Mixed Germ Cell Tumor in Androgen Insensitivity Syndrome: A Case Report*

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ABSTRACT

Androgen insensitivity syndrome (AIS) is a disorder of sexual development characterized by a female phenotype with a 46 XY karyotype. Most patients present with primary amenorrhea; however, 1.1 % of patients present with an inguinal mass. Most commonly, seminoma arising from the gonads are found.

This report presents the case of a 15 year-old female looking adolescent who initially presented with an abdominopelvic mass. A diagnosis of AIS was made based on the physical examination findings, endocrine profiling, imaging studies and karyotyping. She underwent cystoscopy, exploratory laparotomy, adhesiolysis, tumor debulking, frozen section, bowel run, repair of serosal tear, Jackson-Pratt drain insertion, bilateral percutaneous nephrostomy under combined spinal and epidural anesthesia. Histopathologic examination of the excised mass revealed a mixed germ cell tumor. This paper will discuss the diagnostic approach as well as the management and prognosis of patients with AIS associated with mixed germ cell tumor.

Keywords: Androgen insensitivity syndrome, Gonadoblastoma, Mixed germ cell tumor, Testicular feminization

INTRODUCTION

Genetic sex is determined after fertilization. It is the Y chromosome that directs the development of a bipotential gonad to become a testis. The testis then secretes testosterone and anti-mullerian hormone that stimulates further development of the rest of the genital organs. In the absence of these, the human reproductive tract will develop as female. There are, however, reported cases of individuals with XX karyotype appearing as male (female pseudohermaphrodite), and individuals with XY karyotype appearing as female (male pseudohermaphrodite). Previously referred to as intersex, these individuals presenting with a phenotype at variance with their genotype are now regarded as patients having disorder of sexual development (DSD).

DSD occurs in 1 out of 4,500-5,000 live births and are caused by genetic defects occurring during the fetal life.[1] For such cases, clinicians must rely on a thorough physical examination coupled with the appropriate laboratory examinations and imaging tests to arrive at the correct diagnosis. Complications such as development of malignancy from the gonads, the psychological impact associated with sexual dysfunction as well as the endocrinologic implications that goes with removal of the gonads should be addressed.

This report presents the case of a phenotypically female adolescent diagnosed with AIS associated with mixed germ cell tumor. The diagnostic as well as the therapeutic approach will be discussed.

CASE

A 15 year-old, phenotypically female adolescent was admitted at our institution for an enlarging abdominal mass. Personal, social, past medical and family medical histories are non-contributory. She was born at home to a then 32 year-old, gravida 4 para 3 (3003) via spontaneous vaginal delivery with no complications. Her developmental milestones were at par with age and she is currently a third year high school student. The larche and growth spurt was at 13 years-old, but she still has no axillary and pubic hair. She is still amenorrheic.

A year prior to admission, patient noted a fist-sized, movable, non-tender left lower quadrant mass associated with constipation and decrease in stool caliber. Ultrasound at a local hospital revealed a pelvic mass for which she was advised to consult at a tertiary hospital. However, the patient was lost to follow up.

Three months prior to admission, she experienced left flank pain associated with one episode of undocumented fever. There was no associated dysuria, intermittency and hematuria. Consult was done at a local hospital for which she was given unrecalled medications for urinary tract infection. Persistence of symptoms prompted consult at our institution.

The patient was first seen at our institution's OB General Clinic a month prior to admission, still with left flank pain and left lower quadrant mass with associated

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decrease in stool caliber and constipation. She reported 25% weight loss with no anorexia, headache, insomnia, dysuria, hematuria, oliguria, melena, hematochezia.

On physical examination, the patient appeared phenotypically female. She was ambulatory and had stable vital signs. Her height is 145 cm (z < -3) and she weighs 43 kg (BMI: 20.5 kg/m^2 (z=0) and BSA: 1.32 m^2). She had anicteric sclerae, pink conjunctiva and no lymphadenopathies. There was no note of webbed neck, axillary hair and pubic hair (Figure 1). She had unremarkable chest findings. On abdominal examination, abdominal girth was 78 cm. There was a 14x14 cm solid, firm, non-movable, non-tender mass at the hypogastric area. Upon examination of the external genitalia, she was noted to have Tanner stage 1 pubic hair growth. The labia majora and minora were both well developed. Digital rectal examination revealed good sphincter tone, intact rectal vault. The inferior pole of the mass was palpable at the cul de sac. Impression was abdominopelvic mass, to consider ovarian new growth, probably malignant; primary amenorrhea etiology to be determined.

A transrectal and transabdominal ultrasound revealed absence of the cervix and uterus. A 16.2 x 9.4 x 7.8 cm lobulated heterogeneous solid abdominopelvic mass, more to the left and a 2.9 x 2.0 x 1.5 cm solid mass at the right adnexal area were seen (Figure 2). The liver parenchyma was homogeneous with no note of pelvic or paraaortic lymphadenopathies. The bilateral renal calyces were dilated. The sonologic impression was bilateral adnexal masses consider ovarian new growth probably malignant by Sassone=14, Lerner=15, IOTA: unilocular-solid, color score of 3 versus gastrointestinal pathology. Tumor markers, hormonal levels and karyotyping were requested. Surgical removal of the mass was advised and she was referred to the pediatric service for preoperative clearance.

On admission, results of her laboratory examinations were released and karyotyping revealed 46XY (Table 1, Figure 3). Abdominal CT Scan showed a heterogeneously enlarging abdominopelvic mass (15.9 x 11.0 x 6.7 cm), peritoneal and omental carcinomatosis, intraabdominal

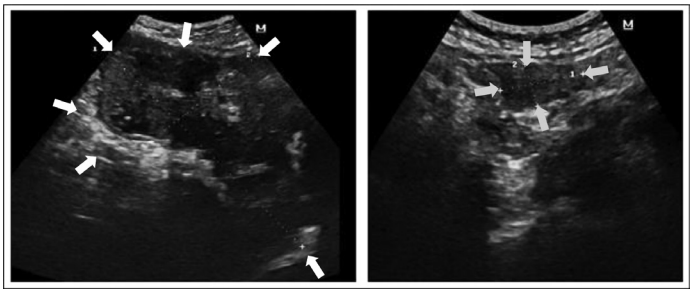

Figure 2. Transrectal ultrasound showing the (a) 16.2 x 9.4 x 7.8 cm lobulated heterogeneous solid abdominopelvic mass (yellow arrow), more to the left and (b) the 2.9 x 2.0 x 1.5 cm solid mass at the right adnexal area (blue arrow).

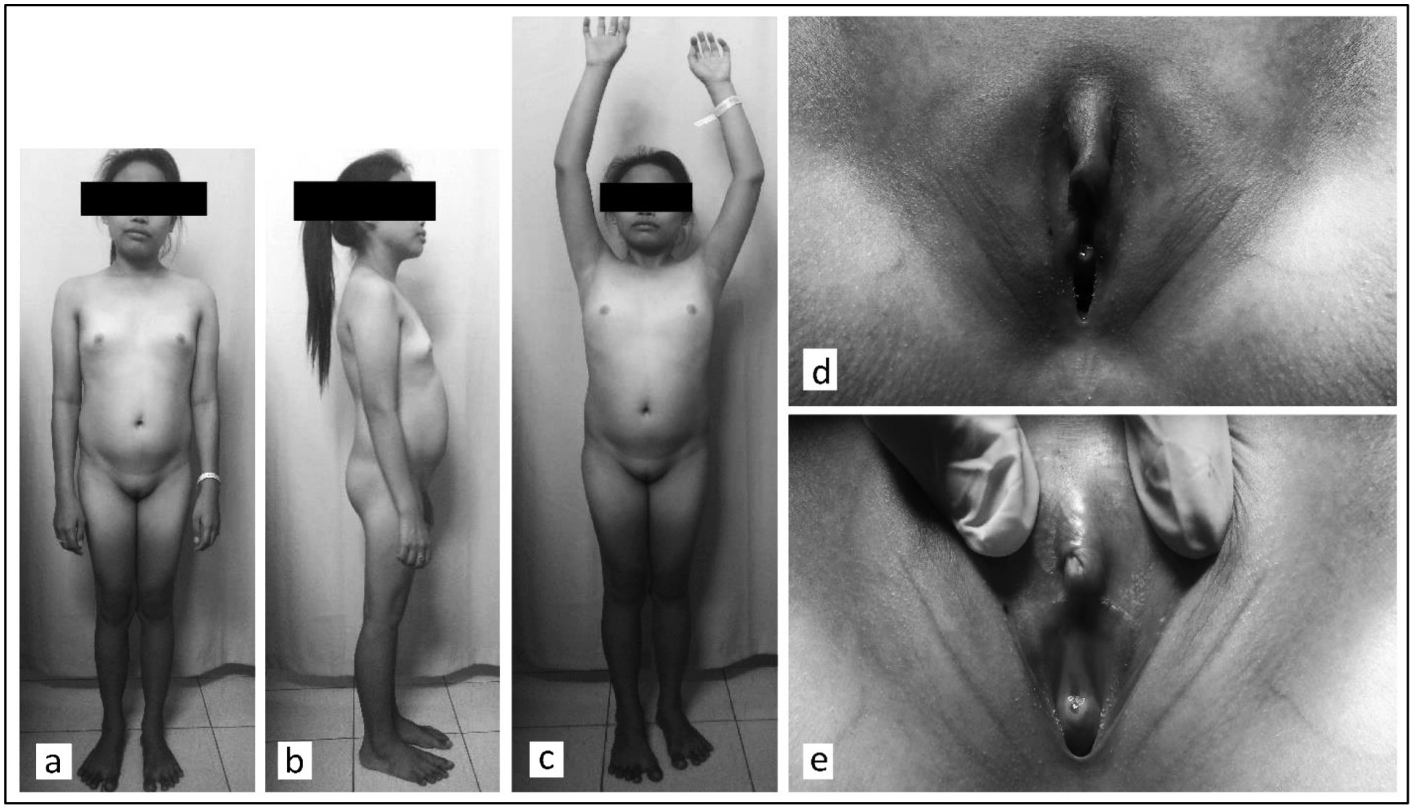

Figure 1. Patient MDC presenting as phenotypically female with absence of webbed neck, axillary hair and pubic hair (a, b, c). The external genitalia was grossly normal. The hymen was intact, urethral and vaginal opening were both patent and no note of clitoromegaly (d, e).

Table 1. Tumor Markers and Baseline Hormonal Status

Tumor Markers				
	Post perative Day 4		**Post perative Day 4**	**Post perative Day 6**
Beta Hcg (NV:<5 mIU/ml)	21.60	High		
Ca125 (NV:35 U/ml)	31.40	Normal		
LDH (NV: 122-261 IU/L)	1,411.00	High	817.00 High	
Ca 19-9 (NV:37 U/ml)	15.81	Normal		
AFP (NV: <5.8 IU/ml)	>1,000.00	High		9,592.00 High
CEA	Not done			
Baseline Hormonal Status				
	Baseline			
Leutenizing Hormone (NV: 0.7-9 mIU/L)	127.4	High		
Follicle Stimulating Hormone (NV: 0.6-9.5 mIU/L)	170.0	High		
Estradiol (NV:127-467 pg/ml)	102.9	Low		
Testosterone (.9-4.5 nmol/L)	2.7	Normal		
Inhibin	Not done			
Anti-Mullerian Hormone	Not done			

NV – Normal values

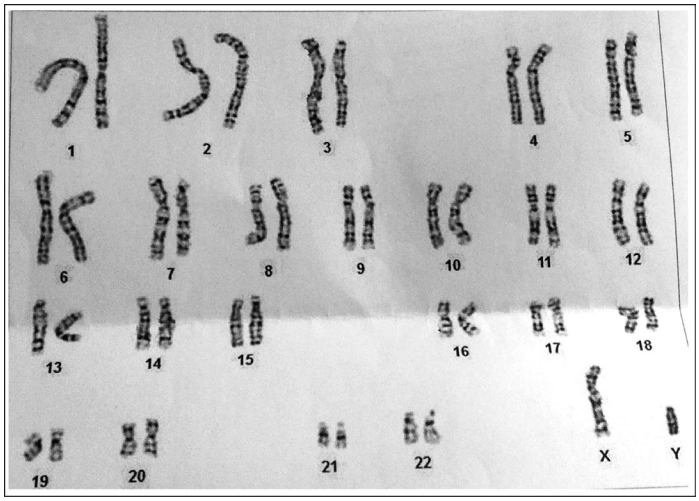

Figure 3. Karyotype of patient MDC

and retroperitoneal nodal metastasis and obstructive uropathy. She was then scheduled for surgery. Internal examination done after induction of anesthesia revealed patent urethral and vaginal openings with no clitoromegaly (Figure 1). The hymen was intact. The vaginal canal was blind-ended and shortened to 4 cm. The posterior pole of the abdominopelvic mass was palpable at the proximal vaginal canal. The patient underwent cystoscopy, exploratory laparotomy, adhesiolysis, tumor debulking, frozen section, bowel run, repair of serosal tear, Jackson-Pratt drain insertion, bilateral percutaneous nephrostomy under combined spinal and epidural anesthesia. Bilateral percutaneous nephrostomy was performed due to the difficulty in inserting ureteral stents.

Intraoperatively, there was a 23.0 x 17.0 x 12.0 cm solid, non-necrotic, lobulated mass, which was densely

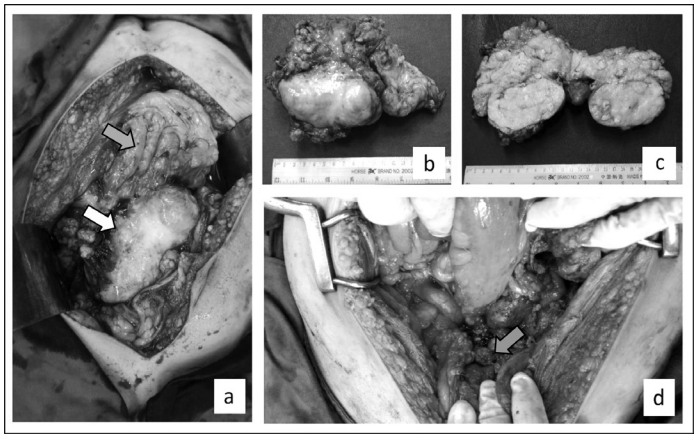

Figure 4. Intraoperative pictures. (a) The 23.0 x 17.0 x 12.0 cm solid, non-necrotic, lobulated mass (yellow arrow) was densely adherent to the omentum (blue arrow), small bowel and surrounding pelvic structures. (b) A 16.0 x 12.0 x 7.0 cm solid, non-necrotic, lobulated mass was removed. (c) Cut section of the resected abdominopelvic mass. (d) A 7.0 x 5.0 x 5.0 cm residual tumor (green arrow) was densely adherent to the lower pelvic sidewall and vagina.

adherent to the omentum, small bowel and surrounding pelvic structure (Figure 4). There were multiple nodular masses on the subdiaphragmatic surface as well as the omentum. After careful adhesiolysis, a 16.0 x 12.0 x 7.0 cm solid, non-necrotic, lobulated mass was removed. A 7.0 x 5.0 x 5.0 cm tumor was left behind due to dense adhesion to the lower pelvic sidewall and vagina. Dilated bilateral ureters were also noted. Frozen section of the excised abdominopelvic mass revealed round cell tumor probably dysgerminoma versus seminoma. Final histopathologic reading was mixed germ cell tumor (seminoma and yolk sac tumor).

The patient had an unremarkable postoperative course. A multidisciplinary conference involving pediatric endocrinology, genetics, hematologic oncology, child psychiatry, pediatric adolescent services was done with the family to disclose laboratory and surgical findings, and discuss treatment options and prognosis. The long term plan was to administer chemotherapy in the form of cisplatin, etoposide and bleomycin and estrogen replacement therapy after chemotherapy.

Six months after her surgery, the patient has undergone six cycles of chemotherapy (cisplatin, etoposide and bleomycin). Her latest AFP level is 9.23 IU/ml. Repeat abdominal CT scan revealed no evidence of tumor except for prominent sized bilateral inguinal lymph nodes.

DISCUSSION

Androgen insensitivity syndrome (AIS), previously known as testicular feminization, is a disorder of sexual dysfunction that was first described by John Morris in 1953. It is the most common form of male pseudohermaphroditism occurring in 1 out of 20,000 to 25,000. [2,3] It is an X-linked recessive disorder characterized by a female phenotype with 46 XY karyotype. Pathogenesis involves mutation in the androgen receptor gene located on the proximal long arm of the X chromosome at Xq11-12, which results in unresponsiveness of the target organs to androgen stimulation.[1,2,4]

During the neonatal period, testosterone and anti-mullerian hormone (AMH) secreted by the Leydig and sertoli cells of the testis, respectively, are responsible for the development of the male reproductive tract. Testosterone is responsible for Wolffian development (epididymis, vas deferens and seminal vesicle) while dihydrotestosterone (DHT), a derivative of testosterone, is necessary for the development of male external genitalia. AMH on the other hand controls the regression of the mullerian ducts thus inhibiting the development of fallopian tubes, uterus, cervix and proximal vagina. Since the receptor organs of patients with AIS are unresponsive to androgens, the male reproductive tract does not develop. Instead, patients present with a normal looking female external genitalia but with a rudimentary or blind ending vagina with absence of the uterus and cervix. Pubic and axillary hair are absent since their development is also androgen dependent. The development of estrogen dependent secondary characteristics (i.e. breast development) is a result of the conversion of testosterone to estradiol via the

Table 2. Rejender Androgen insensitivity severity scale

Grade		Phenotype
PAIS	1	Male genitals, infertility
	2	Male genitals, mildly 'under-masculinized', isolated hypospadias
	3	Predominantly male genitals, severely 'under-masculinized' (undescended testes, and/or bifid scrotum)
	4	Ambiguous genitals, severely 'under-masculinized' (phallic structure that is indeterminate between a penis and a clitoris)
	5	Female genitals (including separate urethral and vaginal orifices, mild clitoromegaly)
	6	Female genitals with pubic hair / axillary hair
CAIS		Female genitals with little or no pubic hair / axillary hair

Lifted from Spataru, R., Costea, G., Spiridon, L., et al. Partial androgen insensitivity syndrome. Multidisciplinary approach - genetic, endocrinological, surgical, psychological, psychiatric, social, ethical and forensic. Romanian Journal of Legal Medicine 2013; 21: 201-206.

action of the enzyme aromatase. Examination findings of our patient were all consistent with AIS.

Depending on their presentation, AIS can be classified as complete, incomplete or mild. Complete androgen insensitivity syndrome (CAIS) occurs in 1 out of 20,400 boys born, while partial androgen insensitivity syndrome (PAIS) occurs in 1 out of 130,000 boys born.[5,6] Between the two, mutation in the androgen receptor gene is found in 95% of CAIS and only in <50% of PAIS.[1] CAIS presents as phenotypically female with adequate breast development, normal external genitalia, absent or little axillary and pubic hair, primary amenorrhea, absent uterus and shortened vagina, as seen in our patient. On the other hand, PAIS may present as female virilization or male feminization. Mild androgen insensitivity syndrome (MAIS) are phenotypic and genotypic males which often present with androgen action defect. This could be manifested as oligospermia, gynecomastia and hyspospadia. Table 2 shows the spectrum of AIS depending on their clinical presentation.

In a patient with a female phenotype presenting with primary amenorrhea, a complete physical examination should be done. In the absence of the secondary sexual characteristics, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) determination should be requested. In their presence, as in our case, imaging studies are necessary to properly assess the presence of mullerian structures. If the uterus is present, outflow obstruction should be suspected since imperforate hymen or transvaginal septum may be present. If no outflow obstruction is noted, patients should be worked up for secondary amenorrhea. However, in the absence of uterus and other mullerian structures, karyotyping should be done. AIS has a 46 XY karyotype while mullerian agenesis has a 46 XY karyotype.

Since AIS is a disorder of hormone resistance, the endocrine profile of such patients shows a normal or above normal testosterone, elevated LH and normal FSH and inhibin levels. The estrogen level is usually higher than those noted in men, but lower than those noted in women.

Management of AIS is multidisciplinary. The major concerns that need to be addressed include the risk of malignancy, the need for hormonal replacement therapy should gonadectomy be performed, and the sexual as well as the psychological issues inherent to the disease. Genetic counseling should also be done.

Cryptorchidism carries a 10% risk of developing testicular tumor, the most common of which is a seminoma.[9,10] Eighty to ninety percent of patients with CAIS will eventually develop inguinal hernia while there is a 1.1% incidence rate of CAIS in children presenting with premenarcheal inguinal hernia.[4] Gonadal dysgenesis carries a 10-30% risk of developing gonadal tumor. On the other hand, a lower risk is seen in CAIS population as their gonads are not dysgenetic.[1,4] However, as they age, there is an increased risk of developing malignant gonadal tumor. The risk of malignancy for undescended intra-abdominal testes is 3.6% at 25 year-old, and 33% at 50 year-old.[2,3,7] PAIS carries a higher risk (15%) of developing malignant gonadal tumor than CAIS (0.8%).[1,8] Our patient presented with an abdominopelvic mass, which on histopathologic examination revealed a mixed germ cell tumor (seminoma and yolk sac tumor). Germ cell tumors are reported in 2% of adult patient with AIS but is very rare during childhood and adolescent with a reported incidence of as low as 0.8%.[8] Patients with germ cell tumors should receive Cisplatin-based chemotherapy, which is usually curative with the overall cure rate of >80%. Our patient has received 6 cycles of cisplatin, etoposide and bleomycin, with good response.

Due to the inherent risk for gonadal malignancy, one important aspect in the management of AIS is the appropriate timing of gonadectomy. Options include early gonadectomy with puberty induction later in life or delayed gonadectomy during early adulthood. Early gonadectomy decreases the chance of malignant transformation as risk of malignant gonadal tumor increases with age. Whereas, delayed gonadectomy allows the individual to have spontaneous puberty with normal breast development and appropriately-timed growth spurt.

Although there is no consensus with regards to the proper timing of gonadectomy, Liu and colleagues (2014) recommends that prophylactic gonadectomy is optimally done at age 16-18 in which secondary sexual development is already completed and the risk of gonadal malignancy is manageable. This is congruent with the current recommendation that gonads should be removed after puberty, that is, when final height and breast development have been achieved.[4]

Once the gonads are removed, hormonal therapy can be instituted. Bone mineral density is decreased in CAIS regardless of the time of gonadectomy as androgens are found to have a direct role in the maintenance of bone density.[4] As such, adequate estrogen therapy and supplementation with calcium and vitamin D are necessary.

Addressing sexual function of an AIS patient should be part of the long term management. This involves creation of a functional vagina. The process involves physical and emotional discomfort especially in young females, hence timing of the procedure is dependent on the patient and the family. The patient should be prepared and properly counseled on the risks and benefits of the procedure. Dilatation is the first-line therapy for the creation of a vagina. If this fails, surgical management could be done.[4] Future concerns may include problems with desire, arousal and dyspareunia.

Amidst these medical and surgical concerns, physicians are most often faced with the dilemma of proper timing and manner of disclosing the disease as well as the genotype of the patient to the family and most especially to the patient herself.[4] The people that should be involved in the disclosure is dependent on the patient's age and cognitive function. Timing is very important as it may cause emotional and psychological distress to the patient and the family. As such, psychological, as well as genetic, counseling should be encouraged. Other concerns should focus on the understanding of the disconnect between the genotypic and phenotypic profile as well as its implication. Questions regarding gender identity and sexual preferences should be properly discussed with the patient and the medical professionals. Proper determination of sexual mentation as well as identification of coping mechanism should also be employed.

Assuming a female identity, exemplifying female-typical behavior and imbibing psychological wellbeing similar to that of other women is a common long-term psychosexual outcome in complete androgen insensitivity syndrome. Most CAIS women reported heterosexual orientation during adolescent (100%) and adulthood (93%). This is similar to our case, as maintenance of a female identity causes less distraught on the part of the patient and the family.

CONCLUSION

Androgen insensitivity syndrome is a rare disorder characterized by a female physique with an XY karyotype. They usually present with primary amenorrhea, normal breast development, absent or scarce axillary and pubic hairs and a shortened vagina. The presence of an undescended testis increases the likelihood of a malignant transformation. The risk of malignancy of undescended intra-abdominal testes is 3.6% at 25 year-old, and 33% at 50 year-old.[2,3,7] As such, bilateral orchiectomy is advocated. Proper timing of which is necessary to allow spontaneous occurrence of puberty. Treatment of AIS requires a multidisciplinary approach involving a gynecologist, oncologist, urologist, endocrinologist, geneticist, pathologist and psychiatrist. ■

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