CASE REPORT

Complete androgen insensitivity syndrome with concomitant seminoma and Sertoli cell adenoma: an unusual combination

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SUMMARY

Androgen insensitivity syndrome is a rare disorder of sex development and its clinical manifestations vary from subtle male infertility to an overt complete androgen insensitivity syndrome (CAIS) with a female phenotype. CAIS is often diagnosed at puberty or in adolescence during investigation for primary amenorrhoea. Undiagnosed patients have an increased risk of development of malignancy in the harboured testes. Inguinal hernia is the commonest mode of presentation of CAIS in childhood and various screening methods are available during the initial herniorrhaphy procedure. Controversy exists in the need to screen and the methods of screening in all cases of premenstrual girls with inguinal hernia. Abnormal observation in a suspicious case requires karyotyping for confirmation. We describe a case of CAIS with simultaneous presence of seminoma and a Sertoli cell adenoma in a 17-year-old patient who had a history of surgery for inguinal hernia at age of 5 years.

BACKGROUND

Androgen insensitivity syndrome (AIS) occurs due to mutations in the androgen receptor (AR) gene.¹ Complete androgen insensitivity syndrome (CAIS) is seen in ~1 in 20 400 to 1 in 99 100 genetic men.² Though primary amenorrhoea is the most common clinical presentation, some of the patients in infancy or childhood have a history of inguinal hernia, which is about 1–12% in all phenotypic women with AIS.³ In our case there was a history of inguinal hernia in childhood. However, due to inadequate investigations in early age, the condition remained undiagnosed until adolescence when she developed malignancy. Early diagnosis and surgical removal of ectopic gonads may prevent such complication. Seminoma and Sertoli cell adenoma are known to occur in undescended testis, but simultaneous occurrence of both the neoplasms is unusual.

CASE PRESENTATION

A 17-year-old girl presented with a history of primary amenorrhoea and a history of surgery for right inguinal hernia at age of 5 years in a private hospital; however, no records were available. Physical examination revealed normal stature for the age, appropriate breast development (Tanner stage IV), normal external genitalia, but scant pubic and axillary hair and short blind-ended vagina.

INVESTIGATIONS

Ultrasonography revealed an absent uterus, hypoplastic vagina and well-defined mass lesions measuring 5 and 3 cm in the right and left side of pelvis, respectively. The lesions were hyperintense on T2/short τ inversion recovery MRI (figure 1). Serum lactate dehydrogenase was 235 U/L (normal 140–280 U/L), luteinizing hormone (LH) 38.4 mIU/mL (normal pubertal value in women 0.3–31.0 mIU/mL), follicle-stimulating hormone (FSH) 18.7 mIU/mL (normal 0.3–10.0 mIU/mL), α -fetoprotein 1.7 ng/mL (normal <10 ng/mL), and β -human chorionic gonadotropin (β -hCG) 28.7 mIU/mL (normal in non-pregnancy <5 mIU/mL). FSH, LH and β -hCG were mildly elevated. Karyotype analysis revealed 46XY complement.

Figure 1 Axial (A) and coronal (B) fat saturated T2-weighted MRI showing large well-defined hyperintense mass (black arrows) on the right side and a small hyperintense mass (grey arrows) on the left side of the pelvis.

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DIFFERENTIAL DIAGNOSIS

Constitutional delay, pregnancy, polycystic ovarian syndrome, AIS and premature ovarian failure are common causes for primary amenorrhoea. Absence of uterus, multiple cysts in gonads, excess body hair and streak gonads, and presence of mildly elevated gonadotropin levels ruled out other possibilities except AIS. The clinical presentation, imaging features and karyotyping confirmed the diagnosis of complete AIS. Mild elevation of FSH and LH can be attributed to androgen resistance; while, increased β -hCG can be seen in a germ cell tumour.

TREATMENT

The patient and parents were counselled by multidisciplinary team including a psychiatrist and a gynaecologist about the condition and its prevalence among population, sexual identity, inability of childbearing capacity and the need for surgical removal of the gonads. They were also explained about regular postoperative follow-up and hormone supplementation. Informed consent was obtained for all the procedures and bilateral pelvic masses were excised.

OUTCOME AND FOLLOW-UP

The right pelvic mass was encapsulated, lobulated, solid and homogeneous with yellowish-white in appearance; while the other tumour was well circumscribed, solid and fleshy. Microscopic examination of the larger tumour revealed monomorphic, large, round cells with centrally located large vesicular nuclei, prominent nucleoli and abundant clear to eosinophilic cytoplasm. Mild lymphocytic and plasma cell infiltrate was present in the stroma (figure 2A, B). No brisk mitotic activity or nuclear pleomorphism was seen. Intratubular germ cell neoplasia and normal seminiferous tubules were seen in adjacent area. No microcystic areas, hyaline globules, immature elements or any components of other germ cell tumours were seen. The tumour cells were immunoreactive with (placental alkaline phosphatase (1:100) and CD117 (1:50)) (Spring Bioscience,

USA) (figure 2C, D); while negative for leucocyte common antigen (1:200) (Biocare Medical, USA), CD30 (Bio SB), epithelial membrane antigen (1:200) (Spring Bioscience, USA), α -fetoprotein (1:50) (Novacastra, UK) and β -hCG (1:2000) (Dako, UK). Histomorphological and immunohistochemical features were that of a classical seminoma. Sections from the left pelvic mass showed uniform tubules lined by low columnar to polygonal cells with uniform round to oval hyperchromatic nuclei, fine granular chromatin, inconspicuous nucleoli and moderate amount of clear cytoplasm. No germ cell or Leydig cells were seen (figure 2E, F). Histological features were that of Sertoli cell adenoma.

The patient is receiving low-dose oestrogen therapy with regular follow-up by ultrasonography and hormone assay every 3 months. No recurrence has been observed for the past 9 months.

DISCUSSION

AIS results from complete or partial resistance to androgens in a genotypic man due to X linked mutations in the AR gene and depending on the degree of responsiveness to androgens are classified into mild AIS (MAIS), partial AIS (PAIS) and complete AIS (CAIS). In MAIS the mutations primarily occur in exon 1 of androgen receptor gene and the clinical manifestations include typical male genitalia often with presence of gynecomastia, high-pitched voice, sparse pubic hair and impotence with or without impaired spermatogenesis.⁴⁻⁶ The phenotypic manifestation of PAIS can be either predominantly female or male, or with ambiguous genitalia.⁴ CAIS was originally described as 'testicular feminisation syndrome' by John Morris in 1953.⁷ The clinical characteristics include a female phenotype with scant or absent axillary and pubic hair, short blind ended vagina with absent uterus, cervix and proximal vagina as seen in our case due to the effects of antimüllerian hormone secreted from the Sertoli cells of the ectopic testis. The prostate and Wolffian duct derived structures such as epididymides, vas deferens and

Figure 2 H&E stained sections showing a tumour with uniform, round cells, large vesicular nuclei, prominent nucleoli and clear to eosinophilic cytoplasm. Mild lymphocytic and plasma cell infiltrate is present in the stroma (A, H&E; $\times 100$, B, H&E; $\times 400$). The tumour cells are immunopositive with placental alkaline phosphatase (C, $\times 200$) and CD117 (D, $\times 200$). Sections from smaller mass show a nodular tumour with uniform tubules lined by low columnar to polygonal cells with uniform round to oval hyperchromatic nuclei, inconspicuous nucleoli and finely vacuolated cytoplasm. No germ cell or Leydig cells are seen (E, H&E; $\times 40$, F, H&E; $\times 200$).

seminal vesicles are also absent. Generally the gonad is found in the intra-abdominal location; but it can be present anywhere along the path of embryonic descent.⁸ The clinical presentations may be bilateral (39%) or unilateral (28%) inguinal hernia, a positive family history (21%), a mismatch between amniocentesis-karyotype and phenotypic sex (6%), and primary amenorrhoea (6%).³ Although the incidence of CAIS in premenstrual girls with inguinal hernias is 0.8–2.4%, it is the commonest mode of presentation in childhood. Controversy exists in the need to screen for CAIS in all cases of premenstrual girls with inguinal hernia because of its low incidence and the practical difficulties in obtaining consent to exclude a life-changing diagnosis during a minor procedure.^{2 9 10} However, the failure to exclude CAIS will lead to a late presentation such as primary amenorrhoea, the sexual complications of a short vagina and the psychological complications of these phenomena. An early diagnosis can help in the mental preparation of the families to decide on the issues of gonadectomy and hormone therapy. Early diagnosis in CAIS is also important because an appropriate timely intervention can prevent the development of gonadal malignancy. Thus an advantage of early recognition may serve as a strong factor to look for this condition during operation of inguinal hernia in prepubertal girls. Various methods to exclude CAIS are ovary/fallopian tube examination via the hernial sac at surgery, rectal examination of cervix at the time of analgesia suppository insertion during general anaesthesia, vaginal length assessment using Hegar's dilator, though none of which is unambiguous. The initial methods rely on the fact that müllerian structures will be absent in CAIS, although rarely uterine anlagen and rudimentary cervix may be present in some cases. Vaginal length assessment can vary depending on the pressure of the probe by the surgeon. Current screening methods such as sonography or karyotype determination are time-consuming and costly.^{11 12} According to Hurme *et al*, during hernia operation, if the round ligament is not found to be normal, a search for an ovary or a fallopian tube is to be made. If no ovary or fallopian tube is found, consent for karyotyping from a buccal mucosa swab should be sought in cases where the vaginal length is <4 cm in girls older than 4 years and <3 cm in younger girls.¹³ There is no definite consensus on which method to employ in this regard. However, the clinician, based on individual circumstances and available expertise, should decide the approach to exclude CAIS in girls with inguinal hernia.

A shortened vagina, an absent uterus and fallopian tubes warrants a karyotype assessment. Screening for CAIS during herniorrhaphy in our case would have helped in early diagnosis, proper monitoring and timely intervention and thereby preventing the complication. Different complications ranging from hamartoma to malignant germ-cell tumours can occur in the ectopic gonads and clinically manifest in a wide age group ranging from 9 to 53 years but often in postpubertal patients. Siminas *et al*¹⁴ presented a case of CAIS associated with bilateral Sertoli cell adenomas and paratesticular leiomyomas. Seminomas are well documented in CAIS including a case with an inguinal hernia in a 31-year-old woman.¹⁵ In our case both seminoma and Sertoli cell adenoma were detected simultaneously but in different gonads.

Germ-cell tumours are classified into five categories on the basis of site of presentation, age, histology and chromosomal constitution. Germ-cell tumours occurring in patients with DSD falls in 'type II germ-cell tumours of the testis and the dysgenetic gonad'.¹⁶ Morris *et al*¹⁷ reported a 22% incidence of malignant gonadal tumours in patients over 30 years of age. The risk of malignancy is considerably lower in CAIS (0.8%)

than in PAIS (5.5–15%) or other intersex disorders and more at a later age.¹⁸ This difference may be explained by the fact that there is a rapid and total loss of germ cells in CAIS since the age of 1 year; whereas, patients with PAIS maintain germ cell population at about two-thirds of the normal number at puberty.¹⁸

Radiography of seminomas in CAIS is similar to that of testicular seminoma and usually displays varying-sized, lobulated, well-margined, homogeneous masses with presence of internal bands. The tumour is hyperintense on T2-weighted (T2-W) MRI. Larger tumours may have a heterogeneous appearance.¹⁹ Sertoli cell adenomas are also well-defined, but smaller than seminoma and have a low-signal-intensity.²⁰ In our case both the tumours were well-defined and homogeneous with hyperintensity on T2-W MRI.

The management of androgen insensitivity syndrome should address functional, sexual and psychological issues such as disclosure, gonadectomy and subsequent hormone replacement, creation of a functional vagina, and provision of genetic advice and thus a multidisciplinary approach is needed. Currently no standard or reliable screening tools can detect early malignant changes in patients with AIS and there is a controversy in the timing of gonadectomy in AIS. Ultrasonography is usually performed to monitor the lesion until early adulthood especially in cases with CAIS.²¹ Though no specific age for gonadectomy is mentioned in the consensus guidelines, gonadectomy in infancy with later puberty induction or gonadectomy in early adulthood is recommended in patients with CAIS to avoid the complications like malignancies.²¹ Once puberty is achieved, prophylactic gonadectomy is recommended and continuous oestrogen replacement is given to maintain bone health.² The treatment of intragonadal seminoma includes standard adjuvant chemotherapy with postoperative irradiation of the para-aortic lymph nodes with or without irradiation of the ipsilateral pelvic lymph nodes. A neoadjuvant chemotherapy regime with bleomycin, etoposide and cisplatin has been tried.²² Benign lesions like Sertoli cell adenomas are cured by simple excision. Our patient is on hormone supplementation with regular follow-up without any chemotherapy.

Learning points

- ▶ Androgen insensitivity syndrome (AIS) is rare disorder of sex development and high index of clinical suspicion is required for the diagnosis especially in early age.
- ▶ Controversy exists in the need and the methods to screen for complete androgen insensitivity syndrome (CAIS) in all cases of premenstrual girls with inguinal hernia and the clinician, based on individual circumstances, should decide in excluding CAIS.
- ▶ Regular ultrasonographic monitoring of ectopic gonads and timely surgical intervention may prevent the development of malignancy in patients with AIS.
- ▶ Seminoma and Sertoli cell adenoma are reported separately in AIS, but concomitant occurrence of both is unusual.

Contributors BT and ARM were involved in conception, designing and critical review of the manuscript and were responsible for overall supervision. NM provided clinical details and treated the patient. SHC provided radiological details.

Competing interests None declared.

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