TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2021-1, Sayfa 27-30
Olgu Sunumu

Bilateral Dysgerminoma and Unilateral Adult Type Granulosa Cell Tumour of the Ovary Accompany B-Cell Acute Lymphoblastic Leukemia in a Young Woman

Genç Bir Kızda Bilateral Disgerminom ve Unilateral Erişkin Tip Granulosa Hücreli Over Tümörünün B Hücreli Akut Lenfoblastik Lösemiye Eşlik Ettiği Olgu Sunumu

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ÖZET

Giriş: Overde eş zamanlı germ hücreli tümör ile seks kord stromal tümör varlığı çok nadir görülen bir durumdur. Overde tek taraflı granüloza hücreli tümör ile çift taraflı disgerminom nedeniyle opere olduktan sonra adjuvan BEP (Bleomisin+Etoposid+cisPlatin) kemoterapisinden sonraki ilk yıl içinde B hücreli akut lenfoblastik lösemi ile presente olan nadir bir malignite kombinasyon olgusunu sunuyoruz.

Olgu: Karyotipi normal olan (46, XX) 17 yaşında bir genç kız, 65 mm çapa kadar ulaşan çift taraflı adneksiyal kitle ile başvurdu. Hastaya fertilite koruyucu cerrahi evreleme yapıldı ve patolojik incelemede çift taraflı disgerminom ile tek taraflı erişkin tip granuloza hücreli seks-kord bileşenleri içeren tümör saptandı. Adjuvan BEP kemoterapi sonrası hasta remisyonda iken, onuncu ayda hastaya akut lenfoblastik lösemi teşhisi kondu.

Sonuç: Gonadal tümör nedeniyle BEP kemoterapisi almış hastalarda, yakın ve dikkatli takip ayrıca önem taşır, Bu hasta grubunda hematolojik malignitelerin de sekonder olarak gelişebileceği mutlaka akılda tutulmalıdır.

Anahtar sözcükler: Bilateral disgerminoma, granüloza hücreli tümör, B hücreli akut lenfoblastik lösemi, senkron tümörler

ABSTRACT

Background: Synchronous germ cell and sex cord stromal tumor is a unique and very rare phenomenon. We present a case of a rare combination of malignancies, bilateral dysgerminoma accompanied by unilateral granulosa cell tumor and acute lymphoblastic leukemia within the first year after adjuvant BEP chemotherapy during the remission period.

Case: We report a case of a 17-year-old female with a normal karyotype (46, XX), presenting with bilateral adnexal masses measuring up to 65 mm in diameter, containing germ cells bilaterally and sex cord components with granulosa cell tumor on the left side unilaterally. While she has been in remission for ten months after adjuvant chemotherapy following surgery, she was diagnosed with acute lymphoblastic leukemia.

Conclusion: Close and careful follow-up is additionally important in patients who have received BEP chemotherapy for gonadal tumors.

Keywords: Bilateral dysgerminoma, granulosa cell tumour, B-cell acute lymphoblastic leukemia, synchronous tumors

Geliş Tarihi: 15/09/2020 Kabul Tarihi: 13/01/2021

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Introduction

Dysgerminomas are the most common malignant germ cell tumor, accounting for approximately 30–40% of all ovarian malignancies of germ cell origin (1) and dysgerminoma is the only germ cell tumor in which the opposite ovary is frequently involved with the tumor process (10%–15% of cases). As dysgerminomas grow rapidly, and often are characterized by subacute pelvic pain related to capsular distention, hemorrhage, or necrosis(2), about 80% of cases are diagnosed at stage I. Granulosa cell tumors (GCTs) comprise 5% of all ovarian malignancies, but account for approximately 70% of malignant sex cord stromal tumours and peak incidence for these tumors occurs during the perimenopausal decade. Adult-type GCTs account for 95% of all granulosa cell tumors. As the adult-type GCTs are low-grade malignancies with a propensity to remain localized and demonstrate indolent growth, ninety percent are stage I at diagnosis (3).

Because the toxicity of BEP chemotherapy (cisplatin, etoposide, bleomycin) has been well documented, most feared late complication of etoposide is the development of secondary leukemia. As risk–benefit analyses have concluded that etoposide-containing chemotherapy regimens are beneficial in advanced germ cell tumors, one case of treatment-induced leukemia would be expected for every 20 additionally cured patients who receive BEP as compared with PVB (cisplatin, vinblastine and bleomycin) (4).

We report a case of 17 year-old female with a normal karyotype (46,XX), presenting with bilateral adnexal masses measuring up to 65 mm in diameter, con¬taining germ cells bilaterally and sex cord compo¬nents with granulosa cell tumor on the left side unilaterally. While she has been in remission for ten months after adjuvan BEP chemotherapy following surgery, she was diagnosed with acute lymphoblastic leukemia.

Case

A 17 year-old girl admitted to our hospital for menstrual irregularity. After detailed examinations, transrectal ultrasonography and magnetic resonance imaging revealed bilateral ovarian solid masses (59 x 65 mm on left, 42 x 47 mm on right). Laboratory finding revealed abnormal tumor markers (LDH: 3653 IU/L, hCG: 59 IU/L). Her karyotype analysis was normal (46, XX). Explorative laparatomy revealed bilateral ovarian tumors with minimal ascites in the pelvis. Malignant signs were found on frozen section, therefore she underwent right parsial oopherectomy, left ovarian wedge resection, pelvik and paraortic lymphadenectomy, omentectomy and peri¬toneal biopsy sampling. Gross examination showed that both masses were capsulated and its outer surface was nodular with dilated congested blood vessels. The cut sections were solid, pale yellow coloured and containing transparent thick material. The histopathological report was bilateral dysgerminoma with unilateral adult-type GCT and adjacent small islet of annular tubules also at left side. Capsule invasion was observed in some areas of tumoral masses by dysgerminoma, which was characterized by aggregates, islands, or strands of large uniform cells surrounded by varying amounts of connective tissue stroma containing minimal lymphocytes, in addition there were vascular invasions, high mitosis number and necrosis. Adult-type GCT exhibited microfollicular pattern and typical features with 10 to 12 mitotic figures per 10 high-power fields which had oval, pale, and grooved nuclei with mild nuclear atypia. No tumor was seen in specimens other than ovarian masses (stage IC' for dysgerminoma and stage 1A for GTC). Three weeks after surgery, she was started on chemotherapy treatment with bleomycin (30,000 IU IV, day1, day8, day15), etoposide (100 mg/m² IV day1- day5) and cisplatin (20 mg/m² IV day1- day5) every three weeks for three cycles (five day BEP regimen). While she has been in remission for ten months after the completion of chemotherapy, she was admitted to our hospital complaining of lassitude and headache. after detailed examination, she was diagnosed with (CALLA negative) B-cell acute lymphoblastic leukemia. In first complete remission treated with a frontline BFM protocol, allogeneic transplantation was performed from HLA 10/10 compatible unrelated donor following 18 Gy cranial radiotherapy. The patient has been in remission for both diseases for more than one year.

Discussion

Dysgerminomas, represent only 1–3% of all ovarian cancers, but represent as many as 5–10% of ovarian cancers in patients younger than 20 years of age and 10–15% of the cases are bilateral. Approximately 5% of dysgerminomas occur in phenotypic females with abnormal gonads. In patients whose contralateral ovary has been preserved, a dysgerminoma can develop in 5–10% of them over the next two years. The treatment is primarily surgical, including resection of the primary lesion and limited staging (5).

On the other hand, granulosa cell tumor is the most common malignant sex cord-stromal tumor. There are two types of granulosa cell tumor; adult-type that occurs mainly in peri and postmenopausal women and juvenile-type that occurs mainly in children. Granulosa cell tumors are usually stage I at diagnosis but may recur 5 to 30 years after initial diagnosis. In the reproductive age group, most patients have menstrual

irregularities or secondary amenorrhea (6). Unilateral salpingo-oophorectomy is appropriate therapy for stage IA tumors in children or in women of reproductive age (7).

According to third WHO classification, both gonadoblastoma and mixed germ cell-sex cord stromal tumor (MGC-SCST) are composed of germ cells and sex cord elements that are closely admixed (8). As the coexistence of both malignant germ cell and sex cord stromal tumors is very rare; in the last 50 years, a few well-documented cases have been described in the literature. MGC-SCSTs occur in patients who are phenotypically, anatomically and genetically normal, whereas most of the gonadoblastomas occur in dysgenetic gonads in patients with a Y chromosome (9). Gonadoblastoma itself is clinically benign, however, an invasive malignant germ cell component frequently develops. If gonadoblastomas are left in situ in patients with gonadal dysgenesis, more than 50% will subsequently develop ovarian malignancies (10). Approximately 10% of MGC-SCSTs have malignant germ cell components, (11) MGC-SCST cases almost always occur in the first decade of life, while the number of cases observed in postmenarchal period and adulthood is less than ten in the literature (12-15)

When the literature is reviewed, all cases with MGC-SCST having malignant germ cell compo¬nents have been unilateral (16), however, there are only two cases which MGC-SCST was bilateral. In our case, there were bilateral dysgerminoma and unilateral adult-type GCT adjacent to small islet of annular tubules on the left ovary of 17 year-old postmenarchal young woman with normal karyotype (46,XX) who was admitted to hospital due to amenorrhea. Interestingly, histopathological evaluation of the left ovary revealed that dysgerminoma and adult-type GCT were existed as two different tumoral structures which are not related to each other, unlike MGC-SCST and gonadoblastoma which are composed of germ cells and sex cord elements that are closely admixed. Although she had a bilateral ovarian tumor, conservative surgery was performed because she was 17 year-old girl, uterus and normal appearing ovarian tissues were left behind, following less than one year after adjuvant chemotherapy, she was diagnosed with acute lymphoblastic leukemia.

An important cause of late morbidity and mortality in patients receiving chemotherapy for germ cell tumors is the development of secondary tumors (17). Etoposide in particular has been implicated in the development of treatment-related leukemias. The prognosis of etoposide-related secondary leukemia is extremely worse than that of spontaneously occurring leukemias (18). Generally, leukemias following etoposide treatment are likely to occur within three years after treatments, and the mean latency period from drug administration to the onset of secondary leukemia is about two years (19). The chance of developing treatment-related leukemia following etoposide is dose related. The incidence of leukemia is approximately 0.4–0.5% (representing a 30-fold increased likelihood) in patients receiving a cumulative etoposide dose of less than 2,000 mg/m² (20) compared with as much as 5% (representing a 336-fold increased likelihood) in those receiving more than 2,000 mg/m² (21). In a typical three or four cycle course of BEP, patients receive a cumulative etoposide dose of 1,500 or 2,000 mg/m2, respectively. Furthermore, additional factors influence the risk of etoposide-related (secondary) leukemia, such as concomitant radiotherapy or high doses of other chemotherapeutics, including platinum (22).

In our case, the patient was treated with etoposide 100 mg/m² for five days per cycle after surgery, therefore she received etoposide dose of 1,500 mg/m² cumulatively with low dose cisplatin (300 mg/m² totally), unexpectedly leukemia has developed within the first year following BEP chemotherapy in contrast to the knowledge and experience in the literature

In summary, we present a case of a rare combination of malignancies, bilateral dysgerminoma accompanied by unilateral granulosa cell tumor and acute lymphoblastic leukemia within the first year after adjuvant BEP chemotherapy during remission period. Although, proper first-line treatment is critical, close and careful follow-up is additionally important in patients who have received BEP chemotherapy for gonadal tumors. As the cumulative risk of a second cancer is 1% in 10 years following diagnosis of primary, long-term follow-up of patients received etoposide-based chemotherapy is particularly vital in detection of treatment-related leukemias.

References

1. Krege S, Beyer J, Souchon R, et al. European consensus conference on diagnosis and treatment of germ cell cancer: A report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): Part I. Eur Urol. 2008; 53: 478–496.
2. Zhang M, Jiang W, Li G, Xu C. Ovarian masses in children and adolescents - an analysis of 521 clinical cases. J Pediatr Adolesc Gynecol. 2014 Jun; 27(3): e73-7.
3. Chen VW, Ruiz B, Killeen J, et al. Pathology and classification of ovarian tumors. Cancer. 2003; 97(suppl. 10):2631–2642.
4. Chaudhary UB, Haldas JR. Long-term complications of chemotherapy for germ cell tumours. Drugs. 2003;63:1565– 1577.

5. Berek JS, Friedlander ML, Hacker NF. Germ Cell and Nonepithelial Ovarian Cancer. In: Berek & Hacker's Gynecologic Oncology. Sixth edition, 2015, Wolters Kluwer, Philadelphia, USA. Chapter 12, pp 828-9.
6. Boyce EA, Costaggini I, Vitonis A, et al. The epidemiology of ovarian granulosa cell tumors: A case-control study. Gynecol Oncol. 2009;115:221–225.
7. Zanagnolo V, Pasinetti B, Sartori E. Clinical review of 63 cases of sex cord stromal tumors. Eur J Gynaecol Oncol. 2004;25(4):431-8.
8. Roth LM, Cheng L. On the histogenesis of mixed germ cell-sex cord stromal tumour of the gonads. J Clin Pathol. 2017 Mar; 70 (3): 222-227.
9. Jacobsen GK, Talerman A (Eds.) In: Atlas of germ cell tumours. Munksgaard, Copenhagen; 1989.
10. Bremer GL, Land JA, Tiebosch A, et al. Five different histologic subtypes of germ cell malignancies in an XY female. Gynecol Oncol. 1993;50:247–248.
11. Prat J, Noglales FF, Cao D. Germ cell-sex cord-stromal tumors. In: Kurman RJ, Carcangiu ML, Herrington S, Yong RH, editors. Who Classific¬aion of Tumours of Female Reproductive Or¬gans. Lyon: IARC; 2014. pp. 67-8.
12. Talerman A, Russell V. Mixed germ cell-sex cord-stromal tumor. In: Kurman RJ, editor. Blaustin's Pathology of the Female Genital Tract. New York: Springer; 2013. pp. 897-901.
13. Arroyo JG, Harris W, Laden SA. Recurrent mixed germ cell-sex cord-stromal tumor of the ovary in an adult. Int J Gynecol Pathol 1998; 17: 281-3.
14. Jacobsen GK, Braendstrup O, Talerman A. Bi¬lateral mixed germ cell sex-cord stroma tumour in a young adult woman. Case report. APMIS Suppl 1991; 23: 132-7.
15. Shujie Pang, Lin Zhang, Yiquan Shi, Yixin Liu. Unclassified mixed germ cell-sex cord-stromal tumor with multiple malignant cellular elements in a young woman: a case report and review of the literature. Int J Clin Exp Pathol 2014;7(8):5259-5266
16. Talerman A, Roth LM. Recent Advances in the Pathology and Classification of Gonadal Neoplasms Composed of Germ Cells and Sex Cord Derivatives. Int J Gynecol Pathol. 2007 Jul;26(3):313-21.
17. Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: An intergroup study. J Pediatr Surg. 2004;39(3):424–429.
18. Pui, C.H. Epipodophyllotoxin-related acute myeloid leukaemia. Lancet 1991, 338.
19. Ezoe S. Secondary Leukemia Associated with the Anti-Cancer Agent, Etoposide, a Topoisomerase II Inhibitor. Int. J. Environ. Res. Public Health 2012, 9, 2444-2453;
20. Schneider DT, Hilgenfeld E, Schwabe D, et al. Acute myelogenous leukemia after treatment for malignant germ cell tumors in children. J Clin Oncol. 1999;17:3226–3233.
21. Kollmannsberger C, Beyer J, Droz JP, et al. Secondary leukemia following high cumulative doses of etoposide in patients treated for advanced germ cell tumors. J Clin Oncol. 1998;16:3386–3391.
22. Houck, W.; Abonour, R.; Vance, G.; Einhorn, L.H. Secondary leukemias in refractory germ cell tumor patients undergoing autologous stem-cell transplantation using high-dose etoposide. J. Clin. Oncol. 2004, 22, 2155–2158.