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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

Adult-type granulosa cell tumor with splenic metastasis: a rare case

Dalak metastazı gösteren erişkin tip granuloza hücreli tümör: nadir bir olgu

Selma Erdoğan Düzcü[1], Nur Tunç[1], Çetin Boran[1]

[1]Bolu Abant İzzet Baysal University Department of Pathology, Bolu, Turkey

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To the Editor,

Granulosa cell tumors are rare malignant tumors defined by Rokitansky in 1855 and consist 2-3% of all ovarian tumors[1]. Incidence rate is 0.5-1.5/100.000 cases per year[2]. Characteristically it grows very slowly yet metastasizes years later after the curative tratment [1]. The mean age is 50 years but it can be seen at any age after the menopause and patients admit to the clinics with complaints of uterine bleeding, pain and symptoms secondary to pressure[2,3]. A case with splenic metastasis after three years of the diagnosis of adult-type granulosa cell tumor on the left ovary is presented as it's a rare case.

A 71-year-old woman admits to the obstetrics and gynecology clinic with the complaints of abdominal pain and distention goes under hysterectomy and bilateral salpingo-oophorectomy after a mass in her left ovary is detected. Previously the patient was diagnosed with diabetes mellitus, hypertension and had the history of cholecystectomy, repair of umblical hernia and cystocele. No history of alcohol or tobacco use. In her family history, her mother was diagnosed with uterine carcinoma. Left ovary had a 35x35x30 cm mass consisting cystic and hemorrhagic fields. Microscopy of the mass consisted of cells with oval round coffee-bean-shaped clefted nuclei and narrow eosinophilic cytoplasm (Figure 1). Tumor cells had macrofollicular and trabecular pattern. Frequent mitosis and necrosis were seen. In immunohistochemistry staining tumor cells were CD56 positive and EMA, SMA negative (Figure 2). The case was diagnosed with adult-type granulosa cell tumor.

Follow-up abdominal computed tomography scan showed a 9x13x17 cm exophitic cystic mass with the solid components from posterior of the spleen to the inferior and suggested to be a complex cystic lesion and were not clear whether it was a metastasis or hematoma. After three years from the removal of the primary tumor, total splenectomy material and biopsy of the mesenteric root were sent to the Pathology department.

Macroscopic examination showed 20x17x11 cm tumor mass with necrosis, hematoma and cysts attached to the 16x9x7 cm splenic tissue (Figure 3). Microscopic examination revealed tumoral tissue making the fibrous margin with the spleen and consists cells of oval round hyperchromatic nuclei and narrow pale eosinophilic cytoplasm. Nuclear clefting in tumor cells was prominent (Figure 4). Tumor had the mixture of macrofollicular, microfollicular and trabecular pattern. Also necrotic areas and atypical mitosis have been seen. Lymphovascular invasion was prominent. In immunohistochemistry staining tumor cells were positive with vimentin and calretinin, focal positive with CD99. Ki-67 proliferation index was approximately 40%. Case reported as adult-type granulosa cell tumor with splenic metastasis. Tumor infiltration was seen in the mesenteric root as well.

Granulosa cells, the precursor of granulosa cell tumor, are sex steroid-producing cells originate from coelomic and mesenchimal precursors[4]. Granulosa cell tumors have low risk of malignancy, however, 25-30 percent of them can carry the risk of being late recurrent[3]. The latest recurrent case report was 40

Yazışma Adresi/Address for Correspondence: Dr. Nur Tunç, Bolu Abant İzzet Baysal University Department of Pathology, Bolu, Turkey E-mail: tncnur@gmail.com
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years later[4]. The survival rate for 10 years is 75-90%[2]. Once recurrent, tumor becomes 80% fatal. Most common recurrency is located in the intraabdominal cavity probably related with the missed peritoneal disease[4].

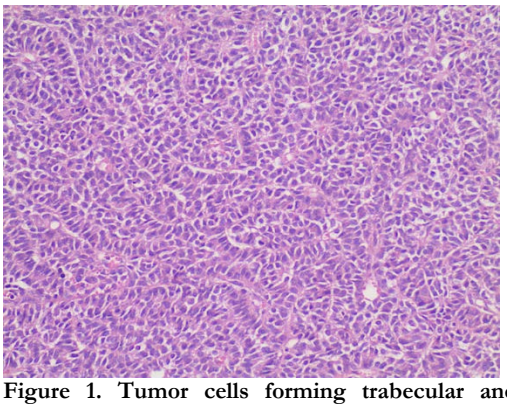

Figure 1. Tumor cells forming trabecular and follicular structures, HEX200

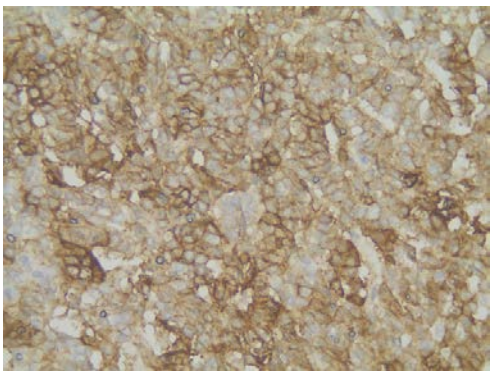

Figure 2. Diffuse positive staining with CD56, X400

Figure 3. Macroscopic view of tumor showing splenic metastasis

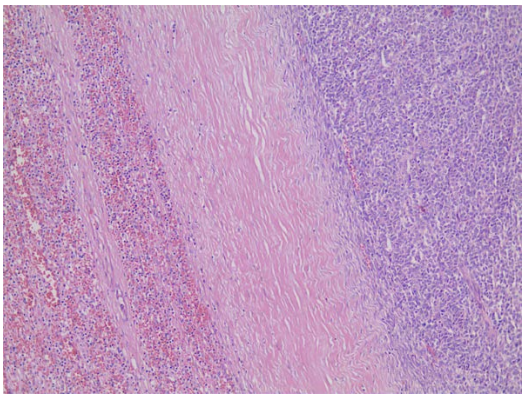

Figure 4. Tumor tissue separated from the spleen tissue with fibrotic border, HEX100

Hyperestrogenism in granulosa cell tumor is related with the estrogen, antimullerian hormone and inhibin-B production[5]. Since the tumor secretes hormones, patients with the tumor can admit with the complaints of menorrhagia, metrorrhagia and post-menopausal bleeding[2]. Simple hyperplasia of endometrium, atypical hyperplasia or endometrial cancer can be seen[6].

Granulosa cell tumor is histologically divided into two subtypes as adult and juvenile granulosa cell tumors. Of these, adult granulosa cell tumor is more common[5]. Usually has a better prognosis than epithelial ovarian tumors. Unlike epithelial tumors, 81% of cases are detected at an early stage [4]. 95% of granulosa cell tumors are unilateral and stage 1[6].

Trisomy 12, monosomy 22 and chromosome 6 deletion may be seen in granulosa cell tumors. In addition, somatic missence mutation in the FOXL2 gene, which is involved in the development of normal granulosa cells, has been reported in most cases. 17b-estradiol, inhibin, anti-mullerian hormone, follicle regulatory protein secretion may be helpful in early diagnosis and recurrence of the disease[4].

Granulosa cell tumor is frequently seen > 10 cm in size[4]. Microscopic examination shows granulosa cells as well as theca cells and fibroblasts[6]. Granulosa cell tumors consist of cells with oval (coffee-bean-like) nuclei. Well-differentiated tumors form microfollicular, macrofollicular, trabecular, insular, tubular structures[4]. The characteristic features of granulosa cell tumor are Call-Exner bodies, which are rosette-like structures formed by eosinophilic material around cells that look like microfollicular structures[3,6]. It shows zigzag (gyriform), diffuse and

corrugated parallel pattern in slightly differentiated tumors. Nuclear atypia and frequent mitosis are common in undifferentiated tumors[4]. Immunohistochemically positive staining is seen with CD56, CD99, inhibin-α, calretinin and S100[3]. Immunohistochemical expression of GATA-4 has been shown to be associated with stage and recurrence[4]. The main treatment protocol is hysterectomy and bilateral salpingo-oopherectomy in the early stages, debulking surgery in advanced or recurrent disease[5]. Advanced adjuvant treatment protocols and radiotherapy in selected cases can be applied [2]. In this case, debulking surgery was performed.

In a retrospective study of 31 granulosa cell tumor cases by Dridi et al., 32% recurrence rate was found. The most common recurrence was in the pelvis with 6 cases and recurrence in liver and abdominal lymph nodes were also seen[5]. Chew et al. reported a case of splenic metastasis 29 years after the treatment of a right ovarian granulosa cell tumor[1]. Ulamec et al. reported granulosa cell tumor metastasis to the spleen 15 years after primary ovarian tumor[7].

Yu et al. reported a granulosa cell tumor metastasizing to the liver 27 years after the initial diagnosis in a 62-year-old female patient[3]. Fujita et al. reported a patient with a diagnosis of granulosa cell tumor in the left ovary, metastasizing to the liver and right ovary 25 years later, with widespread malignant ascites in the abdomen. It had cystic areas as in our case. Although this case is defined primarily as liver cystadenocarcinoma after imaging studies, its pathological diagnosis has been reported as granulosa cell tumor. The rate of metastasis to the liver has been reported to be less than 5-6%[8].

Klair et al. diagnosed as metastasis in the pathology of polypoid lesions detected during endoscopy in a 60-year-old patient with granulosa cell tumor[9]. Sehouli et al. followed a study of 65 granulosa cell tumor cases diagnosed in 10 years and found tumor recurrence in 18 cases. 5.3% of these cases were supradiaphragmatic, 42.1% were exrapelvic-abdominal, 42.1% were pelvic, 5.3% were inguinal. In this study, disease recurrence mean was 69 months[2]. The previous cases that make intraperitoneal metastasis are summarized in Table-1.

Table 1. Similar case reports from literature

	Year	Age	Location	Tumor Size	Stage	Metastasis	Location of Metastasis	Metastasis Size
Chew et al.	2003	61	Right ovary	12cm	Stage Ic	After 29 years	Spleen, pelvis	12,5 cm
Ulamec et al.	2012	64	Ovary			After 15 years	Spleen	8 cm
Yu et al.	2015	62	Ovary		Stage I	After 27 years	Liver	25 cm
Fujita et al.	2015	43	Left ovary			After 25 years	Liver	10 cm
Klair et al	2018	60	Ovary		Stage I	After 2 years	Stomach	
Our case	2019	71	Left ovary	35 cm		After 3 years	Spleen	20 cm

Granulosa cell tumor metastasis is very rare and often shows local recurrence with peritoneal spread[7]. Most recurrences occur within the first 10 years after the initial diagnosis (median 4-5 years)[9]. Although the most important prognostic factor is stage, the relationship between tumor rupture, tumor mitosis rate and tumor recurrence with poor prognosis has been reported[8,9]. Being younger than 40 years, tumor size greater than 10-15 cm, high mitosis rate and presence of lymphovascular invasion are also considered as poor prognostic factors[6]. The most common site of metastasis is pelvis and lower abdomen, and rare metastasis of lung, brain, bone, diaphragm, abdominal wall and adrenal gland have been reported[9].

Although granulosa cell tumor is the most common ovarian stromal tumor, it is rare. The stage of the tumor is the most important prognostic factor. Since it is a tumor that recurred after many years, clinical and tumor markers follow-up is important in the follow-up of the disease. Although metastasis is often located in the pelvis, it should be kept in mind during the differential diagnosis since it can rarely metastasize to different organs.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SED, NT, ÇB; Veri toplama: SED, NT, ÇB; Veri analizi ve yorumlama: SED, NT; Yazı taslağı: SED. NT; İçeriğin eleştirel incelenmesi: SED, NT, ÇB; Son onay ve sorumluluk: SED, NT, ÇB; Teknik ve malzeme desteği: SED, NT, ÇB; Süpervizyon: SED, NT, ÇB; Fon sağlama (mevcut ise): yok.
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