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Case Report

Complete androgen insensitivity syndrome: A tale of two sisters with primary amenorrhea

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ABSTRACT

Complete androgen insensitivity syndrome (CAIS) is a rare disorder that is often diagnosed in the pubertal period during the evaluation of primary amenorrhea. Diagnosis is important not only in the context of early removal of undescended testis but also in terms of the grave psychological outcome of the diagnosis on the adolescent and family members. Here, we present case reports of two sisters who presented with primary amenorrhea. It is imperative to keep CAIS as a differential during the evaluation of primary amenorrhea. CAIS may also present as a case of a childhood inguinal hernia.

Keywords: Complete androgen insensitivity syndrome, Primary amenorrhea, Childhood inguinal hernia

INTRODUCTION

Androgen insensitivity syndrome (AIS) is a rare form of 46,XY disorder of sex development which can present with a spectrum of clinical features varying from complete external female phenotype to genital ambiguity in a male to isolated gynecomastia. Complete androgen insensitivity syndrome (CAIS) is important not only for the endocrinologist but also to the gynecologist and/or urologist, as these patients primarily take gynecological consultation in the context of primary amenorrhea or sometimes urology consultation for inguinal masses.

The androgen receptor (AR) gene is on the long arm of the X chromosome (Xq11–12). Androgen-mediated transcription is coded by the C-terminus of the ligand-binding domain.[1] Mutations of the *AR* gene alter the AR, with subsequent inefficient binding of androgens and failure of action. Patients with CAIS usually present as primary amenorrhea in peripubertal age. Rarely, they may present as inguinal masses in childhood. Presentation of CAIS as inguinal hernias in girls has been estimated to be between 0.8% and 2.4%.[2] The risk for gonadal malignancy increases with age and is reported to reach up to 33% at 50 years.[3]

In view of the rarity of presentation and benefits of early diagnosis and treatment, here, we present case reports of two sisters with CAIS reared as female, presenting with primary amenorrhea.

CASE REPORT

A 17-year-old adolescent, raised as female, presented with primary amenorrhea and poor development of secondary sex characteristics [Case 1 and Figure 1a]. She had a history of surgery for the right inguinal hernia at the age of 3 years. She was started on combined estrogen

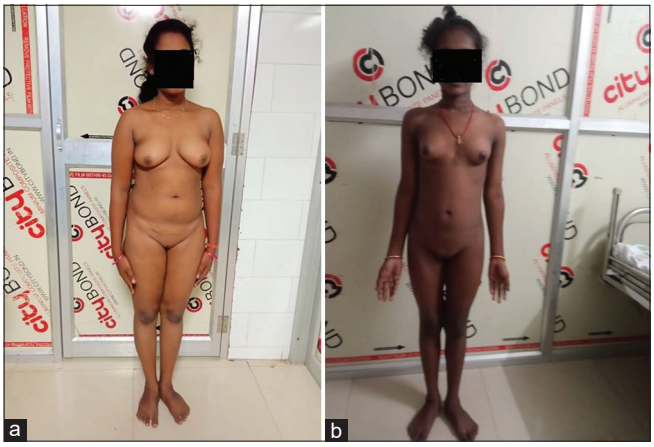

Figure 1: (a) Case 1 (Elder sibling) and (b) Case 2 (Younger sibling).

and progesterone pill for approximately 6 months before presenting to us. There was a history of similar presentation in a 15-year-old younger sibling [Case 2 and Figure 1b].

On examination, Case 1 had sexual maturity rating of Tanner stage I for axillary and pubic hair and Tanner stage V for breast, respectively. The patient had a horizontal surgical scar of ~6 cm in the right inguinal region and a palpable gonad in the left inguinal region. Karyotype analysis revealed karyotype of 46,XY. The hormonal profile revealed luteinizing hormone (LH) 65 mIU/mL, follicle-stimulating hormone (FSH) 39 mIU/mL, and serum testosterone 23.92 nmol/L (690 ng/dL), respectively. Ultrasonography (USG) of the abdomen and pelvis revealed an oval hypoechoic structure in the left Iliac fossa (?testis) and a hypoechoic structure posterior to the urinary bladder (?prostate) with no evidence of any Müllerian structures, respectively.

Case 2 had sexual maturity rating of Tanner stage I for axillary and pubic hair and Tanner stage III for breast, respectively, with bilateral palpable gonads in the inguinal region. Karyotype analysis revealed karyotype of 46,XY. The hormonal profile of case 2 revealed LH 15 mIU/mL, FSH 23 mIU/mL, and serum testosterone 42.1 nmol/L (1217 ng/dL), respectively. USG of the abdomen and pelvis showed bilateral gonads in respective inguinal canals and rudimentary prostate posterior to the urinary bladder with no evidence of any Müllerian structures, respectively.

Both cases were planned for gonadectomy. Case 1 underwent left gonadectomy. Histopathological examination of the gonad revealed testicular tissue [Figure 2]. Case 1 is currently on estrogen therapy (Tablet Estradiol valerate 0.5 mg once a day). Metabolic parameters are screened at every visit. Case 2 is planned for gonadectomy and is on regular follow-up.

DISCUSSION

CAIS has been reported widely in the literature. Few case reports have mentioned CAIS presentation in siblings. A case

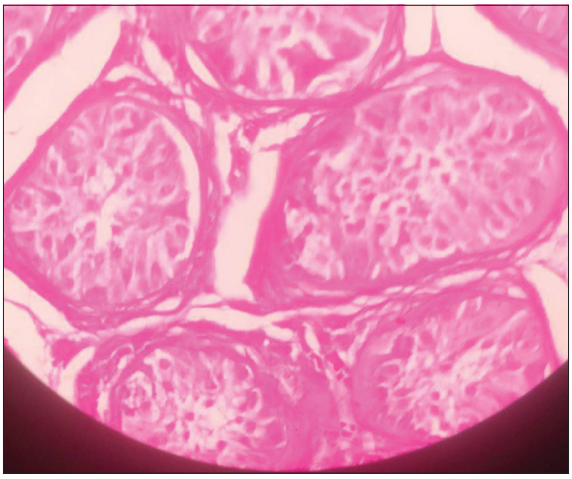

Figure 2: Histopathological image of surgical specimen (high-power field): Testicular tissue with no evidence of spermatogenesis.

report by Nichols *et al*., has reported CAIS in two sisters with the similar clinical presentation but differing Müllerian remnant tissue.[4] Khollová *et al*. reported CAIS in two sisters with a family history of an amenorrheic maternal aunt.[5]

In our case, the elder sibling had undergone surgery for an inguinal mass in childhood. Close suspicion by the operating surgeon could have yielded an earlier diagnosis in this case. The younger sibling of our index case had not presented to us initially. On taking a detailed family history of our index case, we suspected the younger sibling to have CAIS. This highlights the relevance of family history in such cases.

Early diagnosis is critical to plan a gonadectomy and eliminate the future risk of a gonadal tumor. The incidence of gonadal tumors (dysgerminoma and gonadoblastoma) has been reported to be 0.8% in CAIS and 5.5% in AIS overall, with a progressive increase in risk after puberty.[2]

Genetic analysis could not be done in this case due to the unaffordability of the caregivers of the patients. However, the diagnosis of CAIS can be made, reliably based on 46,XY karyotype with female external phenotype, with imaging revealing testis with absence or presence of degenerated Müllerian remnants and biochemical report of normal or elevated testosterone levels and normal or increased LH concentration.[6] The psychosocial impact of a diagnosis of CAIS cannot be ignored. In our case, revealing the outcome of the diagnosis to parents and explaining the future prospects of fertility and marital life of their children whom they raised as females is a challenge in itself considering the conservative background of our patients. It is particularly challenging for a patient who has been reared as a female to accept that she is genetically a male and infertile.

CONCLUSION

Early diagnosis of CAIS is imperative for timely management to ameliorate the risk of gonadal malignancies. The grave impact of the diagnosis on the psyche of the patient and the family members should be considered and dealt with sensitivity.

Learning points

1. Inguinal masses in a child reared as female should be seen with a watchful eye
2. All cases of primary amenorrhea should be evaluated before initiating hormonal pills. (A note for physicians)
3. Family history is an important wheel while suspecting CAIS
4. Early treatment with gonadectomy and subsequent estrogen therapy is the way to go
5. Psychosocial impact of CAIS is profound and should not be ignored. Formal assessment should be made a component of routine work-up in such cases.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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