Pure bilateral endodermal sinus tumor in a female case of Ullrich-Turner syndrome with 45,X/46,XY karyotype

45,X/46,XY karyotipli Ulrich-Turner sendromlu dişi bir vakada saf bilateral endodermal sinüs tümörü

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Abstract

The presence of mosaic 45,X/46,XY is a very rare chromosomal anomaly. The presence of Y chromatin in individulas with Ullrich-Turner syndrome confers a risk for gonadoblastoma. The case presented with short stature, primary amenorrhea and a hypoplasic uterus. Karyotype was determined as 45,X/46,XY by cytogenetic analysis of peripheral blood. We performed molecular genetic analysis for Y chromosomal loci (SRY, ZFY, SY84, SY86, SY127, SY134, SY254, SY255) in both blood leukocytes and paraffin-embedded gonadal tissue.The case was positive for all sequences tested and developed an bilateral endodermal sinus tumor diagnosed by a pathologist. Adequate counseling regarding gonadectomy should be given because of the high proportion (33%) of gonadal tumors in patients with Y-chromosome sequences. It is the first report about bilateral EST in a UTS patient with 45,X/46XY karyotype to our knowledge.

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Key words: Ullrich-Turner syndrome, Y chromosomal loci, endodermal sinus tumor

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Özet

Mozaik 45,X/46,XY varlığı çok nadir bir kromozomal anomalidir. Ullrich- Turner sendromlu bireylerde Y kromatininin varlığı gonadoblastom için bir risk faktörüdür. Vaka kısa boy, hipoplazik uterus ve primer amenore göstermekteydi. Karyotip periferik kandan yapılan sitogenetik analizlerle 45,X/46,XY olarak tespit edildi. Biz hem kan lökositlerinde hem de parafine gömülü gonadal dokularda Y kromozomal lokusları için moleküler genetik analizler yaptık. Olgu test edilen tüm diziler için pozitifti ve bir patolog tarafından tanısı konmuş bilateral endodermal sinüs tümörü vardı. Y-kromozom dizilerine sahip hastalarda gonadal tümörlerin yüksek oranından dolayı (%33) gonadoktomi ile ilgili olarak danışmanlık verildi. Bilgilerimize göre 45,X/46,XY karyotipli UTS'li bir hastada bilateral EST ile ilgili olarak yapılan ilk rapordur.

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Anahtar kelimeler: Ullrich-Turner Sendromu, Y kromozomal lokusları, endodermal sinüs tümörü

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Introduction

Turner's syndrome (TS) is one of the most common chromosomal abnormalities. Incidence of TS is reported to be between 1/2500 and 1/5000 live births among girls. Various studies have shown that 40%–60% of TS patients were monosomic for the X chromosome. The remaining cases had a structurally abnormal X or Y chromosome, or were mosaics with a second cell line containing a normal or abnormal sex chromosome (1, 2). The presence of a cell mosaic 45,X/46,XY is a very rare chromosomal anomaly, having an incidence of 1.5 in 100 000. The phenotype can vary from a normal male child to a classical Ullrich Turner Syndrome (UTS) (3). The majority of mosaics are not detectable by means of cytogenetic techniques. The development of polymerase chain reaction (PCR)-based tests have permitted a more detailed study of UTS patients (4).

Malignant sacrococcygeal Yolk sac tumor (Endodermal Sinus) (EST) is an extremely rare extra-gonadal germ cell tumor, which is found in adolescents and young women. Yolk sac tumors occurring as pure or mixed germ cell tumors are rather common in the ovaries of young girls. The incidence of malignant yolk sac carcinoma is less than 1 per million per year (5). EST of the ovary is a rare malignant germ cell tumor. It is generally seen in young patients, presenting with a combination of abdominal pain and an abdominal or pelvic mass. It is a highly malignant tumor that metastasizes early and invades all the intraabdominal structures (6). We report on the clinical, cytogenetic and molecular diagnosis of a UTS patient with bilateral endodermal sinus tumor of the ovary.

Case Report

A 21-year-old Caucasian woman was referred because of primary amenorrhea. On physical examination, her height was

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151 cm and weight was 48 kg. The external genitalia were normal, except for hypoplasia of the labia minora. There was no breast development. Other pertinent findings were a low posterior hairline, a high palate, widely spaced nipples, and cubitus valgus. Abdominal and pelvic ultrasonograph detected uterine and gonadal hypoplasia, bilateral uronephrosis, and an 11cm solid mass with multifocal calcification in the left ovary. Radiography showed a normal bladder, urethra, and vagina. Hormonal dosages demonstrated hypergonadotrophic hypogonadism with high levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Other hormones examined included serum 17-hydroxyprogesterone, dehydroepiandrosterone and a thyroid function test. Skeletal densitometry revealed mild osteopenia. Serum alpha-fetoprotein a-FP: >30000IUl/ml (normal range: 0.5-5.5) and beta human chorionic gonadotropin b-HCG: 5.47mlU/ml, (normal range: 0-4) were high and serum CA-125: 2.75UI/ml, (normal range: 1.9-16.3) was normal. Gonadectomy was performed and the anatomopathological study showed that one of the structures consisted of ovarian-type stroma with no germinal cells, whereas the other was described as a wisp of fibrous tissue, containing vasa, nerves, and a focus of hilar hyperplastic cells. The patient had total abdominal hysterectomy (TAH), bilateral salpingoopherectomy (USO), omentectomy, as an initial mode of surgical therapy. The frozen biopsy specimen revealed a right EST. The patient was also subjected to lymphadenectomy as a part of the initial operation with a resected lymph node number of 29. No serious complications occurred during surgery and her postoperative recovery was excellent. No tumor cells were identified in lymphoid nodes excised from different regions (4 from left external iliac, 7 from right external iliac, 2 from right obturator, 5 from paraaortic, 4 from pre-adnexes, 2 from sigmoid, total 29). Pathology results showed bilateral endodermal sinus tumor in both ovaries (Figs. 1,2,3,4). However, the tumor had metastasized in the pleural fluid. Cytologic examination of the peritoneal washing fluid was positive. Figure 5 shows the cytology of pleural fluid taken duringsurgery. The patient was staged as stage-II and BEP (Bleomycin 15 U/m^2/wk x 5; then on day 1 of course 3; Etoposide 100 mg/m^2/d × 5 days every 3 wk; Cisplatin 20 mg/m^2/d × 5 days every 3 wk) chemotherapy regimen was initiated following

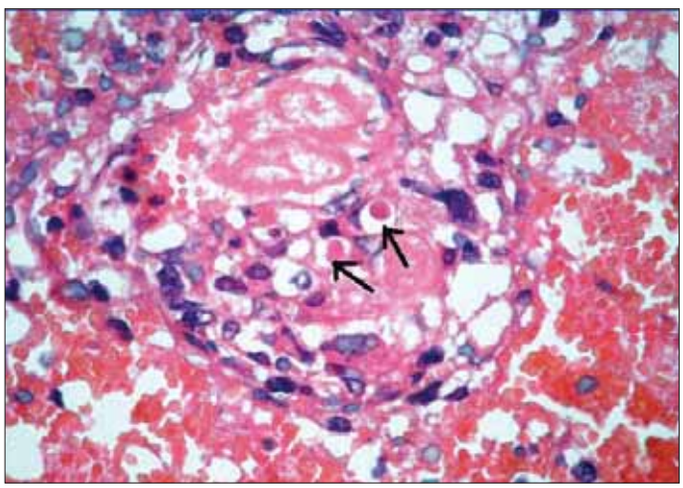

Figure 1. Right ovary 1: Yolc sac tumor showing glomerular formation with solid structure (H&EX200)

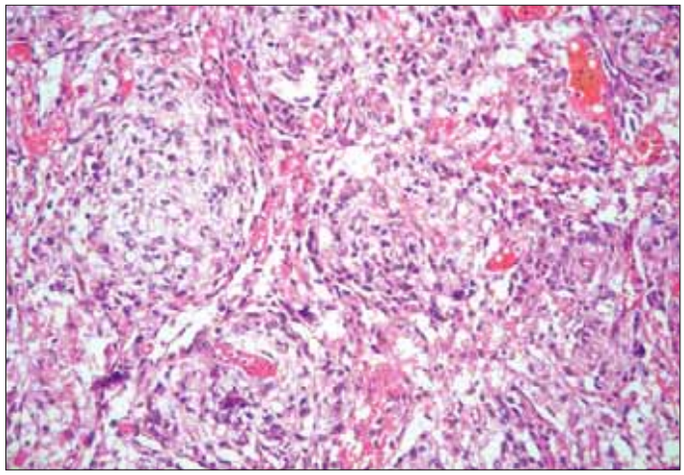

Figure 2. Right ovary 1: Photomicroscopy of endodermal sinus tumor showing circular hyaline globule (H&EX400)

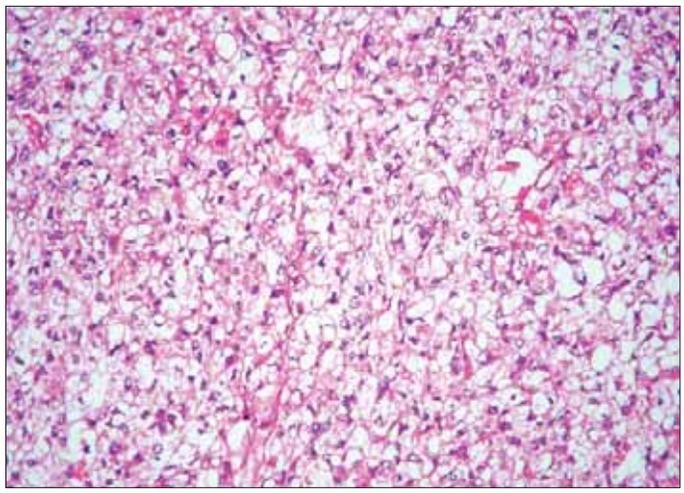

Figure 3. Left ovary 1: The microcystic pattern of the malignant cells (H&EX200)

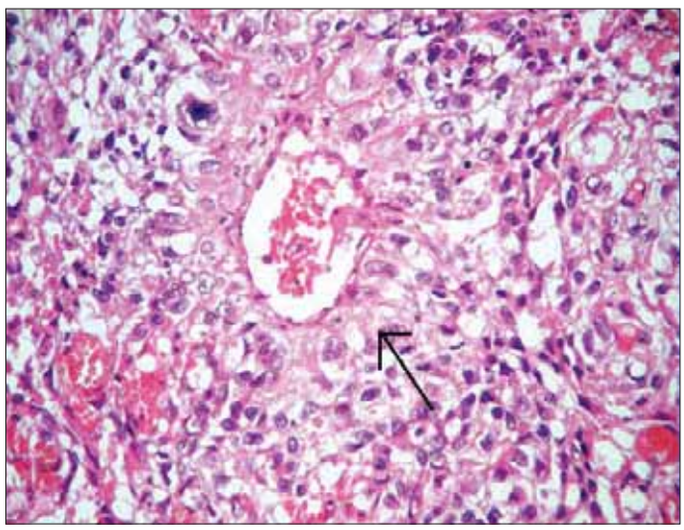

Figure 4. Left ovary 2: A classic Schiller-Duval body: central blood vessel covered by an inner rim of tumor cells and separated from an outer rim of tumor cells by a space (H&EX400)

embedded gonadal tissue. DNA sequences from Y chromosome (SRY, ZFY, SY84, SY86, SY127, SY134, SY254, SY255) were all amplified by polymerase chain reaction (PCR) using Y chromosome deletion kit (Dr. Zeydanlı Life Science, Ankara, Turkey). After PCR amplification, reaction products were run on a 1.5% agorose gel with a molecular weight marker (Figure 6). In all experiments, normal males and controls were included. PCR analysis for Y chromosome sequences was positive throughout all studied regions, both blood leukocytes and paraffin-embedded gonadal tissue.

Discussion

In the present study we identified Y material in a patient with a mosaic a 45,X/46,XY (73%: 27%) karyotype who developed bilateral EST. To our best knowledge, this is first case of pure bilateral yolk sac tumor in the ovary.

EST is a primitive malignant germ cell tumor characterized by a variety of distinctive microscopic patterns, some of which recapitulate phases in the development of the normal yolk sac. EST of the ovary is a rare germ cell tumor that occurs primarily in adolescent girls and young women and is considered to be the second most common form of malignant germ tumor of the ovary. It is mostly seen in 10–29-year-old patients, with median ages reported between 16 and 19 years (7). In the published literature, there were three reported cases with EST in UTS. It was reported that monolateral EST was detected in all three patients (4, 8, 9).

High a-FP level in serum indicated EST. However, the main diagnosis was made by the pathologist. Our patient had elevated serum a-FP and b-HCG level similar to others. The assay of serum a-FP can potentially aid in the preoperative diagnosis, monitor effectiveness of treatment, and detect recurrences before clinical manifestation and staging. The treatment of EST requires conservative surgery and combination chemotherapy because it has an improved prognosis and preserves adolescent bearing potential. The component of endodermal sinus tumor patterns tended to occupy recurrent tumors after chemotherapy, which suggests that the chemosensitivity of the component of EST patterns determined yolk sac tumor outcome (10). Malignant ovarian germ cell tumors are clinically very aggressive. Cases with yolk sac components have a particularly poor prognosis, but respond well to cisplatin-based chemotherapy (11). Nawa et al stated that the regimen of cisplatin, vinblastine, and bleomycin was significantly more effective than that of vincristine, actinomycin, and cyclophosphamide (12). Therefore, we decided to include cisplatin in the adjuvant chemotherapy regimen.

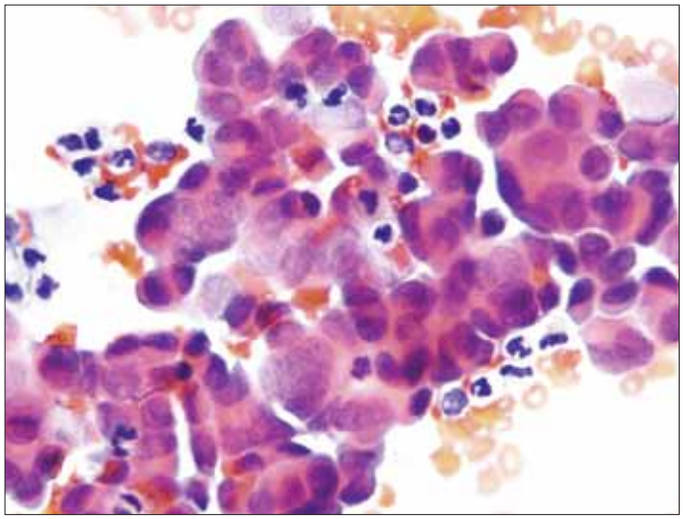

Figure 5. Compact, irregular and restricted tumoral cell groups with pleomorphic atypical nucleus is present (PAPXImmersion Oil)

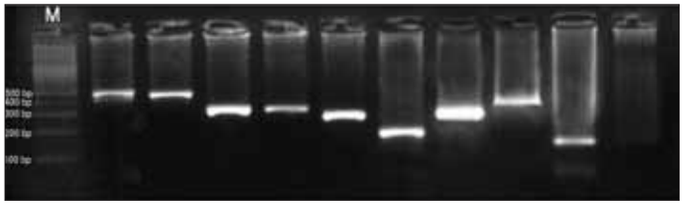

Figure 6. Gel photograph showing microdeletion region of ZFY, SRY, SY84, SY86, SY127, SY 133, SY134, SY254, SY255 and double distilled water

Early detection of Y-derived sequences in the genome of TS individuals is of great importance because of the relative high risk (10–30%) of developing gonadal tumors (i.e., gonadoblastoma or dysgerminoma). Gonadoblastoma is a neoplasm composed of germ cells and sex cord elements. Prophylactic gonadectomy should be recommended in patients with TS and Y chromosome mosaicism (4). Prophylactic gonadectomy is the procedure of choice to exclude gonadal malignancy in TS patients carrying Y chromosome sequences (1). Several karyotypes (45,X, mosaics and patients with a marker chromosome) were included, and previous studies have demonstrated the presence of Y-derived material in frequencies ranging from 4 to 61%, depending on the methodological approach. Cytogenetic and molecular data demonstrated the Y origin. These findings support the importance of searching for Y-chromosome sequences in patients with a mosaic or nonmosaic 45,X/46,XY karyotype. We predict that PCR analysis in patients with UTS will identify caseswith cypriptic or whole Y chromatin presence. Such identification will enable us to engage in better counselling and clinical management for these patients. The sift ultrasonographic investigations can be helpful in the early diagnosis of germ cell tumours of the ovary in TS. Therefore, for the moment, laparoscopy and preventive gonadectomy of the dysgenetic gonads remains the procedure of choice for UTS patients with identified Y-chromosomal material, and it should be performed as early as possible (4).

In conclusion, EST is rarely found in UTS. This case seems to be an extremely rare case of developing a bilateral pure yolk sac tumor in a patient with mosaic Turner syndrome with a Y-Chromosomal fragment. EST are highly malignant and lethal germ cell tumors which can terminate in early metastasis and rapid invasion of abdominal and pelvic structures. There is a growing body of evidence of literature related with complete responses of metastatic and primary disease to chemotherapy with long-term survival rates. Therefore, it appears reasonable to conclude that all patients, even for those with completely resectable tumours, should receive adjuvant chemotherapy. The results show that surgery plus combination chemotherapy is the best treatment for this type of disease and indicate that a-FP assay may be a useful tool for monitoring patient progress. The patient is still healthy and under observation at the outpatient clinic.

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