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Partial Androgen Insufficiency Syndrome with Müllerian duct remnants complicated by a testicular seminoma

Journal:	<i>Journal of Clinical Urology</i>
Manuscript ID:	Draft
Manuscript Type:	Case Report
Keywords:	Partial androgen insensitivity syndrome, Mullerian duct, androgen receptor, cryptorchid testes, seminoma
Abstract:	<p>Androgen insensitivity syndrome (AIS), a rare inherited form of male pseudohermaphroditism is caused by mutations in the androgen receptor gene and affect reproductive and genital development. AIS has a wide spectrum of clinical presentations with mismatch between phenotype and genotype.</p> <p>We present a 23-year old male with underdeveloped genitals and cryptorchid testes who was investigated for subfertility. Investigations confirmed Partial Androgen insensitivity syndrome (PAIS) and a seminoma in the accidentally detached cryptorchid testis. This emphasizes the importance of considering malignancy in cryptorchid testes particularly in relation to PAIS.</p>

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Summary

Androgen insensitivity syndrome (AIS) has a wide spectrum of clinical presentations. This case involves a 23-year old male with underdeveloped genitals and cryptorchid testes initially referred for subfertility. Investigations confirmed Partial Androgen insensitivity syndrome (PAIS) with an incidentally discovered seminoma in one of cryptorchid testis. This highlights the importance of considering malignancy in all cryptorchid testes in relation to PAIS.

Keywords:

Partial androgen insensitivity syndrome, Mullerian duct, androgen receptor, cryptorchid testes, seminoma.

Introduction

Androgen insensitivity syndrome (AIS) is the most common form of male genital virilisation and can be either complete (CAIS) or partial (PAIS), depending upon the extent of residual functional androgen receptors (AR) or clinical presentation.

Mutations of AR have been reported in approximately 95% of persons with CAIS and in 10% with PAIS(1).

Genital ambiguity is variable in PAIS with a frequent phenotype comprising a micropenis with posterior hypospadias, cryptorchidism and a higher risk of associated malignancy than CAIS(2). Current evidence recommends cryptorchid testes retention through puberty to obtain hormone production benefits including bone and secondary sexual development(3).

Mullerian derivatives are usually absent in AIS but can be seen in occasional cases, raising the possibility of either defective production or response to Mullerian Inhibitory Factor (MIF)(4).

Case report

A 23-year old phenotypic male was referred with a complaint of underdeveloped genitals. Examination showed an empty scrotal sac and an underdeveloped penis. Magnetic resonance Imaging (MRI) confirmed the empty scrotum showing bilateral well-defined symmetrical masses posterior to the external iliac vessels consistent with testes (Figure 1). There was dilatation of what was thought to be the left seminal vesicle. Serum biochemistry showed markedly raised LH and FSH (18.4 and 22.8 IU/L respectively) and lowered Testosterone (11nmol/L).

A provisional clinical diagnosis of PAIS was made and the patient counselled about the associated cancer risk. As the patient declined consent for orchidectomy, a

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3 bilateral Fowler Stevens procedure was attempted. At the first stage, when the blood
4 supply to the right gonad was being disconnected, the surgeon noticed a possible
5 uterus and broad ligament which had not been identified on preoperative radiology.
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7 The left gonad was therefore biopsied and showed partially atrophic testicular
8 tubules, absent spermatogenesis and focal Sertoli cell hyperplasia. Though the
9 patient was advised to consider a bilateral orchidectomy, he wished to proceed with
10 orchidopexy and removal of the embryological remnants. A laparoscopic second
11 stage of the Fowler Stevens procedure with left orchidopexy was attempted. Given
12 the devascularisation and difficult detachment from the right fallopian tube, this testis
13 was removed.
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26 Histology showed extensive atrophy with absent spermatogenesis and a completely
27 excised pT1 classical seminoma (Figure 3). The endometrium and cervix were
28 atrophic and lined by mucinous glands with Müllerian duct remnants (Figure 3). The
29 seminal vesicle was normal with no ovarian or fallopian ducts. No AR mutations were
30 identified and PAIS with defective production and/or response to MIF was
31 diagnosed.
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40 Postoperative tumour markers were normal, with no metastatic disease seen on
41 abdominal and pelvic CT scans and chest radiographs. The patient developed
42 symptom of hypogonadism after the left orchidopexy experiencing hot sweats and
43 flushes.
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49 Following further consultation a right orchidectomy was performed and the histology
50 showed infarcted testes. The patient commenced testosterone replacement therapy
51 followed by insertions of bilateral testicular prosthesis inserted and is asymptomatic
52 to date.
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Discussion

AIS has three categories depending on the degree of genital development. PAIS is characterised by partial masculinisation of the external genitalia, partial inability of cellular response to androgens, impaired male genital masculinisation in developing foetus and underdevelopment of secondary sexual characteristics at puberty(5).

Presence of Müllerian duct remnants such as uterus, fallopian tube and vagina have been reported in PAIS but are less common in CAIS. It can result from failure of synthesis or release of MIF, defective release timing or failure of end-organ response. In genotypic males, MIF production by testicular Sertoli cells after the 8th week leads to ipsilateral regression of the Müllerian duct(4).

There is a significant association between testicular cancer and undescended testes, with seminoma being the commonest. Undescended testes in AIS are at a higher risk with an increase after puberty, from 3.6% at 25 years, to 33% at 50 years. The majority of these case reports include females with AIS and seminomas.

Our case emphasizes the importance of decision making and meticulous radiological review in addition to association of PAIS and malignant changes in patients with cryptorchidism. As even a 'normal' gonad may contain an occult tumour, use of a retrieval bag is recommended, to prevent dissemination of potentially malignant cells that may occur with unprotected morcellation.

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Figure legends

Figure 1. MRI images showing empty scrotum (A), bilateral cryptorchid testes (B), dilated seminal vesicle (C) and a micro-penis (D).

Figure 2. Intraoperative image from the orchidopexy procedure.

Figure 3. Haematoxylin & Eosin stained sections of the pT1 seminoma (A & B; x10 and x20 objective), C- uterus (x 20) and D- seminal vesicle (x20).



Figure 1. MRI images showing empty scrotum (A), bilateral cryptorchid testes (B), dilated seminal vesicle (C) and a micro-penis (D).
87x87mm (300 x 300 DPI)

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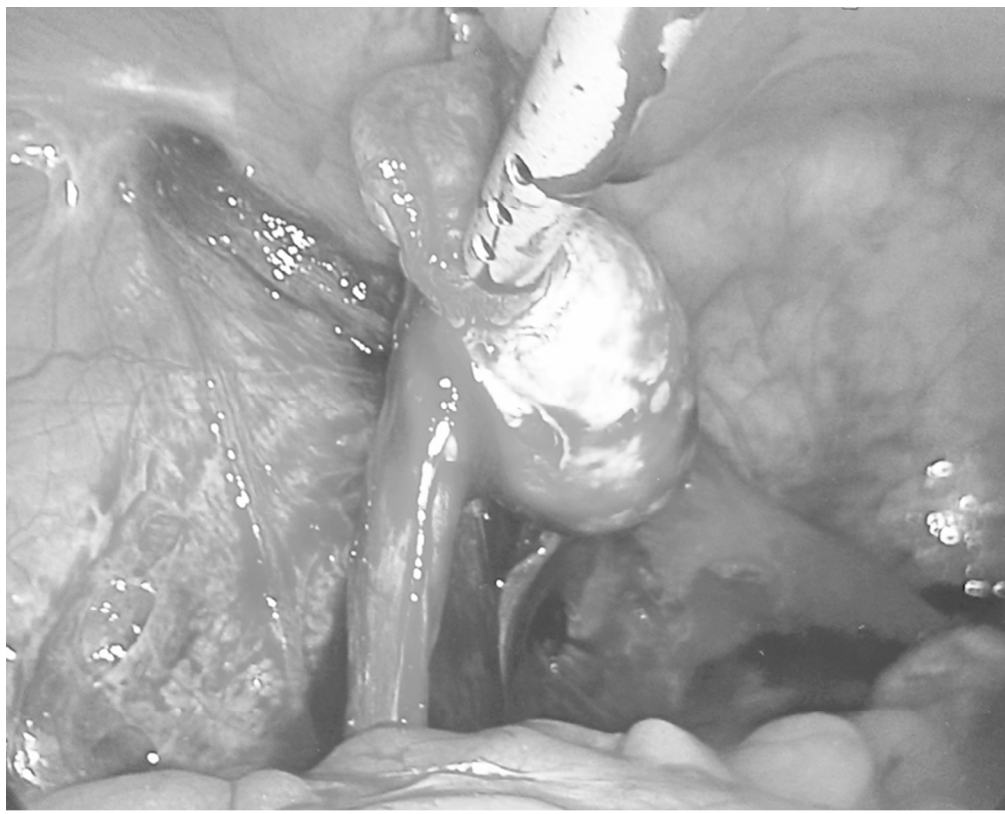


Figure 2. Intraoperative image from the orchidopexy procedure.
87x69mm (300 x 300 DPI)

Review

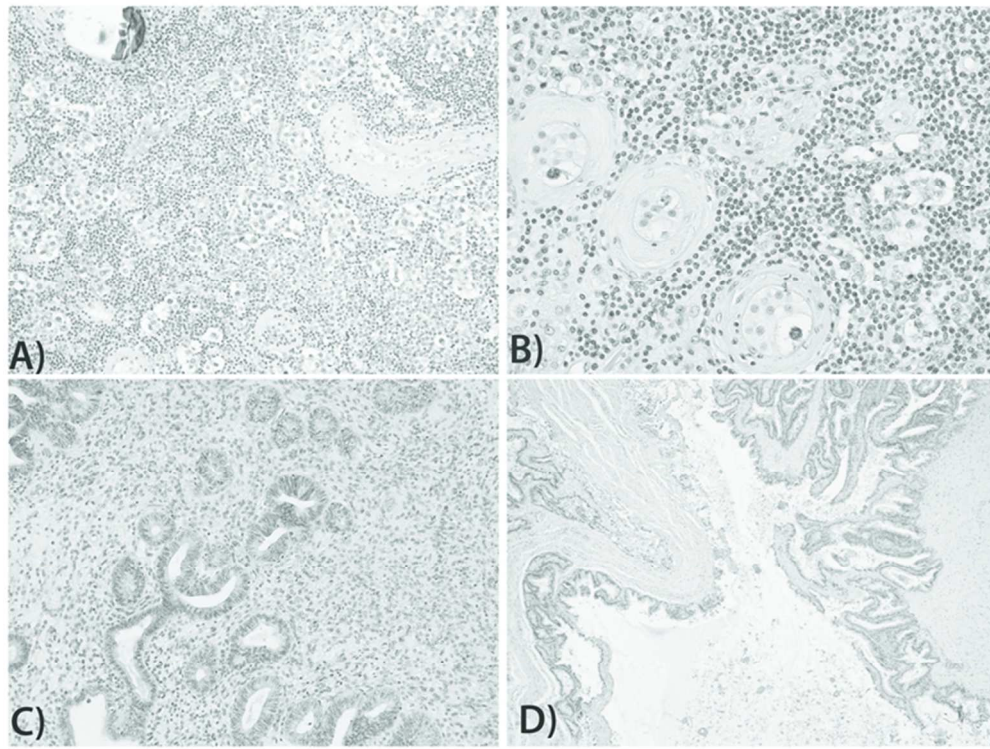


Figure 3. Haematoxylin & Eosin stained sections of the pT1 seminoma (A & B; x10 and x20 objective), C-uterus (x 20) and D- seminal vesicle (x20).
66x50mm (300 x 300 DPI)