

Case Report

Anaplastic large cell lymphoma in undescended testis of a patient with 46, XY disorder of sex development (DSD): a case report

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Received January 9, 2018; Accepted June 20, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: A rare congenital abnormality, 46, XY DSD affects development of chromosomal, gonadal, or anatomical sex characteristics. Disorders of sex development (DSD) patients frequently present with an undescended testis or cryptorchidism, which may result in low levels of testosterone and high levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The LH receptor is involved in development of T-cell lymphoma. Cryptorchidism is associated with increased risk of development of malignancies, although lymphoma is rare in DSD patients. This present study presents a case of a 54-year-old woman with low levels of testosterone and high levels of FSH and LH due to 46, XY DSD. She was diagnosed with cryptorchidism-related anaplastic large cell lymphoma. Based on this case, it was hypothesized that testicular dysfunction and secondary increases in FSH and LH levels increase the risk of lymphomagenesis in individuals with congenital 46, XY DSD.

Keywords: 46, XY DSD, anaplastic large cell lymphoma, cryptorchidism, testicular dysfunction

Introduction

Disorders of sex development (DSD) are congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex characteristics. Although overall birth prevalence of conditions associated with DSD may be as high as 1 in 300 [1], incidence of the individual pathophysiological condition is much lower. Patients with DSD can be divided into three groups according to karyotypes: sex chromosome DSD, 46, XX DSD, and 46, XY DSD, with 46, XY DSD accounting for approximately 50% of all DSDs. Sex chromosome DSDs are subdivided into four diagnostic categories: 45, X (Turner syndrome and variants), 47, XXY (Klinefelter syndrome, KS), 45, X/46, XY (mixed gonadal dysgenesis), and 46, XX/46, XY (chimerism or ovotesticular DSD).

Undescended testis or cryptorchidisms, frequently seen in DSD patients, are associated with increased risk of infertility and testicular cancer. DSD patients have a significantly increased risk of developing specific types of ma-

lignancies, although lymphoma is rare. This study presented the first case report of lymphoma in a 54-year-old woman with 46, XY DSD, providing a review of relevant literature.

Case report

A 54-year-old woman of Han ethnicity was admitted to the hospital, in January 2014, after presenting with pain in the left inguinal area for 2 weeks. She had a history of surgical resection of a right inguinal mass, 30 years prior, and she had never menstruated. On admission, a female phenotype was recorded. There was no history of cyclic abdominal pain, hormonal intake, radiation exposure, or chemotherapy. Upon physical examination, the patient's blood pressure was 121/82 mmHg, with a pulse rate of 82 beats/min, and respiratory rate of 18 breaths/min. There was no cyanosis, clubbing, edema, obesity, acne, hirsutism, thyroid swelling, or cushingoid features. Her breast development was grade II. There was no axillary or pubic hair. There was no clitoris majora hypertrophy. The labia majora were separate

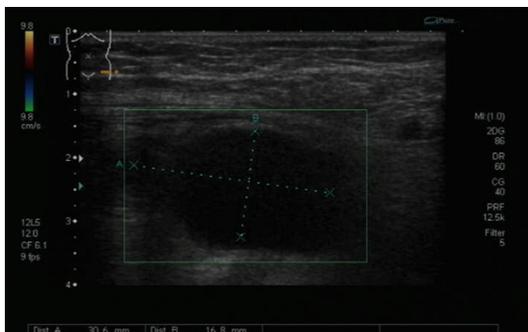


Figure 1. B ultrasound scan of superficial lymph nodes. Image shows several enlarged lymph nodes in the left inguinal area, unclear corticomedullary boundaries, and no enlarged lymph node in the bilateral cervical, bilateral axillary fossa, and right inguinal regions.

and the vagina was hypoplastic. Examination of parameters including the chest and cardiovascular system were within normal limits. There was a palpable painless lump (approximately 3 × 4 cm in size, obscure boundary, immobile) in the left inguinal area. Laboratory test results were as follows: red blood cell count, $4.57 \times 10^{12}/L$; hemoglobin, 13.2 g/dl; hematocrit, 40.3%; platelet count, $290 \times 10^9/L$; white blood cell count, $9.1 \times 10^9/L$; neutrophils, 75%; and lymphocytes, 15.7%. Hormone analysis results were as follows: testosterone, 61 ng/dl (normal range (N): 241-827 ng/dl); luteinizing hormone (LH), 19.2 mIU/mL (N: 1.5-9.3 mIU/mL); follicle-stimulating hormone (FSH), 53.3 mIU/mL (N: 1.4-18.1 mIU/mL); estradiol < 11.8 pg/ml (N: 0-44.5 pg/mL); prolactin, 30.2 ng/mL (N: 2.1-17.7 ng/mL); progesterone, 0.58 ng/mL (N: 0.28-1.22 ng/mL); and 17-hydroxyprogesterone (17-OHP), 7.47 ng/mL (N: 0-30). Biochemical and immunological analyses were within normal limits and lactate dehydrogenase (LDH) was 321 IU/L (N: 109-245 IU/L). X-rays of the chest and electrocardiography (ECG) were normal. Superficial B ultrasound showed several enlarged lymph nodes in the left inguinal area. The largest was approximately 3.1 × 1.9 cm in size. Corticomedullary boundaries were unclear and there were no enlarged lymph nodes in the bilateral cervical, bilateral axillary fossa, and right inguinal regions (**Figure 1**). Computed tomography of the whole abdomen showed multiple nodules in the retroperitoneal area and the left pelvic wall as well as multiple lymph nodes in the left inguinal area, while the uterus and adnexa were

absent (**Figure 2**). Cytogenetic analysis of peripheral blood cells showed a 46, XY karyotype (**Figure 3**).

She received a lumpectomy on February 7, 2014. The size of the tumor mass was approximately 4 × 5 cm, with a hard texture and adhesions to the iliac blood vessels. An ovary was identified in the patient's abdomen. Immunohistochemical analysis revealed anaplastic large cell lymphoma: CK(pan)(-), VM(-), OCT3/4(-), PLAP(-), CD30(Ki-1)(+), CD117(-), AFP(-), HCG(-), inhibin-a(-), CD3(-), CD20(-), CD79a(-), ALK(+), CD5(-), CD10(-), Bcl-2(-), Bcl-6(-), EBV(-), MUM1(+), Ki-67(+,70%), PAX-5(-), and CD21(-) (**Figure 4**). Bone marrow aspiration and the biopsy were normal. A 46, XY karyotype was also found during cytogenetic analysis of the bone marrow. The patient was diagnosed with anaplastic large cell lymphoma (ALCL; stage II, group A). After six cycles of a CHOP plus pegaspargase regimen, she achieved complete remission. She was followed up every three months. The last follow up, in February 2015, showed no signs of relapse.

Discussion

ALCL, also known as anaplastic lymphoma kinase (ALK)-positive (ALK+ ALCL), occurs most commonly in young individuals, with a median age of about 35. It is more prevalent in males. This distinct and aggressive subtype of non-Hodgkin lymphoma (NHL: 2%-8% of cases) of CD30-positive T-cell lineage is characterized by a chromosomal translocation in the ALK gene. Although ALCL is primarily a nodal disease, extranodal involvement is not uncommon. ALK+ ALCL frequently involves both lymph nodes and extranodal sites, commonly including skin (21%), bone (17%), soft tissues (17%), lungs (11%) and liver (8%). Involvement of testes is rare [2]. Specific risk factors for ALCL have not yet been identified. Although many viruses, including Epstein-Barr virus and members of the human T-cell leukemia virus family, are associated with NHL, there is no convincing evidence that this is the case for ALCL. Neither has any correlation with immunological disorders. Furthermore, studies have suggested that people exposed to solvents, pesticides, and fertilizers are at an increased risk of NHL. This correlation, however, has not been confirmed in ALCL [3].

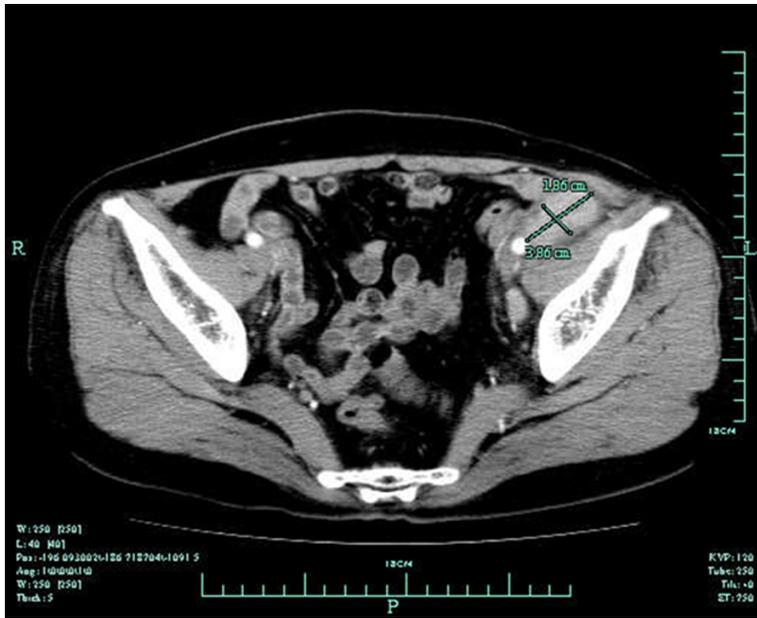


Figure 2. Computed tomography of the whole abdomen. Image shows multiple nodules in the retroperitoneal area and the left pelvic wall, multiple lymph nodes in the left inguinal area, and absent uterus and adnexa.

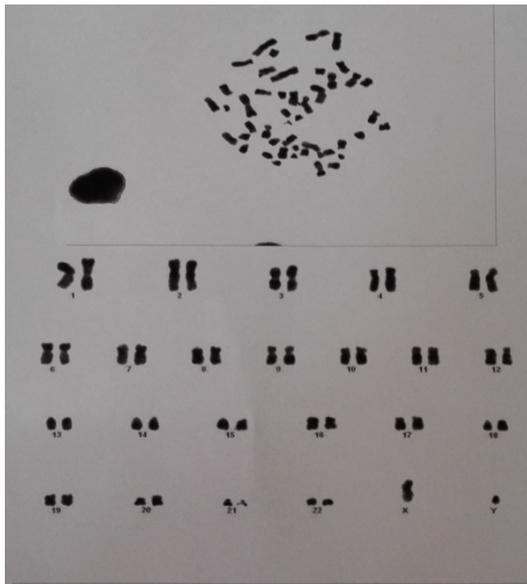


Figure 3. Cytogenetic analysis of peripheral blood cells showing 46, XY.

DSD patients have a significantly increased risk of developing specific types of malignancies. There have been several studies reporting other solid organ malignancies as well as hematologic malignancies in patients with DSD. A large UK cohort study of patients with KS showed that the risk of NHL was higher among

patients with KS than among the general population. This study also revealed a modest association between leukemia and KS [4].

The incidence of lymphoma in KS patients is high. Hodgkin lymphoma patients are often accompanied by testicular dysfunction before treatment [5, 6]. These reports suggest that testicular dysfunction may be associated with the pathogenesis of lymphoma. In mice, castration has been shown to promote radiation-induced lymphomagenesis, while testosterone has been shown to inhibit lymphoid tumor development in castrated or intact adult male mice [7]. The patient in this case was identified with the 46, XY DSD congenital abnormality with associated cryptorchidism and testicular dysfunction.

She also presented with low levels of testosterone and high levels of FSH and LH. It has been reported that low levels of testosterone lead to high levels of FSH and LH, via a feedback mechanism, and that FSH promotes the combination of LH and its receptor. Furthermore, a negative correlation has been identified between serum LH levels and ovarian LH receptors in perimenopausal patients, while neither FSH receptors nor LH receptors were detectable in postmenopausal patients [8]. These reports suggest that high levels of LH may induce LH receptor-deficiency. LH receptor-deficiency increases susceptibility to alkylating agent-induced lymphomagenesis in mice [9]. Therefore, it was hypothesized that, in the case presented here, testicular dysfunction and secondary high levels of FSH and LH may be involved in the pathogenesis of ALCL.

Primary NHL of the testis (PTL) accounts for approximately 9% of testicular neoplasms and 1-2% of all NHLs, with an estimated incidence of 0.26/100,000 per year [10]. Anecdotal reports have indicated an association of PTL development with trauma, chronic orchitis, cryptorchidism, or filariasis, although the etiologic significance of this correlation remains to

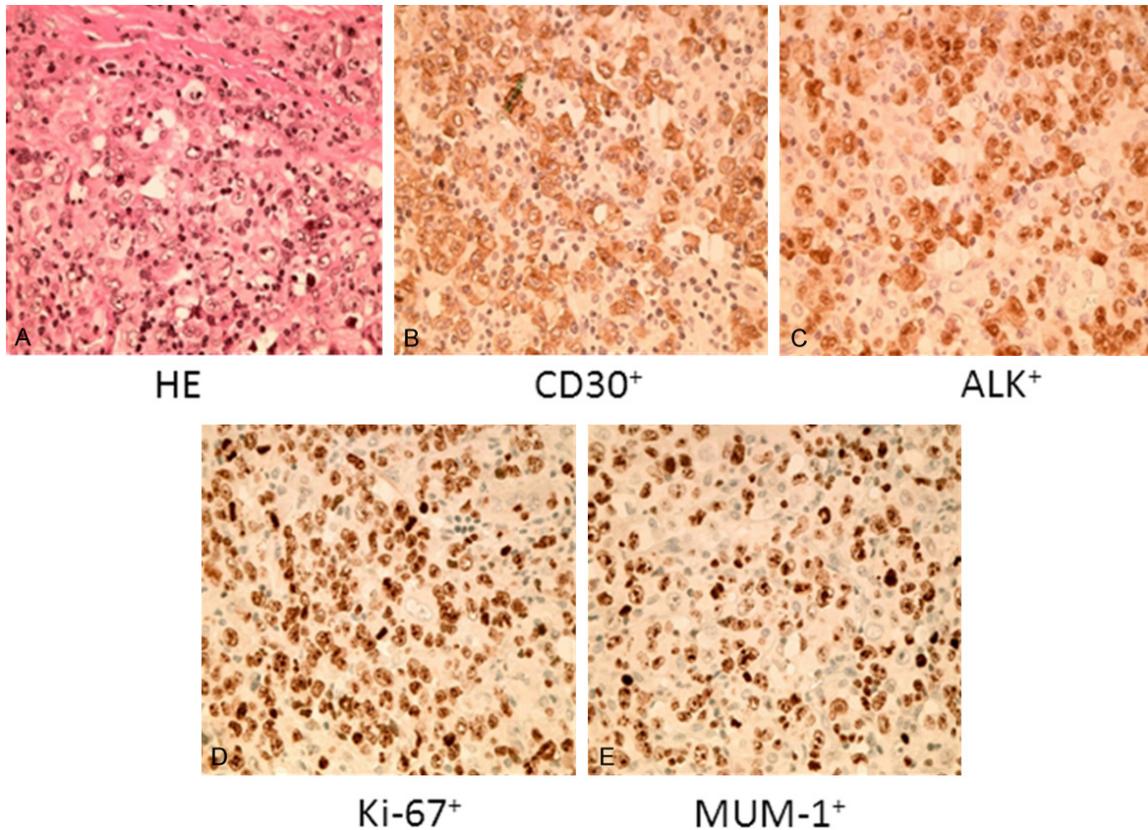


Figure 4. Immunohistochemical analysis of tumor mass resected from the retroperitoneal area of a patient with 46, XY DSD. (A) Hematoxylin and eosin staining. (B-E) Staining for: CD30 (B). ALK (C). Ki-67 (D). MUM (E). (Magnification $\times 100$).

be confirmed in case-control studies [11]. Most PTLs display a B cell immunophenotype, being diffuse large B cell lymphoma in 69-75% of cases [12]. T-cell lymphomas involving the testes have rarely been reported.

In this case, the patient was diagnosed as ALCL (stage II, group A). To the best of our knowledge, only five cases of primary ALCL of the testis have been reported [13, 14] and no case of DSD patients with ALCL have been reported. The most important prognostic factor in ALCL is ALK-positivity, which is associated with good prognosis. Overall five-year survival in ALK-positive patients is 70-86%, compared with 30-49% in ALK-negative cases [15]. Clinically, ALK-positive ALCLs typically show an aggressive course, but are usually responsive to standard CHOP or CHOP-like therapies. In the case reported here, the patient was ALK-positive and achieved complete remission, according to PET-CT, after receiving six cycles of CHOP plus peg-asparaginase.

In conclusion, DSD patients with an undescended testis have an increased risk of developing malignant disease. This study presented a female patient with 46, XY DSD diagnosed with ALK-positive ALCL in the undescended testis. This patient also had low levels of testosterone and high levels of FSH and LH. This present study suggests that testicular dysfunction and secondary increases in FSH and LH levels increase the risk of lymphomagenesis in individuals with congenital 46, XY DSD.

Acknowledgements

This work was supported in part by grants from the National Natural Science Foundation of China (81201868, 91429302, and 81560030), Zhejiang Provincial Natural Science Foundation of China (LY16H080001), and Specialized Research Fund for the Doctoral Program of Higher Education (20120101120100). We are very grateful to the patient for agreeing to share details of her case.

Disclosure of conflict of interest

None.

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