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Case Report

Persistent Müllerian Duct Syndrome and Germ Cell Tumor: A Case Report and a Review of the Literature

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Abstract

Persistent Müllerian Duct Syndrome (PMDS) is a rare disease of sexual differentiation characterized by the presence of Müllerian duct structures in a male with a normal phenotype. All patients with this condition are considered males regarding the genotype (46, XY) and they usually have a normal virilization.

We report the case of a man with a history of Germ Cell Tumor (GCT) who was found to have a right hydronephrosis condition during the follow-up. The subsequent CT scan revealed a Pyeloureteral Junction Syndrome (PUJS) and surgery was planned. Throughout the right nephrectomy, the surgeon accidentally found the presence of Müllerian duct structures, particularly the uterus with the cervix and left adnexal tissue.

Given the rarity of this condition and the peculiarity of our case, we performed literature research available on the link between PMDS and GCT.

Keywords: Persistent Müllerian Duct Syndrome; Germ Cell Tumor; Anti Müllerian Hormone Gene; Anti Müllerian Hormone Receptor 2 Gene; Müllerian Derivates

Introduction

Persistent Müllerian Duct Syndrome (PMDS) is a rare disease defined as the presence of Müllerian derivates, i.e., uterus and Fallopian tubes, occurring in normally masculinized 46 XY subjects. Since its first description by Nilson in 1939 [1] approximately 300 additional cases of PMDS have been reported in the literature [2,3,4].

PMDS is transmitted as an autosomal recessive trait. The condition is due to mutations inactivating genes of either Anti Müllerian Hormone (AMH) or its receptor (AMHR2) [3]. AMH is synthesized by Sertoli cells and is responsible for the regression of fetal Müllerian ducts.

Infertility is the most frequent complication of PMDS; fertility is preserved only if at least one testis is scrotal and its excretory ducts are intact [4].

There are three possible clinical presentations: bilateral cryptorchidism (most frequent), unilateral cryptorchidism with a contralateral hernia, and transverse testicular ectopia [4].

Cryptorchidism is a well-known risk factor for GCT, and it was reported to be associated with PMDS [5,6,7]. A recent literature review showed that Germ Cell Tumor (GCT) was identified in up to 33% of patients with PMDS, which suggests that factors in addition to non-descent of the testis may contribute to the malignant degeneration. The most frequent GCT histology is seminoma, whilst non-seminoma and Müllerian derivate cancers are much less frequent [4]; in fact, only 11 cases of malignant degeneration of Müllerian derivate have been reported among a total of 200 PMDS up to 2011 [8,9].

GCT accounts for only 1% of all tumors in males, but it is the most common cancer in men between 15 and 39 years old [10]. The incidence of GCT is increasing worldwide, albeit with marked regional differences: this malignancy is very rare in Africa, among Afro-American populations and in Asia, and it is more frequent in Nordic European countries especially Denmark, Norway, and Sweden [11].

Due to the high sensitivity to chemotherapy and also radiotherapy for seminoma, GCT patients have a high cure rate, even in advanced disease. Survival rates are excellent for the localized stages (95–100%) and are still good for the advanced stages (70–90%) [12].

Regardless of the stage, the treatment protocol for GCT in PMDS remains the same as for the other testicular cancer patients, with a good cure rate. However, presentation at the advanced stage is more frequent, with a consequent need for systemic therapy [2].

In GCT, cytogenetic abnormalities can be found, as isochromosome 12p: particularly, i(12p) is a highly non-random chromosomal marker seen in about 80% of GCT with evaluable cytogenetic abnormalities [13]. Among extra-gonadal GCT, association with Klinefelter syndrome and hematologic malignancies are also reported [14].

Methods

A web-based search of MEDLINE/PubMed library data published from 2013 to January 2023 was carried out by associating “Persistent Müllerian duct syndrome” with “germ cell cancer” or “cancer”. We limited our search to reviews and meta-analyses, which provided five articles in English. We focused on three of them as they were most consistent with the topic. The first two articles, published in 2017 and 2019 by Picard et al, had the objective to review the clinical, anatomical, and molecular features of PMDS based upon a review of the literature and 157 personal cases detected [3,4]. The third article, published in 2016 by Kathrins and Kolon, is a review of the current understanding of the types of gonadal tumors that arise in DSD (Disorders of Sex Development) [9].

Case Presentation

Herein we report the case of a 45-year-old male who was diagnosed with testicular cancer when he was 34. Right orchifunicolectomy and staging with whole body CT scan revealed a stage I seminoma. He was a healthy male, without comorbidity; the patient reported only a right orchidopexy surgery for cryptorchidism when he was six; a scrotal ultrasound performed did not reveal the left testicle. After the surgery, he received adjuvant radiotherapy.

One year later he had a retroperitoneal relapse treated with three cycles of BEP (Bleomycin, Etoposide and Cisplatin), with a complete remission of the disease.

Ten years later, during the follow-up, an abdomen CT scan showed right fourth-grade hydronephrosis. The patient underwent percutaneous nephrostomy due to the pyeloureteral junction syndrome; no signs of cancer recurrence were documented. After a few months, a CT scan showed persistent hydronephrosis, with radiological signs of a not functioning right kidney. A contrast-enhanced MRI showed a rudimental uterus and a mass, suggesting a small testis (Figure 1). The patient underwent laparoscopic surgery, with the primary aim of performing a right nephrectomy. During the intervention, a rudimentary uterus with a Fallopian tube and a left adnexal was detected and removed. Bilaterally, the presence of cord-like tubular structures referable to deferent ducts was documented in the parametrial position.

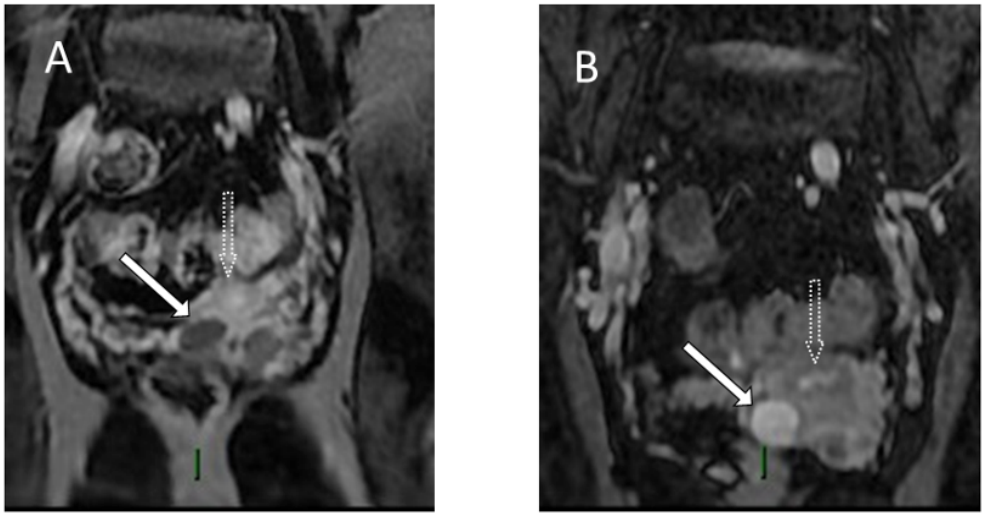

Figure 1: Patient MRI with PMDS. Coronal views shows the endometrial cavity of the uterus (dotted arrows), which are normally enhanced in Figure 1A (T1 post-contrast imagine) and normally hyperintense in Figure 1B (T2 image). The infero-lateral right ovoidal mass corresponds to the testis (white arrows).

Histopathology revealed a kidney with markedly atrophic parenchyma and chronic inflammatory infiltrate, a uterus showing normal features, and the left adnexal consisting of testicular parenchyma.

In suspicion of PMDS, Whole-Exome Sequencing (WES) was performed using Twist Human Core Exome Kit (Twist Bioscience) on a NovasSeq6000 platform (Illumina, San Diego, CA). Variant filtering and prioritization were performed by exploiting the eVAI tool (EnGenome) and an in-house developed gene panel for neurodevelopmental disorders. The study allowed the identification of the c.1332_1358del (p. Gly445_Leu453del) homozygous variant in the AMHR2 gene (NM_020547.3). No other potentially relevant variants were identified and coverage-based analysis of CNVs excluded genomic imbalances. Sanger sequencing confirmed the presence of the variant in the proband. The mutation is a well-known loss of function variant causative of PMDS [15,16].

Discussion and Conclusion

The PMDS is a 46 XY disorder of sexual development characterized by the persistence of Müllerian duct derivatives, uterus, and tubes, in otherwise normally masculinized males. PMDS is generally a poorly reported diagnosis due to its rarity, but it is important to recognize this condition for the risk of infertility and the epidemiological correlation with GCT. In adults affected by PMDS, the incidence of GCT has been estimated at up to 33%, exceeding the risk associated with isolated cryptorchidism. Seminoma is the most frequent histotype, but choriocarcinoma, mixed germ cell tumor, embryonal cell carcinoma, gonadoblastoma or yolk sac tumor have also been described [3,4].

Testicular cancer in PMDS often presents in adults with advanced-stage disease resulting from neglected or inadequate management of cryptorchidism. Appropriate management of cryptorchidism in childhood is therefore likely to decrease the occurrence of malignant transformation and enable early-stage diagnosis [2].

Although Müllerian structures in a male have a lower risk of malignant degeneration, a literature review identified eleven cases of malignancy among about a total of 200 PMDS cases analyzed up to 2011. Therefore, in these patients, it would be useful to perform orchidopexy and laparoscopic excision of Müllerian remnant structures [8,9].

Due to its rarity, PMDS diagnosis is often suspected based on radiological or intraoperative findings, as presented in this paper.

In conclusion, the diagnosis of PMDS should be always suspected in case of bilateral cryptorchidism, and the patient promptly referred to genetic counselling. This is important to reduce the risk of developing GCT and infertility.

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