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CONTINUUM OF CARE IN CANCER CONTROL & MANAGEMENT

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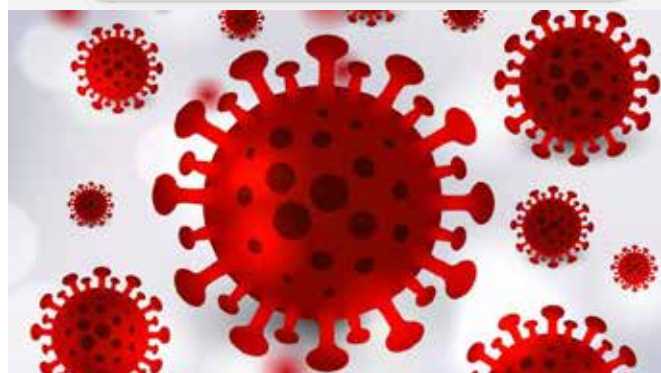
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Case Report

Germ Cell Tumors Revealing a Familial Persistent Müllerian Duct Syndrome

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Abstract:

Persistent Mullerian duct syndrome (PMDS) is a congenital disorder related to male sexual development. PMDS is usually diagnosed during an inguinal hernia cure. The diagnosis of PMDS following a testicular germ cell tumor is less common. We report the cases of three infertile male patients who were diagnosed with PMDS after surgery for germ cell tumors. They were 39, 27, and 37 years old men with a medical history of neglected cryptorchidism. All patients had a male karyotype and the ELISA test for the anti-Müllerian hormone was undetectable. Patients

underwent chemotherapy followed by resection of residual mass in one patient. One patient is currently alive and disease-free. The two other patients died of systemic relapse.

These cases highlight how early recognition and treatment of PMDS can prevent malignant germ cell tumors. The diagnosis of PMDS relies on a systemic assessment and analysis of mutations in the gene coding for AMH and AMHR-II.

Key words: Persistent Müllerian duct syndrome (PMDS), anti mullerian hormone, germ cell neoplasia

Introduction :

Persistent Mullerian duct syndrome (PMDS) is a rare form of internal male pseudohermaphroditism characterized by the presence of Mullerian duct derivatives (uterus, fallopian tubes and upper two-thirds of the vagina) in phenotypically as well as genotypically male individuals^(1,2). It was first described by Nelson in 1939, who called it “hernia uteri inguinale”⁽³⁾. PMDS is usually diagnosed incidentally during an inguinal hernia cure or undescended testis operation. The diagnosis of PMDS following a testicular germ cell tumor is less common accounting for 15% to 40%^(4,5). Correct diagnosis and timely treatment of PMDS may help prevent testicular neoplasm⁽⁶⁾.

Our study aimed to report three cases of familial testicular germ cell carcinoma revealing a PMDS and to discuss its management.

Methods :

We conducted a retrospective study including patients with malignant germ cell tumors associated with a

PMDS. We asked about the familial history of infertility and cryptorchidism and made family pedigree to establish a pattern of transmission. We reported results of karyotype as well as measurements of circulating anti-Müllerian hormone (AMH) and testosterone level before chemotherapy. Malignant germ cell tumors were classified according to the IGCCCG risk classification using pre orchietomy tumor markers (7). Patients' brothers underwent after an informed consent a testicular ultrasound examination.

Results :

Three infertile patients aged respectively 39, 37 and 27 years old had a medical history of neglected cryptorchidism. They were born from consanguineous marriage. Figure 1 shows a family tree of two patients with PMDS.

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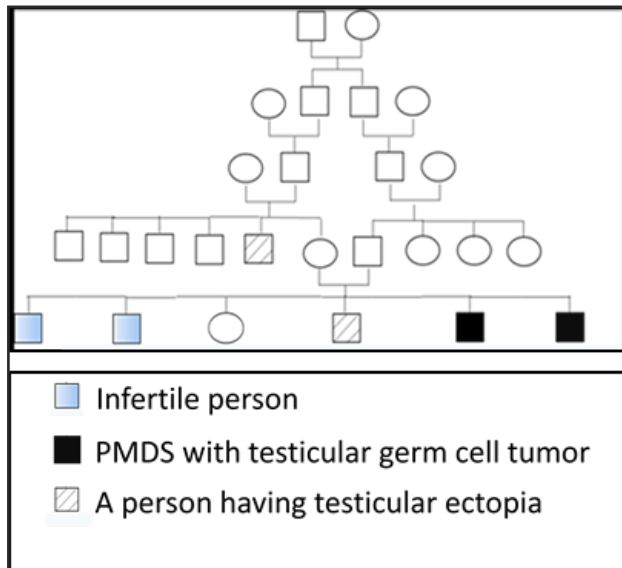


Figure 1: Family tree showing the transmission of persistent Mullerian duct syndrome among a family of two patients

Each of the three patients experienced lower abdominal pain and distention. Physical examination of scrotum showed in all of the three patients a bilateral testicular ectopia. They had also fixed mass in the lower abdomen. Contrast-enhanced abdominal computed tomography (CT) showed a mass with heterogeneous contrast enhancement (Figure 2).



Figure 2: CT scan: heterogeneous mass of the left spermatic cord developing on an ectopic testicle

Patients had a peripheral blood karyotype showing a 46 XY male karyotype and an ELISA test for the anti-Mullerian hormone in the blood, which was undetectable.

Patients were operated on by a laparotomy. Intraoperative exploration found an abdominal tumor developing on gonads. The tumor was developing on a cryptorchid testicle with the persistence of Mullerian derivatives. Complete excision of the tumor and Mullerian

duct derivatives were performed. Histopathological findings showed mixed germ cell tumors (2 patients) and seminoma (1 patient). All patients received chemotherapy with BEP 4 cycles. One patient is currently alive after 3 years follow up. One has had, eight years later, systemic relapse and died from disseminated intravascular coagulation. One patient died from early relapse and did not receive further chemotherapy.

Discussion :

PMDS is rare and fewer than 300 cases have been reported in the literature⁽⁶⁾. It is characterized by the presence, in a normally virilized male, of a uterus, fallopian tubes and the upper part of the vagina⁽⁶⁾. PMDS is frequent in North Africa where consanguineous marriages exist at a high rate. The transmission is autosomal recessive and manifests only in male subjects⁽⁹⁾. Two patients of our study were brothers and were born from a consanguineous marriage. They had a brother and an uncle with bilateral testicular ectopia. Some cases of X-linked transmission have been reported in the literature⁽¹⁰⁾. However, in our study, given the the context of consanguinity, the transmission is likely to be autosomal recessive. Parents of individuals with autosomal recessive syndrome each have a copy of the mutated gene but are phenotypically normal⁽¹¹⁾.

This syndrome is the consequence of an intrauterine deficit of anti mullerian hormone or of a hereditary insensitivity to these hormones. The sexual differentiation during intra uterine life is done thanks to two hormones which are testosterone and anti mullerian hormone (AMH⁽¹⁾).

In these three cases, while the AMH level was undetectable, testosterone was normal, explaining the presence of primary and secondary male sexual characteristics. The interpretation of the undetectable level of AMH must be made with caution because during the post-pubertal period, AMH levels are physiologically low⁽⁹⁾. A low AMH level does not necessarily mean the existence of an inactivating mutation⁽¹²⁾. In a study of 157 patients with PMDS, degeneration of an ectopic testicle was observed in 33% of cases⁽¹⁾. The high frequency of testicular tumors in PMDS is not only due to the ectopic position of the testes, but also to an hormonal imbalance (WT1 / β -catenin and inhibin balance)⁽¹⁾. Diagnosis of PMDS is made frequently while surgery for an inguinal hernia or cryptorchidism or less frequently after hematuria of genital origin secondary to a low testicular production of androgen and the presence of an excessive rate of estrogen⁽¹⁾. The PMDS diagnosis was not suspected in our patients before surgery of cell germ tumor. These structures were confused with tumor nodal masses on CT. MRI has the best performance in the diagnosis

of Mullerian Channel Persistence Syndrome⁽¹³⁾. In the absence of testicular tumors, several teams recommend carrying out an orchidopexy and leaving the Mullerian derivatives in place given the difficulties of dissection and the low probability of malignant transformation of these derivatives⁽¹⁴⁾. However, in recent years, an increasing number of cases of malignant tumors developed on Mullerian residues have been reported in the literature^(15–19). In a review of the literature, Farikullah et al⁽²⁰⁾, showed that laparoscopic surgery of Mullerian residues performed at the same time as orchidopexy reduced the risk of degeneration with satisfactory results.

Conclusion :

High degree of suspicion and awareness is needed to diagnose and treat PMDS before the occurrence of malignancy. Correct diagnosis depends on a systematic endocrine assessment and genetic analysis.

Funding and Conflict of Interest : No

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