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Complete androgen insensitivity syndrome with Sertoli cell tumour in a 27-year-old married woman: a case report

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Abstract

Background Androgen insensitivity syndrome is a rare X-linked disorder of sex development that results from mutations in the androgen receptors leading to failure of normal masculinization of the external genitalia in genetically male individuals. Our aim was to report this rare case of complete androgen insensitivity syndrome with Sertoli cell tumour, and our objective was to relate our experience on the challenges of the case and its successful management of the case.

Case presentation We report a case of a 27-year-old married Nigerian woman who presented at the surgical outpatient of our centre with a complaint of primary amenorrhea. She had an attendant history of coital difficulty following marriage. Clinical examination revealed a female phenotype with left groin swelling. A diagnosis of complete androgen insensitivity syndrome was made following hormonal evaluation, advanced imaging studies, karyotyping, and cytogenetic study. She and her parents including her husband were duly counselled on the natural history and principles of treatment of this clinical condition. She subsequently had a bilateral orchidectomy, and she was placed on oestrogen replacement therapy as well as serial vaginal dilation. The outcome was satisfactory.

Conclusion We reported a rare case of complete androgen insensitivity syndrome in a married woman. We documented our experience with successful conservative vaginal dilatation, which allowed satisfactory vaginal sexual intercourse.

Keywords Androgen insensitivity syndrome (AIS), Disorder of Sex Development (DSD), Complete androgen insensitivity syndrome (CAIS)

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1 Introduction

Androgen insensitivity syndrome (AIS) is a cause of a disorder of sex development (DSD) in which the genetic sex or gonadal sex or phenotypical sex is atypical [1]. Androgen insensitivity is characterized by end-organ resistance to androgen where normal male development of the individual with 46XY karyotype is prevented [2]. It is the most common cause of DSD [3]. AIS is a rare disease with an estimated prevalence of 1 in 100,000 individuals. The degree of androgen unresponsiveness of this condition ranges from mild androgen insensitivity syndrome (MAIS), partial androgen insensitivity syndrome (PAIS) to complete androgen insensitivity syndrome (CAIS) [4]. AIS is an X-linked recessive genetic disorder that is a result of a mutation in the androgen receptor gene (Xq11-q12) [5]. The diagnosis of CAIS is made following hormonal evaluation, imaging, and genetic studies [6, 7]. The principles involved in the management of cases of CAIS include gender assignment which more often than not, who are raised as females, delayed vs. early gonadectomy to prevent the risk of malignancy, oestrogen replacement therapy to maintain secondary sexual characteristics, bone and cardiovascular health [4]. The other part of the treatment principles are provision for satisfactory vaginal intercourse either by serial vaginal dilation or by vaginal reconstruction and reproduction, which is limited to either adoption or surrogacy via donor oocytes [8]. Few cases of CAIS have been reported in the literature [9]. In Nigeria, a case of CAIS was reported in Benin [10]. This is the first case of DSD in our hospital and perhaps second reported case in Nigeria. Our aim was to report this rare case of complete androgen insensitivity syndrome with Sertoli cell tumour, and our objective was to relate our experience on the challenges of the case and its successful management of the case.

2 Case presentation

We present a case of a 27-year-old married Nigerian woman with a complaint of primary amenorrhea and eight month's history of coital difficulty. Her pregnancy and neonatal history were unremarkable. She was initially not worried about her lack of menstruation as she was told it was familiar until shortly after her marriage when she noticed her husband could not fully penetrate with attendant dyspareunia and reflux of ejaculates. She had no history of urinary symptoms and no history of cyclical abdominal pain. There was no family history of similar problems. Clinical examination revealed well-developed breasts (tanner stage iii), absence of axillary hair, paucity of pubic hair, bilateral groin swellings, and female external genitalia that was characterized by blind ending vaginal of 5 cm in length and 4 cm in width. Her height and weight were 1.76 m and 60.5 kg, respectively. The pelvic sonogram was suggestive of the rudimentary uterus (Fig. 1). This, however, necessitated magnetic resonance imaging (MRI) that demonstrated the presence of the left and right inguinal gonads which measures 2.7×1.3×1.8 cm and 2.4×1.4×1.9, respectively, as demonstrated in Fig. 2b. The axial T2W MRI of the pelvis shows the absence of pelvic organs such as the uterus and ovaries as shown in Fig. 2a. Thus, sagittal T2W MRI also demonstrates similar findings as illustrated in Fig. 2c. The hormonal evaluation revealed luteinizing hormone (LH)—28.3Miu/ml, follicular-stimulating hormone (FSH)—4.4Miu/ml, prolactin—21.5 ng/ml, oestradiol—35 pg/ml, progesterone—0.1 ng/ml and testosterone—5.2(0.2–0.95 ng/ml). Karyotyping was done by extracting DNA from the patient's peripheral blood sample using the ZymoResaerch Quick-DNA Miniprep kit; PCR was done with a pair of the sex-determining regions on the Y chromosome (SRY) forward (tacaggccatgcacagagag) and reverse (tcttgagtgtgtggctttcg) primers and tag DNA revealed XY. Appropriate positive and negative controls were used. Electrophoresis of the PCR product was done in 2% agarose gels, and the bands were visualized under UV light. This established the diagnosis of complete androgen insensitivity syndrome (Fig. 3a and bs). Although Mayer–Rokitansky syndrome was initially entertained before karyotyping. Full blood count, electrolyte urea and creatinine, and intravenous urography were clinically unremarkable. A multidisciplinary team meeting involving the patient and relatives, urologist, psychiatrist, obstetrician, and gynaecologist was held, and the patient including her relative was duly counselled on the diagnosis and management of this clinical condition. She had left inguinal orchidectomy and right transperitoneal

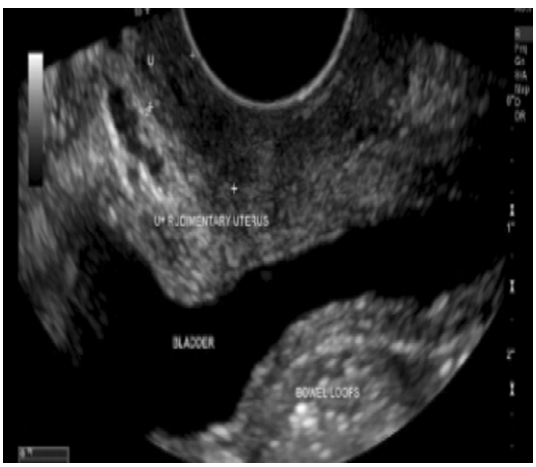


Fig. 1 Transvaginal sonogram demonstrating what looked like a rudimentary uterus

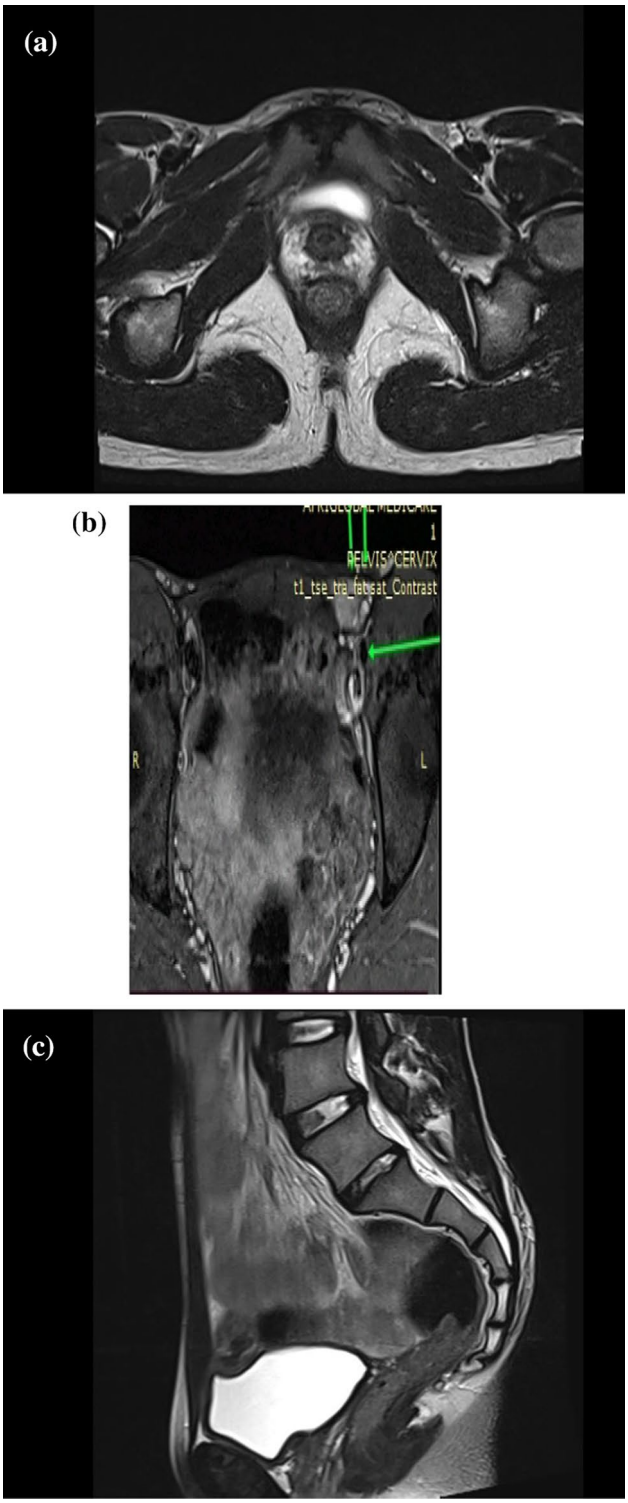


Fig. 2 **a** Axial T2W MRI of the pelvis showed an absent uterus and ovaries, **b** Coronal pelvic MRI demonstrating the presence of left and right inguinal gonads with an arrow, and the absence of Mullerian structures. **c** Sagittal T2W MRI showing absent uterus and ovaries

orchidectomy as shown in Fig. 4a, b and c, including the histomicrographs. The histology of the gonads revealed a Sertoli cell tumour, sclerosing variant (Fig. 4b and c), without any evidence of invasive disease. She was placed on oral oestrogen replacement therapy in the form of estroprogestinic therapy a pill/day (oral contraceptive pill) and serial self-vaginal dilatation using plastic vaginal dilators after she was thought. Her vaginal now measured 8 cm by 6 cm. She now enjoys satisfactory vagina intercourse and her secondary sexual feature is maintained. There was no clinical or radiological evidence of bone or cardiovascular disease. The patient and her husband are currently working on the adoption of a child.

3 Discussion

The management of an individual with CAIS is very challenging. The areas of concern are gender assignment, the timing of gonadectomy, the mode of oestrogen replacement therapy, satisfactory vaginal intercourse, and reproduction [11]. This case report illustrated that a multidisciplinary team approach was required for a satisfactory outcome. Our patient presented late with primary amenorrhea and coital difficulty although patients with CAIS are expected to seek medical help as soon as they reach the age of puberty without menstruation. Some of the patients with CAIS may also be seen early in the hospital when it is associated with visible groin swelling [12]. This was not the case in our patient as the groin swellings were only detected on examination at presentation. This may be the reason for the delay. It may also be due to the poor health-seeking behaviour that is rampant in our environment. The patient's height was 1.76 m. This is above the average height for African women, which has been anecdotally reported to be between 1.58 and 1.64 m [13]. The relatively higher height observed in this case may not be unconnected to the presence of Y chromosome in patients with CAIS [14]. Our patient had well-developed breasts, which are not unusual in patients with this condition. The breast development was a result of peripheral aromatization of androgen to oestradiol. There was, however, paucity of pubic and axillary hair. This is due to the androgen unresponsiveness that characterizes CAIS. Magnetic resonance imaging confirmed the absence of Mullerian structures (uterus, tube, ovary and upper part of the vagina). The computed tomography (CT scan) of the abdomen showed the presence of left inguinal gonads, while the right gonads were obscured. Both testes were, however, found intra-operatively. The left was seen in the groin, while the right was seen in the abdomen. This lays credence to the low sensitivity of CT scans in locating intra-abdominal testes as it was also noted by some researchers [15]. The presence of testes indicated the secretion of Mullerian inhibiting

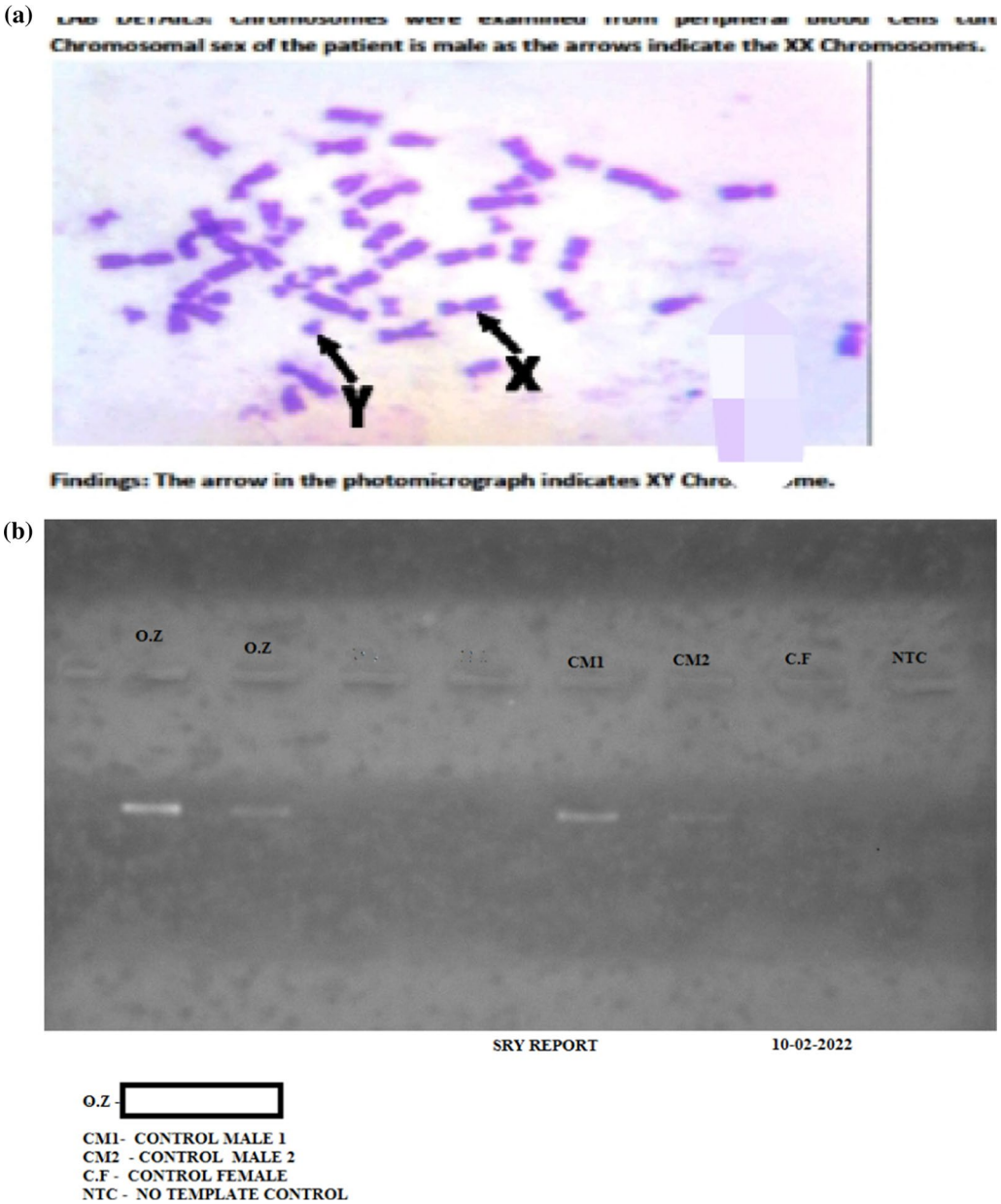
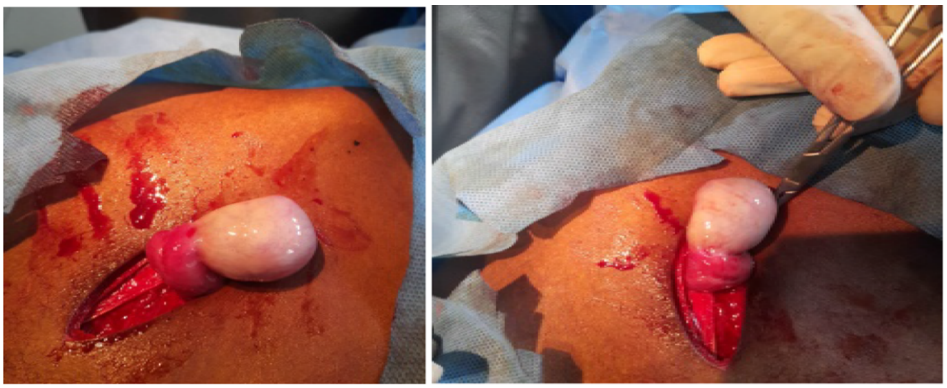
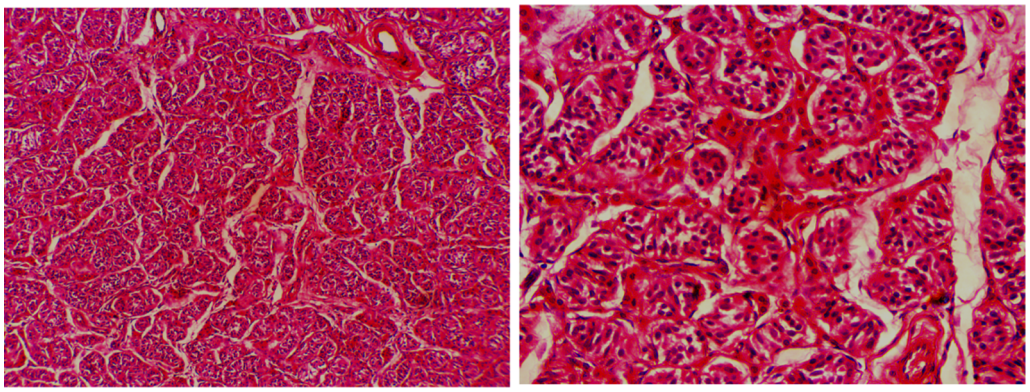


Fig. 3 **a** The arrow in the photomicrograph indicates XY chromosomes. **b** Polymerase chain reaction sex-determining region Y(SRY) protein gel product confirming the absence of X gene

hormone, which results in Mullerian structures agenesis. The lower part of the vaginal is present because this is embryologically derived from the urogenital sinus [16]. Cases of complete androgen insensitivity syndrome with persistent Mullerian structures are very rare. Some have been reported in the literature [9]. This is different from Mayer–Rokitansky–Kuster–Hauser syndrome in which there is a primary amenorrhea with the presence of Mullerian structures in a genetically XX individual [17]. This was initially entertained in our patient because of a suggestive feature of the uterus following a pelvic sonogram. This differential was dropped following the results of pelvic MRI and karyotyping. The hormonal evaluation result of our patient is in keeping with the normal limit for a normal male individual as our patient is genetically male [18]. The diagnosis of CAIS is confirmed by the identification of an androgen receptor gene mutation [4]. This was, however, not done in our patient due to non-availability. The time of gonadectomy was not a challenge for our patient as she had already attained secondary



(a)



(b) (c)

Fig. 4 **a**. The macrograph of right and left testes as seen intra-operatively. **b** x100Magnification. The above histologic section shows tumour tissue with histological features that are consistent with the Sertoli cell tumour. It is arranged in tubule and glandular patterns and surrounded by the basement membrane. **c**. × 400.Magnification. The above histologic section shows a Sertoli cell tumour (sclerosing variant). It is arranged in tubule and glandular patterns and surrounded by the basement membrane

sexual characteristics at presentation. The presence of the Sertoli cell tumour sclerosing variant on histology, which is a risk factor for testicular cancer apart from spermatocytic seminoma, is a shred of evidence that patients with CAIS are at risk of testicular malignancy [19]. Notably, this tumour is often seen in a patient with CAIS [19]. The risk is said to be higher in post-pubertal patients [20] as we observed in our case. This observation may support delayed orchidectomy to allow for the development of secondary sexual characteristics in patients with CAIS. Our patient did well following serial vaginal dilatation as her vaginal depth improved from 5.0 cm × 4.0 cm to 8.0 cm × 6.0 cm. This is closer to the average vaginal length in normal individuals [21]. Her secondary sexual features and bone and cardiovascular health are good following bilateral total orchidectomy and hormone replacement therapy (HRT). The protocol for oestrogen replacement therapy following orchidectomy has not been uniformly established. We considered estroprogestinic therapy (oral contraceptive pill) because it is readily available and sustainable in our environment. Although this oral pill has progestin in addition to oestrogen, it has not been shown to be of any additional benefit since the cases of CAIS do not have a uterus. She is still on oral oestrogen replacement therapy, which she will be taking until menopause. Some other similar series have reported the use of other formulations of oestrogen as hormone replacement therapy with a good outcomes.

4 Conclusion

We reported a rare case of complete androgen insensitivity syndrome in a married woman. We documented our experience with successful conservative vaginal dilatation, which allowed satisfactory vaginal sexual intercourse. Gonadectomy can be delayed to allow for natural puberty. Oral contraceptive pills are a good alternative for hormone replacement therapy in patients with CAIS. We also illustrated the role of the multidisciplinary team approach in managing this condition. There is a need for government to make comprehensive newborn genetic

screening available to all newborns to prevent the psychological problem attached to its discovery at an older age and its attendant marital complications.

Abbreviations

DSD	Disorder of Sex Development
AIS	Androgen insensitivity syndrome
CAIS	Complete androgen insensitivity syndrome
PAIS	Partial androgen insensitivity syndrome
MAIS	Mild androgen insensitivity syndrome

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Not applicable.

Author contributions
The list of authors' contributions, credits, and other information are as follows: MWR was involved in conception and design of the work; data acquisition; data analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; manuscript preparation; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; NAI performed manuscript reviewing and editing; literature review, editing and critical appraisal for intellectual content and final approval of the version to be published; AAA did literature review and critical reviewing, editing for intellectual content; JOO done interpretation of the cytogenetic report for the work, drafting the work and revising it critically for important intellectual content; LTO done review of CT scan, MRI and critical reviewing, editing for intellectual content; FOO did review of CT scan, MRI and critical reviewing, editing for intellectual content FAO (review of chemical pathology report and editing; ATO reported review of CT scan, MRI and critical reviewing, editing for intellectual content.

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Declarations

Ethics approval and consent to participate
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Consent for publication
Consent was obtained from the patient.

Competing interests
All authors have declared no competing interest.

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