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Testicular carcinoma in a female with 46-XY karyotype: a case report



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Siti Nurul Hapsari,* Betty Agustina

ABSTRACT

Background: Testicular cancer is now the most common malignancy in young males. Markers available in the management of patients with testicular cancer are alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH). Female patients with androgen insensitivity syndrome (AIS) and pure gonadal dysgenesis have a pure XY karyotype and an increased risk of developing a gonadal malignancy.

Case Description: A 26-year-old female presented with a hardened stomach and primary amenorrhoea. Physical examination revealed Tanner Stage I for both the right and left breast and no pubic or axillary hair. On local examination, there was a large firm non-tender mass extending across the abdominopelvic region. Gynecological examinations revealed normal labia; however there was clitoromegaly,

the vagina was blind (5 cm) with the absent cervix. Laboratory tests with increased abnormal results were as follows: LDH 3,448 U/L, AFP 1,842.6 ng/mL, Cortisol 22.41 ug/dL and Testosterone 128.7 ng/dL. An MSCT of the abdomen showed a solid mass with no signs of a vagina or uterus. Blood karyotyping results were 46 XY with the presence of the SRY gene. Due to an increase in LDH, AFP, Cortisol and Testosterone, with 46 XY karyotyping, Tanner stage 1 breasts, pubic and axillary hair, female genitalia phenotype and abdominal MSCT showing a solid mass with no signs of vagina and uterus, this patient was diagnosed with non seminoma testicular cancer with widespread disease and 46, XY karyotype (male).

Conclusion: Testicular cancer is common in patients with gonadal dysgenesis, due to an increase in malignancy risk.

Keywords: Female, Karyotype, Nonseminoma, SRY gene, Testicular cancer,

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Department of Clinical Pathology,
Faculty of Medicine Airlangga
University, Dr. Soetomo Hospital,
Surabaya, Indonesia

INTRODUCTION

Testicular cancer is now the most common malignancy in young males (aged 15 -34 years) in many populations worldwide; 95% of all testicular cancers are germ cell tumors (GCT), with an approximately equal division between seminomas and nonseminoma GCT (NSGCT). The global incidence of testicular cancer has doubled over the past three decades, occurring most commonly in young males, and is curable in most instances. Prompt diagnosis is important for the management and survival rate of the patient.¹

Testicular GCTs are unique in that tumor markers are readily available to guide clinicians in disease management. Despite the extensive evidence regarding the importance of tumor markers in testicular cancer care, there is data indicating that they are underutilized. The commonly available GCT markers in the management of patients with testicular cancer are Alpha-Fetoprotein (AFP), Human Chorionic Gonadotropin (hCG), and Lactate Dehydrogenase (LDH).²

As many as 1 in 3,000 babies are born intersexed. Normal females and males are characterized by XX and XY karyotype, respectively. Disorders of sex development (DSD) are congenital conditions characterized by atypical development of

chromosomal, gonadal and phenotypic sex.³ Female patients with Androgen Insensitivity Syndrome (AIS) and pure gonadal dysgenesis have a pure XY karyotype.⁴ Gonadal dysgenesis, is a condition in which gonadal development is interrupted leading to gonadal dysfunction, a unique subset of Disorders of Sexual Development (DSD) that encompasses a wide spectrum of phenotypes. In XY gonadal dysgenesis, the presence of a Y chromosome or Y- chromosome material renders the patient at increased risk of developing a gonadal malignancy.⁵ So, the purpose of this case review is to present a case of testicular cancer in a female with 46, XY karyotype.

CASE DESCRIPTION

A 26-year-old female, presented with a firm stomach and primary amenorrhoea to the Outpatient Clinic in 2017. There were no constitutional symptoms or weight loss. Physical examination revealed a phenotypic female with Tanner Stage I for both the right and left breast and no pubic or axillary hair (Tanner pubic hair stage 1). On local examination, there was a large firm non-tender mass extending across the abdominopelvic region. Gynecological examinations revealed normal labia; however there was clitoromegaly, the vagina was blind (5 cm) with

*Correspondence to:
Siti Nurul Hapsari; Department
of Clinical Pathology, Faculty of
Medicine Airlangga University,
Dr. Soetomo Hospital, Surabaya,
Indonesia
nu.neemo@gmail.com

the absent cervix. The mass in her stomach was suspected as an ovarian solid tumor.

Laboratory examinations showed an increase of serum LDH (Lactate Dehydrogenase), AFP (Alpha Feto Protein), Cortisol and Testosterone; and normal levels of Beta hCG (Human Chorionic Gonadotropin), Progesterone FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone), ACTH (Adrenocorticotrophic Hormone), CA125, CA 19-9 and CEA. Laboratory results of the patient were as follows:

A Multiple Section CT of the abdomen showed that there was a solid mass in the abdominal cavity attached to the wall of the bladder, abdominal aorta

and inferior cava vein with no sign of a vagina, uterus or adnexa.

Blood karyotyping was performed from peripheral blood lymphocytes and revealed results of a normal male (46 XY) (Figure 1). Presence of Sex-determining Region on Y-chromosome (SRY) was confirmed by Polymerase Chain Reaction (PCR) by the molecular study.

The patient was recorded with 1) no menstruation and hardened stomach; 2) physical examination with Tanner 1 breasts, pubic and axillary hair; female external genitalia with clitoromegaly; 3) laboratory results of increased LDH, AFP, and testosterone with normal Ca 125, Ca 19-9 and CEA levels; 4) MSCT of solid mass with no uterus and vagina; and 5) cytogenic results of 46 XY karyotype and SRY gene detected. Thos signs and symptoms lead to the diagnosed with non seminoma testicular cancer with primary ammenorhoea and DSD with 46, XY karyotype.

DISCUSSION

Intersex disorders result from a genetic defect in the chromosomal presentation. They often present with ambiguous external genitalia and on the basis of their gonadal presentation, are categorized into true hermaphrodites and mixed gonadal dysgenesis (pseudohermaphrodites). The propensity of the gonads to develop malignant tumors have been documented in 46, XY with mixed gonadal dysgenesis and male pseudohermaphroditism.⁶

Tanner staging, also known as Sexual Maturity Rating (SMR), is an objective classification system that provides users to document and track the development and sequence of secondary characteristics of children during puberty.⁷

Ovarian cancer screening usually uses two different kinds of test, either the *transvaginal ultrasound (TVUS)* and the CA-125. The TVUS uses sound waves to look at the uterus, fallopian tubes, ovaries by putting an ultrasound wand into the vagina.⁵ This patient underwent an MSCT scan that showed that there was indeed a mass, but no uterus was found. Many females with ovarian cancer have high levels of CA-125, but an increase in CA-125 can also be linked to endometriosis and inflammatory states.⁸ CA 19-9 elevation has been linked to ovarian cyst and neoplasms. In patients with an undiagnosed tumor in the pelvis, the CA-125/CEA ratio may be used to identify a substantial fraction of patients with non-ovarian malignancies.⁹ This patient had normal levels of CA-125, CEA and CA19-9 thus, excluding ovarian cancer.

Testicular cancers secrete tumor markers, high levels of certain protein that can be detected through blood tests. These markers of testicular

Table 1 Laboratory Results of the Patient

Variables	Results	Interpretation	Reference Range
LDH (U/L)	3.448	Increased	100 - 190
AFP (ng/mL)	1.842,6	Increased	< 15
Cortisol (µg/dL)	22.41	Increased	4.30 - 22.40
Testosterone (ng/dL)	128.7	Increased	Female: 14 - 76 Male: 241 - 827
Beta hCG (mIU/mL)	< 2.00	Normal	Cyclic woman: <4 Men: < 3
Progesteron (ng/mL)	0.56	Normal	0.21 - 60
FSH (mIU/mL)	6.59	Normal	
LH (mIU/mL)	14.57	Normal	
ACTH (pg/mL)	33.4	Normal	< 46
CA 125 (23.2 U/mL)		Normal	< 35
CA 19-9 (U/mL)	16.94	Normal	< 37
CEA (ng/mL)	0.44	Normal	< 5

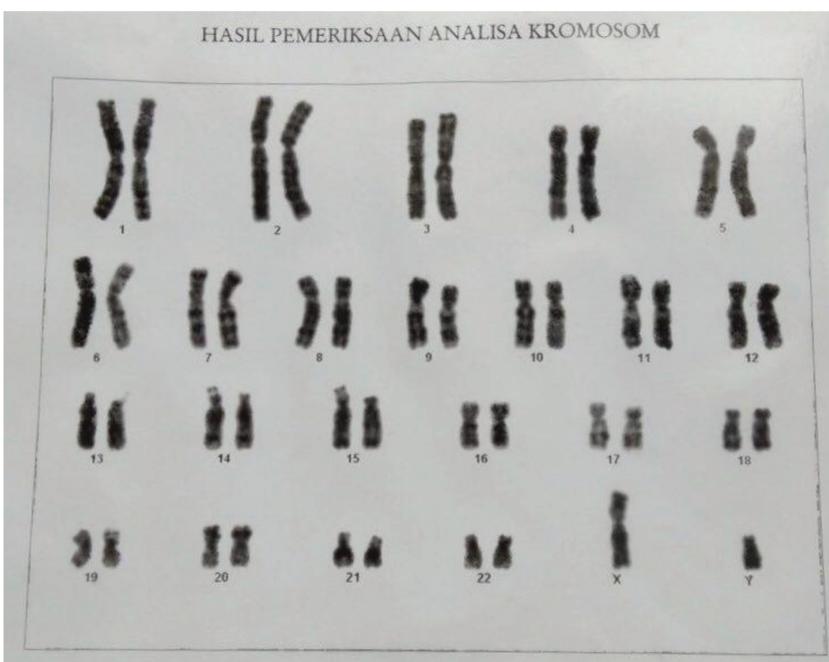


Figure 1 GTG-banded karyotype of Proband 46 XY

cancer include alpha-fetoprotein (AFP), beta human chorionic gonadotropin (beta hCG) and lactate dehydrogenase (LDH). Increased AFP or hCG with abnormalities in testis suggest testicular cancer.² Rises in levels of AFP and hCG levels give information about the type of testicular cancer. Nonseminomas often raise AFP and/or hCG levels, whereas pure seminomas occasionally raise hCG levels but never AFP levels. A testicular tumor might also increase the levels of an enzyme called lactate dehydrogenase (LDH). High levels of LDH often indicate widespread disease. LDH is elevated in 40% - 60% of testicular GCT, and has limited sensitivity and specificity for seminoma, but LDH levels > 2,000 U/L is more consistent with bulky disease, and rising levels are an accurate indicator of recurrence.² This patient had a rise in AFP and LDH indicating a non seminoma testicular cancer with widespread disease.

The 46, XY female, can be subdivided into two major subdivisions: (1) Conditions with abnormal testicular development (e.g., gonadal dysgenesis alias Swyer syndrome) and (2) conditions with defective androgen action (e.g., androgen insensitivity syndrome alias Morris syndrome).⁸

Androgen Insensitivity Syndrome (AIS) was designated "testicular feminization syndrome" or Morris syndrome because the testes produce hormones with estrogen-like actions. AIS is caused by mutations in the Androgen Receptor (AR) gene, with the presentation of several differentiations from genetic defects to end organ resistance thereby producing ambiguous gender dispelled by sex hormones signature. Shortcomings of the AR gene prevent the normal development of both internal and external genital structures in 46, XY individuals, causing a variety of phenotypes ranging from complaints of male infertility to completely normal female external genitalia. It is an X linked disorder associated with vaginal and uterine agenesis in females with 46, XY karyotype.⁴

46, XY pure gonadal dysgenesis, previously known as Swyer syndrome, can be caused by a mutation in the sex-determining region on Y (SRY) gene located on the short distal arm of the Y chromosome (Yp11.3).³ The mutations involved in testicular development, of undifferentiated streak gonads, which do not produce anti-mullerian hormone or androgens. Consequently, the vagina, cervix, uterus and fallopian tubes develop, and external genitalia is those of female due to the absence of androgen action.⁴ This patient had external female genitalia with no uterus, 46, XY karyotype with positive SYR gene, suggesting a 46, XY, DSD with positive SYR gene or also known as Sewer syndrome.

Hormone analysis can make the differential diagnosis. In AIS, the androgen is up to male levels, whereas in pure gonadal dysgenesis the levels are elevated compared to female level, but they will not reach normal male levels.⁴ This patient has testosterone levels of 128.7 ng/dL which exceeds the normal female range of 14 - 76 ng/dL but is still far from the normal male range of 241 - 827 ng/dL. Normal serum FSH and LH were within normal range for males, assisting in the evaluation of hypo gonadal males.

CONCLUSION

Testicular cancer is now the most common malignancy in young males (aged 15 -34 years) in many populations worldwide; 95% of all testicular cancers are germ cell tumors (GCT), with an approximately equal division between seminomas and nonseminoma GCT (NSGCT). The commonly available GCT markers in the management of patients with testicular cancer are alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH). Disorders of sex development (DSD) are congenital conditions characterized by atypical development of chromosomal, gonadal, and phenotypic sex. The diagnosis of patients with 46, XY DSD is mainly clinical and usually identified during the investigation for primary amenorrhea or delayed puberty. Prophylactic gonadectomy should be considered for patients with DSD who have Y chromosomes, due to an increased risk of gonadal malignancy. The estimated risk of malignancy in testicular feminization is 5%. Patients with DSD need proper counseling and education according to their psychosexual make-up and socio-culture factors.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding manuscript

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AUTHOR'S CONTRIBUTION

The authors are contribute equally to the content of manuscript from data preparation until data analysis.

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