting with testicular masses.

KEYWORDS

Persistent Müllerian duct syndrome, cryptorchidism, germ cell tumour, hypospadias

LEARNING POINTS

- The occurrence of a metastatic mixed germ cell tumour in a patient with untreated cryptorchidism, hypospadias, and underlying persistent Müllerian duct syndrome is rare.
- It is important to consider disorders of sex development when evaluating adult males with testicular malignancy and a history of genitourinary anomalies.
- A collaborative approach involving urology, oncology, radiology, and genetics is essential for accurate diagnosis and optimal management.

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INTRODUCTION

Persistent Müllerian duct syndrome (PMDS) is a rare autosomal recessive disorder of sexual development. It is characterized by the persistence of Müllerian duct derivatives, which include the uterus, cervix, and fallopian tubes, in genetically and phenotypically normal 46, XY males[1]. PMDS results from a failure of normal Müllerian regression during foetal development, typically caused by a deficiency in anti-Müllerian hormone (AMH) production by Sertoli cells or a defect in the AMH type II receptor (AMHR-II). Typically, AMH secretion begins during the seventh week of gestation, leading to the regression of Müllerian structures. In PMDS, this process is interrupted, resulting in the retention of these female reproductive organs.

PMDS is an exceptionally rare condition, with fewer than 150 cases reported in the global literature[2]. The diagnosis is most often made incidentally during surgical exploration for undescended testes or inguinal hernia repair because affected individuals otherwise exhibit normal male phenotypic development. Although recognized, the association between PMDS and testicular malignancy is infrequently reported.

We present an unusual case of PMDS that was diagnosed late in adulthood during the surgical treatment of metastatic mixed germ cell tumours. This case emphasizes the importance of considering PMDS in patients with cryptorchidism and testicular cancer and highlights the potential for delayed presentation of this congenital anomaly.

CASE DESCRIPTION

A 32-year-old man presented to the urology department with a 6-month history of a persistent mass in the left inguinal region and an empty right scrotum. His medical history was significant for an untreated right cryptorchidism since birth and second-degree hypospadias, for which he underwent surgical correction at the age of 12 years. He was born at full term via an uncomplicated vaginal delivery. He had no siblings, and his parents were non-consanguineous with no history of infertility. The patient had no other comorbidities.

A physical examination revealed that the patient was a healthy-looking male with normal secondary sexual characteristics and typical male hair distribution. Genital examination revealed an empty and small right scrotum. A firm, non-tender, mobile mass measuring approximately 3 × 3 cm was palpated within the left scrotal sac. Painless left inguinal lymphadenopathy and persistent second-degree hypospadias were noted.

Scrotal ultrasound confirmed a 3 × 3 cm solid mass within the left testis, as well as an empty right scrotal sac and enlarged left inguinal lymph nodes.

Contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis revealed a 3 × 3 cm tumour in the left testicle with metastatic involvement of the left inguinal, external iliac, and para-aortic lymph nodes.

Laboratory investigations showed that serum tumour markers were markedly elevated: Alpha-fetoprotein (AFP) was 1,265 ng/ml (normal range: 0–10 ng/ml), beta-human chorionic gonadotropin (β-hCG) was 65 IU/l (normal range: 0–5 IU/l), and lactate dehydrogenase (LDH) was 994 U/l (normal range: 125–243 U/l), which is consistent with a mixed germ cell tumour.

Therefore, the patient underwent a left radical inguinal orchiectomy with concurrent left inguinal lymph node dissection. The histopathology report confirmed the presence of a mixed germ cell tumour, comprising both seminomatous and non-seminomatous components, which had metastasized to the inguinal lymph nodes.

The patient subsequently received four cycles of adjuvant BEP chemotherapy (bleomycin, etoposide, and cisplatin) administered at 21-day intervals. A post-chemotherapy restaging CT scan revealed a significant partial response, with 87% regression of the intraperitoneal, retroperitoneal,

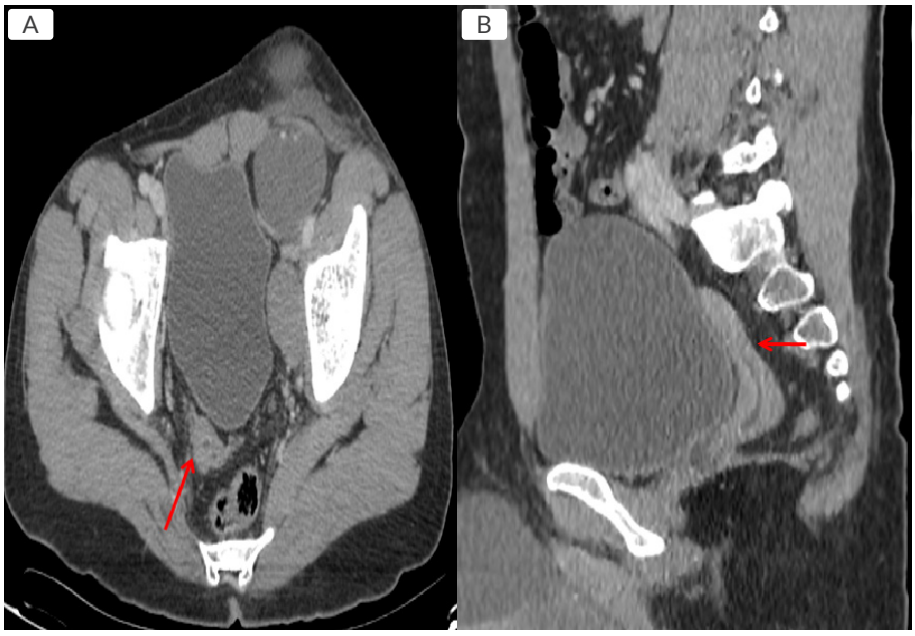


Figure 1. Contrast-enhanced computed tomography scan showing a hypodense homogeneous mass (red arrow) between the rectum and urinary bladder: A) Axial and B) Sagittal image.

and inguinal lymphadenopathy, as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, the scan revealed a hypodense, homogeneous mass in the rectovesical pouch, located between the rectum and urinary bladder *(Fig. 1)*.

Tumour markers normalized (AFP: 5.79 ng/ml, β-hCG: 1.2 IU/l, and LDH: 230 U/l).

Following a multidisciplinary team discussion, the decision was made to perform a surgical resection of the residual masses. An explorative laparotomy revealed an unexpected finding: a globular structure resembling a uterus with a cervix, fallopian tubes, and proximal vagina situated between the bladder and rectum *(Fig. 2)*. Surgical resection of this Müllerian remnant and all residual disease was performed. Histopathological examination of the removed structure confirmed the presence of uterine parenchyma consisting of endometrial glands surrounded by well-organized myometrial smooth muscle bundles *(Fig. 3)*. Analysis of the residual lymph nodes confirmed the presence of a metastatic mixed germ cell tumour *(Fig. 4)*.

The patient's postoperative recovery was uneventful, and he was discharged 4 days after surgery. Given the pathological findings, a postoperative karyotype analysis was performed, revealing a normal 46, XY karyotype with a mutation in the AMHR-II gene. These results confirmed the diagnosis of PMDS. The patient was referred back to the oncology department for further adjuvant chemotherapy. At the 6-month follow-up, he was clinically stable and still undergoing treatment.

DISCUSSION

PMDS is a rare form of internal male pseudohermaphroditism first described by Nilson in 1939[3]. This condition occurs when the Müllerian ducts fail to regress during foetal development. This regression is physiologically mediated by AMH, also known as Müllerian-inhibiting factor, which is produced by Sertoli cells. PMDS is therefore typically caused by a deficiency in AMH synthesis or secretion, or by a defect in its specific receptor[4]. Individuals with PMDS are genotypically and phenotypically male, with normally developed external genitalia and typical secondary sexual characteristics at puberty. However, their internal genitalia are incompletely virilized due to the persistence of Müllerian duct structures such as the uterus, fallopian tubes, and upper vagina[5].

PMDS is classified into three anatomical categories based on the location of the testes[6]:

- *Type 1 (feminine type):* The testes and Müllerian structures (the uterus and fallopian tubes) are both located in the pelvis, resembling female internal anatomy. Patients typically present with bilateral cryptorchidism.
- *Type 2 (male type):* One testicle is in the scrotum or inguinal canal, and the other testicle and Müllerian structures are in the inguinal region or pelvis. This is the most common form.

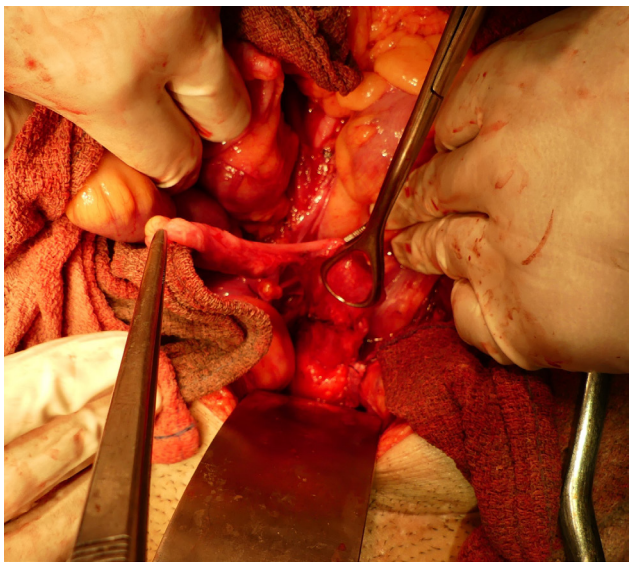


Figure 2. *Intraoperative view during midline laparotomy showing a globular structure resembling the uterus with the cervix, Fallopian tubes, and vagina positioned between the bladder and rectum.*

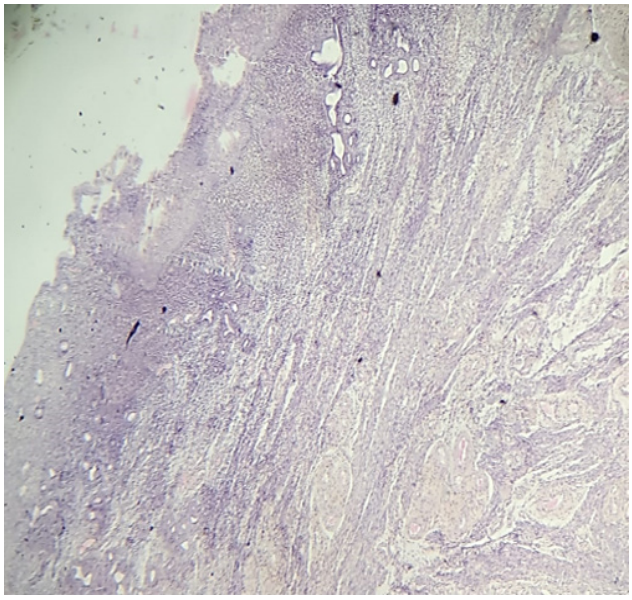


Figure 3. *Microscopic examination of removed structures between the bladder and rectum. This image shows uterine parenchyma consists of an endometrium composed of endometrial glands, resting on a myometrium formed by well-organized smooth muscle bundles.*

- *Type 3 (transverse testicular ectopia):* Both testes and the Müllerian remnants are found on the same side within the same inguinal canal or scrotal sac.

In the present case, the patient was classified as type 2. Intraoperatively, the right testis was found in the pelvis with the uterus, fallopian tubes, and ovaries, and the left testis was in the normal scrotal position. Although the patient presented with hypospadias since birth, this condition is not considered a typical feature of PMDS[6].

PMDS is most often diagnosed incidentally during surgical exploration for cryptorchidism or inguinal hernia repair. Its identification in the context of malignancy is exceptionally rare. Modern imaging modalities such as ultrasonography, computed tomography, and magnetic resonance imaging

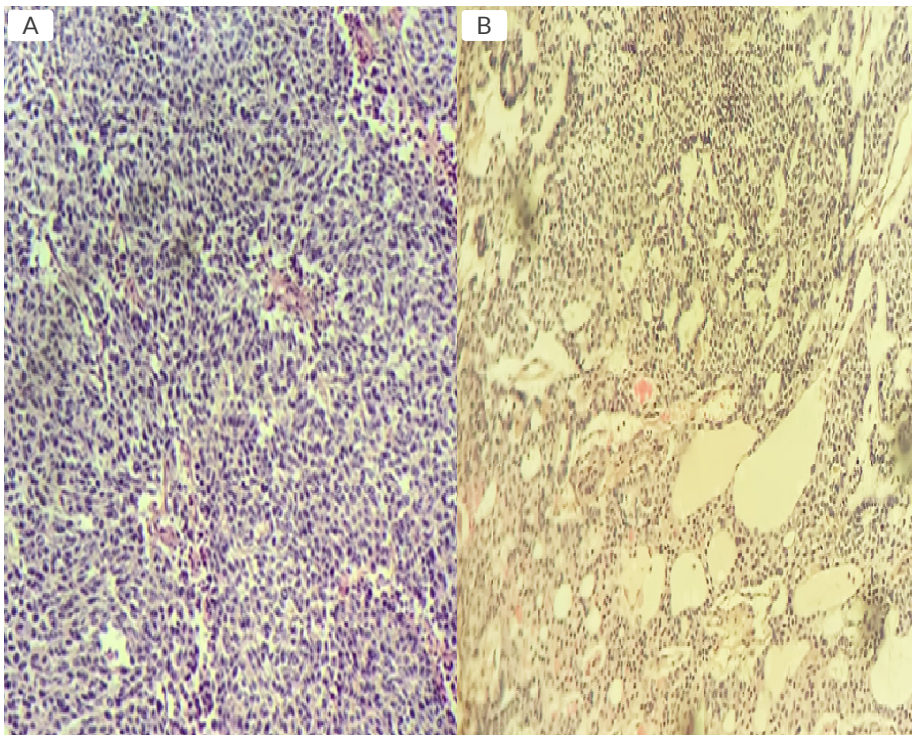


Figure 4. Microscopic examination showed a mixed germ cell tumour composed of a seminomatous component and a non-seminomatous component (yolk sac tumour): A) Seminomatous component: Tumoral proliferation arranged in solid nests separated by thin fibrous septa. B) Non-seminomatous component (yolk sac tumour): Neoplastic proliferation was arranged in the tubules, papillary structures, microcystic areas, and solid sheets.

can facilitate preoperative diagnosis[7]. The condition often remains unrecognized until direct visualization during surgery.

In the present case, the diagnosis of PMDS was made late during the surgical resection of residual disease after chemotherapy for a metastatic mixed germ cell tumour. To our knowledge, no previous report has described the occurrence of PMDS, unilateral cryptorchidism, and a germ cell tumour in a normally positioned contralateral testis. Furthermore, the concurrent presence of hypospadias adds to the clinical complexity as this anomaly is not typically associated with PMDS. These findings make this case particularly noteworthy and underscore the importance of considering underlying disorders of sex development in patients presenting with complex urological anomalies and testicular malignancy.

Patients with PMDS have a significantly higher risk of malignant transformation in undescended testes, estimated at 15 to 33%[6]. This rate is considerably higher than that observed in men with isolated cryptorchidism. This increased risk emphasizes the importance of early identification for both fertility preservation and malignancy prevention. Consequently, current management guidelines recommend prophylactically removing Müllerian duct remnants due to their frequent association with ectopic testicular tissue and subsequent potential for malignant degeneration[8].

Regarding oncological management, the treatment protocol for testicular tumours arising in the setting of PMDS is the same as that for standard testicular cancers. Patients should receive stage-appropriate therapy according to established guidelines, including radical orchiectomy, chemotherapy, and surgical resection of residual disease, if necessary.

CONCLUSION

This case report presents a rare and complex clinical situation involving the diagnosis and management of a metastatic mixed germ cell tumour in a patient with untreated cryptorchidism, a history of hypospadias, and underlying PMDS.

This case underscores the importance of considering underlying disorders of sex development in adult males presenting with testicular malignancies and a history of genitourinary abnormalities, such as cryptorchidism and hypospadias.

The delayed diagnosis of PMDS, which was only identified during post-chemotherapy surgery for residual disease, highlights the silent nature of this condition in phenotypically normal males. However, the Müllerian remnant complicated the initial presentation and post-chemotherapy radiographic evaluation by mimicking residual disease.

This case adds to the limited literature on PMDS presenting with testicular malignancy. It emphasizes the need for a high level of suspicion, a multidisciplinary management approach, and the importance of histopathological and genetic analyses for establishing a definitive diagnosis.

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