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Sarcomatous transformations causing early recurrence in malignant mixed germ cell tumor: from case to analysis

Malign miks germ hücreli tümörde erken nükse neden olan sarkomatöz dönüşümler: Vakadan analize

Zehra O. BASARIR[1], Mustafa SAHİN[2], Tufan ARSLANCA[1]

[1]Department of Gynecologic Oncology, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Gynecologic Oncology, Konya City Hospital, Konya, Türkiye

ABSTRACT

Aim: Our aim is to analyze the malignant mixed germ cell tumors of the ovary that recur due to sarcomatous transformation in the literature, with a case report.

Materials and Methods: An electronic database search was conducted from January 1980 to January 2023 using PubMed/MEDLINE. We evaluated the 10 cases included in these articles together with our own case. Patient age (years), first surgery type, tumor types, adjuvant therapy type, recurrence time, recurrent tumor types, and recurrence site were analyzed.

Results: We evaluated 11 cases, including our own. The mean age of the 11 patients was 27.36±16.39 years. Nine patients (81.8%) had rhabdomyosarcoma differentiated areas in primary pathology. Ten patients (90.1%) received adjuvant chemotherapy. The mean recurrence time was 10±8.94 months, ranging from 2 to 24 months. Reported areas of recurrence included retroperitoneal, peritoneal, pelvic, scapula, aortic bifurcation, abdominal cavity, and mediastinal area.

Discussion: We compiled ten cases in the literature with rhabdomyosarcoma transformation, including our case. Although the prognosis of GCT depends on the clinical stage and location, the presence of a sarcomatous area in GCT is a factor indicating a more aggressive behavior. Diagnostic imaging, including PET-CT scans, can be used for staging recurrent lesions and demonstrating local lymphatic metastasis or lung metastasis, which may indicate sarcomatous differentiation.

Conclusion: In patients with sarcomatous differentiation, the choice of chemotherapy may vary according to this component. It is important to determine the presence of the sarcomatous component in malignant germ cell tumors with detailed pathological examination. Close follow-up with radiological means is crucial to detect early recurrence and distant metastases as a result of sarcomatous transformation, as in our case.

Keywords: Mixed germ cell tumors, ovarian mass during pregnancy, sarcomatous transformation

ÖZ

Amaç: Amacımız literatürde sarkomatöz transformasyona bağlı olarak tekrarlayan overin malign mikst germ hücreli tümörlerini bir olgu sunumu eşliğinde incelemektir.

Gereç ve Yöntemler: PubMed/MEDLINE kullanılarak Ocak 1980'den Ocak 2023'e kadar elektronik veri tabanı araştırması yapıldı. Bu yazılarda yer alan 10 olguyu kendi olgumuzla birlikte değerlendirdik. Hasta yaşı (yıl), ilk ameliyat tipi, tümör tipleri, adjuvan tedavi tipi, nüks zamanı, nüks tümör tipleri ve nüks bölgesi analiz edildi.

Bulgular: Kendi vakamız da dahil 11 vakayı değerlendirdik. 11 hastanın yaş ortalaması 27,36±16,39 yıldı. Dokuz hastada (%81,8) primer patolojide rabdomiyosarkomun farklılaştığı alanlar vardı. On hasta (%90,1) adjuvan kemoterapi aldı. Ortalama nüks süresi 10±8,94 ay olup 2 ile 24 ay arasında değişmektedir. Bildirilen nüks alanları arasında retroperitoneal, peritoneal, pelvik, skapula, aort bifürkasyonu, karın boşluğu ve mediastinal alan yer alıyordu.

Tartışma: Literatürde rabdomiyosarkom dönüşümü olan 10 olguyu, bizim olgumuz da dahil olmak üzere derledik. GCT'nin prognozu klinik evreye ve lokasyona bağlı olmakla birlikte, GCT'de sarkomatöz alanın varlığı daha agresif davranışı gösteren bir faktördür. PET-CT taramaları da dahil olmak üzere tanısal görüntüleme, tekrarlayan lezyonları evrelemek ve sarkomatöz farklılaşmayı gösterebilecek lokal lenfatik metastazı veya akciğer metastazını göstermek için kullanılabilir.

Sonuç: Sarkomatöz farklılaşma olan hastalarda kemoterapi seçimi bu bileşene göre değişiklik gösterebilmektedir. Malign germ hücreli tümörlerde sarkomatöz bileşenin varlığının ayrıntılı patolojik inceleme ile belirlenmesi önemlidir. Bizim olgumuzda olduğu gibi sarkomatöz dönüşüm sonucu ortaya çıkan nükslerin ve uzak metastazların erken tespiti açısından radyolojik yöntemlerle yakın takip çok önemlidir.

Anahtar Kelimeler: Mikst germ hücreli tümörler, gebelikte over kitlesi, sarkomatöz transformasyon

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Sorumlu Yazar/Corresponding Author: Mustafa SAHIN, Department of Gynecologic Oncology, Konya City Hospital, Konya, Türkiye
E-mail: bmustafasahin1163@gmail.com

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INTRODUCTION

Malignant ovarian germ cell tumors (OGCTs) are rare ovarian cancers that comprise less than 5% of all ovarian tumors (1,2). The mixed form of malignant OGCT includes more than one pathological component, most commonly combinations of dysgerminoma, endodermal sinus tumor, and immature teratoma (3). In contrast with more common epithelial ovarian cancers, they usually occur in younger women of childbearing age, grow rapidly, and therefore become symptomatic earlier (4). They may also occur during pregnancy, which may cause obstetrical complications (2,5). These tumors are usually chemosensitive, and prompt diagnosis with multimodal management may improve both prognosis and fertility (4,5).

Mixed malignant OGCTs may undergo sarcomatous transformation extremely rarely. This transformation can alter the oncological behavior, potentially causing recurrences and negatively affecting prognosis (6,7,8). These tumors have a variable prognosis depending on the type of sarcomatous differentiation and stage. Sarcomatous areas may cause early metastasis, indicating a poor prognosis. Early diagnosis, prompt treatment, and close follow-up of early metastasis play a critical role in management. We aimed to present our case as a very rare example of sarcomatous differentiation into rhabdomyosarcoma in a mixed malignant germ cell tumor of the ovary and to review the literature.

MATERIALS AND METHODS

Ethics committee approval was received from Ankara Bilkent City Hospital Medical research scientific and ethical review board for this study (TABED 1-25-961). Written informed consent was obtained from the patient for publication of this case report and accompanying images. Data regarding the patients were obtained from our hospital's electronic database system and patient files.

Literature Review: A systematic review of the medical literature was performed to identify articles. An electronic database search was conducted from January 1980 to January 2024 using PubMed/MEDLINE. The search terms included "Malignant Mixed Germ Cell Tumor", "Sarcomatous Transformation", "adnexal mass", "lung cancer", "ovarian cancer", "medical subject headings" (MeSH), or "keywords". At the end of the search, 10 articles were eligible for further analysis. We evaluated the 11 cases included in these articles together with our own case. Patient age (years), first surgery type, tumor types, adjuvant therapy type, recurrence time, recurrent tumor types, and recurrence site were analyzed.

Case Presentation: A 20-year-old primigravid woman was referred to our center after detection of a 150x100 mm heterogeneous mass during an ultrasonographic control of her 34-week, 3-day pregnancy. She had no history of myoma or adnexal mass prior to pregnancy. Tumor markers were cancer antigen 125 (CA125): 50 U/mL, CA19.9: 33 U/mL, CA15.3: 33 U/mL, carcinoembryonic antigen (CEA): <0.5 ng/mL, Alpha-fetoprotein (AFP): 5448.5 µg/L.

A detailed transabdominal ultrasound was performed and showed a single fetus and a 100x104x117 mm heterogeneous mass located in the lower segment of the uterus, filling the Douglas pouch. Magnetic resonance imaging (MRI) on T1-weighted images showed the lesion was multilocular cystic in nature, compressing the cervix anteriorly and the rectosigmoid colon posteriorly (Figure 1).

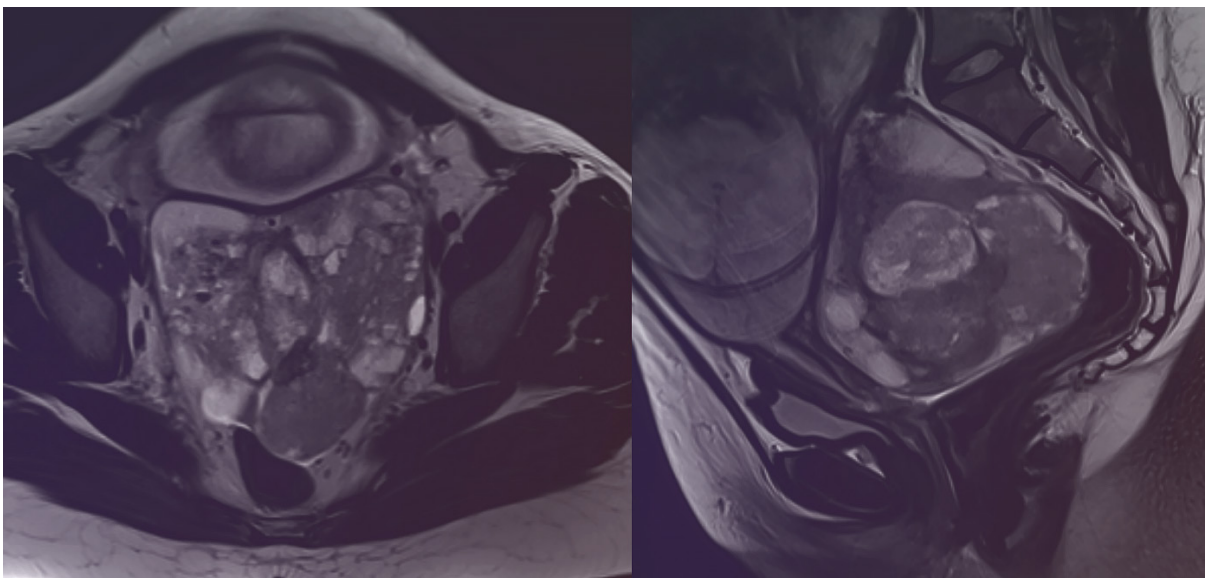
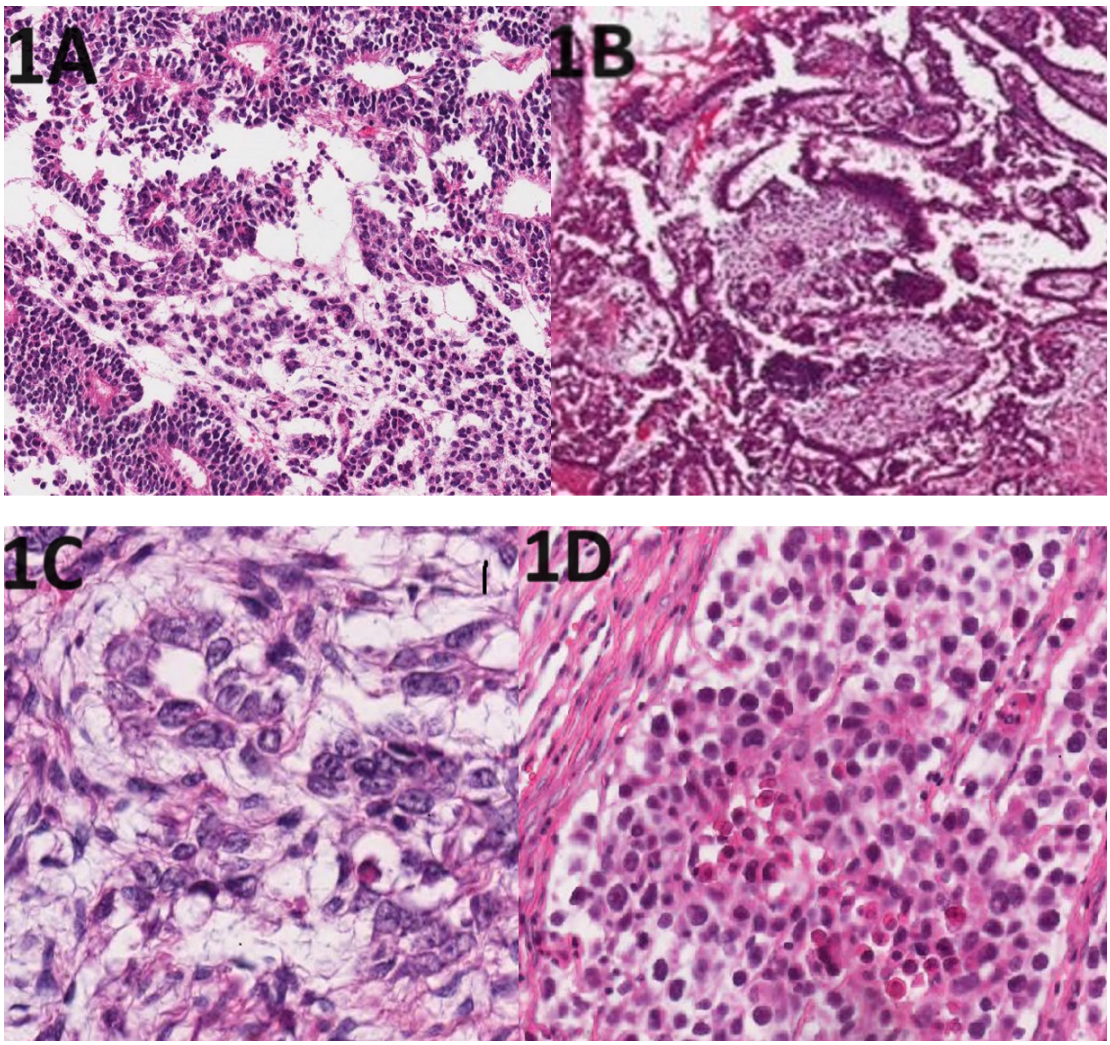


Figure 1. Non-contrast pelvic diffusion magnetic resonance imaging (MRI) on T1-weighed images, the lesion was multilocular cystic nature, and compressing the cervix anteriorly and the rectosigmoid colon posteriorly.

She underwent cesarean section at term and subsequent abdominal cytology. Mass resection and unilateral salpingo-oophorectomy were performed. There were no palpable lymph nodes in the pelvic and paraaortic areas. The appendix was microscopically normal. No implants were found on the surface of the diaphragm, bladder, or mesothelium of the colon and intestine. Frozen sections were reported as immature cystic teratoma, and multiple biopsies were taken from the omentum and peritoneum. Pathologically, the mass was diagnosed as a mixed malignant germ cell tumor of the ovary. Macroscopically, the left ovary measured 25×27×8 cm and weighed 3980 grams. Microscopically, the tumor was composed of 65% mature teratoma, 15% embryonal carcinoma, 10% yolk sac tumor, and 10% dysgerminoma. Immunohistochemical studies showed diffuse positivity for OCT3/4 and D2-40 in dysgerminoma areas, focal staining for AFP in yolk sac tumor areas, and OCT3/4 in embryonal carcinoma areas. Trophoblastic cells within embryonal carcinoma were stained for B-HCG. CD-34 was positive in vessel walls and some components of teratoma. CD30 and glypican-3 couldn't be evaluated for technical reasons (Images 1A, 1B, 1C, 1D).

The patient then received chemotherapy consisting of 3 cycles of BEP (bleomycin, etoposide, and cisplatin).

Radiological examination after three months of additional chemotherapy demonstrated disease progression as increased size of pelvic mass on abdominal CT up to 87x75x80 mm, increased number of pelvic lymph nodes, increased FDG uptake on PET scan (SUV max 18.95), and a newly formed 36x20 mm anterior mediastinal mass (Figure 2). Blood tests were total hCG: <2 mIU/mL, CEA: 1.2 ng/mL, CA 125: 31 U/mL, CA15.3: 15 U/mL, CA19.9: <1.3 U/mL, AFP: <1.3 µg/L.



Images 1. 1A. Photomicrograph (Haemotoxyline and Eosin, original magnification ×200) of immature teratoma shows presence surrounding primitive mesenchyme. **1B**. Yolk sac tumor tissue immunohistochemically positive for alpha fetoprotein. **1C**. Embryonal carcinoma component (large pleomorphic cells with cytologic atypia). **1D**. Dysgerminoma component in tumor tissues (Centrally located, round to oval nuclei, often with angulated, squared off borders with granular or coarse chromatin).

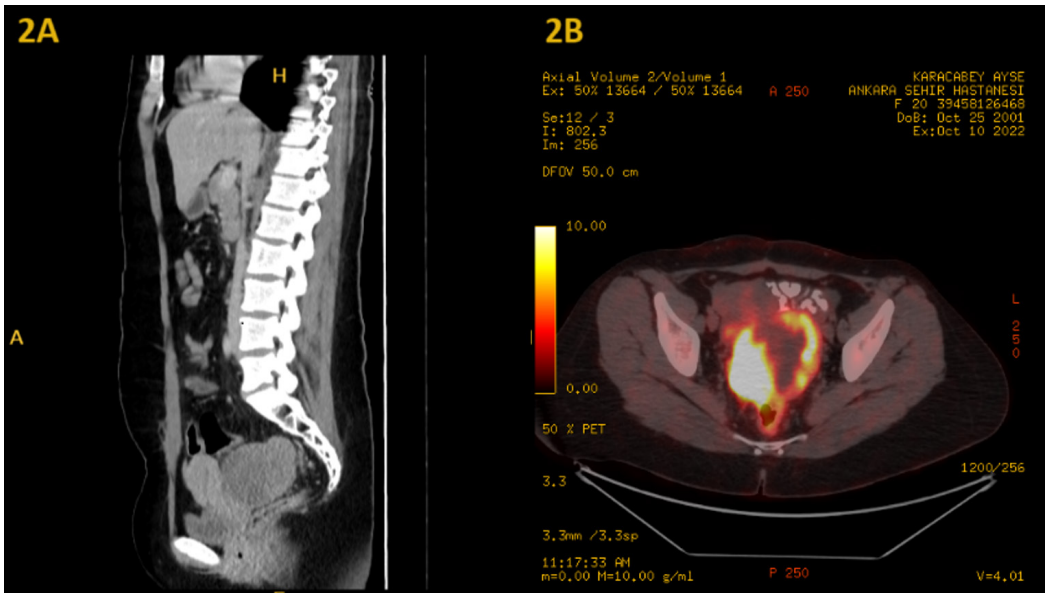
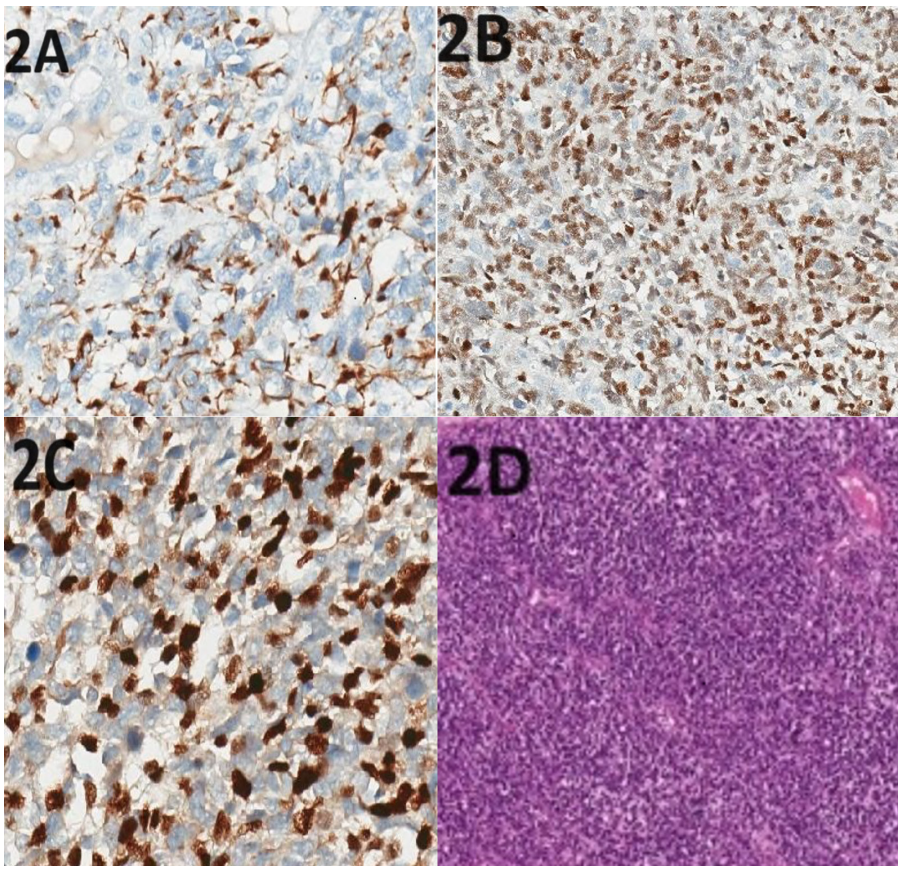


Figure 2. Postcontrast abdominal CT and PET images of pelvic recurrens after 3 months. 2A. Abdominal CT: As size of recurrence pelvic mass up to 87x75x80 mm, increased number of pelvic lymph nodes. 2B. PET scan: İncreased FDG uptake on (SUV max 18.95) and newly formed 36x20 mm anterior mediastinal mass.

She underwent second-look laparotomy (SLL). A solid fixed mass of 90x75x85 mm was detected in the left adnexal region. Along with excision of the mass, total abdominal hysterectomy, right unilateral salpingo-oophorectomy, low rectal anastomosis, total omentectomy, and pelvic and para-aortic lymph node dissection were performed. Frozen analysis was reported as malignant germ cell tumor.

Detailed pathological examination revealed rhabdomyosarcoma (RMS) metastasis with reactive lymph nodes. Immunohistochemical staining showed myoD1, myogenin, desmin, WT1, vimentin, p16, and CD56 positivity in tumor tissue (Images 2A, 2B, 2C, 2D). The tumor was negative for SMA, calretinin, GFAP, CD117, LCA, HMB45, MelanA, CK8/18, panCK, EMA, DOG1, CD34, betaHCG, glypican, OCT3/4, CK7, CK20, CD30, AFP, D2-40, PAX8, CD99, chromogranin, and synaptophysin.



Images 2. 2A. Desmin positivity in tumor cells. **2B**. myoD1 positivity in tumor cells. **2C**. Myogenin positivity in tumor cells. **2D**. Abundant acidophilic cytoplasm with small pleomorphic spindle cells with hyperchromatic nuclei in slightly myxoid matrix (H&E X40) Rhabdomyosarcoma differentiation.

Table 1. Sarcomatous transformation in ovarian germ cell tumors

Ref. no	Case	Age	First surgery	Tumor types	Adjuvant therapy	Recurrence time	Recurrent tumor	Recurrence site
13.	Malagon et al.	25	Oophorectomy	MT, IT, ***RMS***	Chemotherapy	24 months	RMS	Retroperitoneal
13.	Malagon et al.	25	Oophorectomy	MT, IT, D, ***RMS***	Chemotherapy	21 months	IT, RMS	Peritoneal
14.	Yanai et al.	6	Oophorectomy	IT, ***RMS***	VAC	10 months	RMS	Pelvic
15.	Ergeneli et al.	44	Staging	MCT, ***RMS***	CI	2 months	RMS	Scapula
16.	Kabukcuoglu et al.	23	Right SO	IT, D, YS, ***RMS***	VAC	NR	NR	FR
17.	Amada et al.	33	BSO	IT	VAC	5 months	RMS	Aortic bifurcation
18.	Al-Jumaily et al.	12	Right SO	MCT, ***RMS***, YS, EC, CC	BEP, VAC	NR	None	DFS (36 months)
19.	Kefeli et al.	65	BSO, omentectomy	MCT, ***RMS***, SC	Platinum based	NR	None	Follow-up 3 months
20.	Haj Salah et al.	15	Left cystectomy	IT, YS, ***RMS***	NR	NR	NR	NR
21.	Kawaı et al.	33	Right SO	IT, ***RMS***	FAMT	5 months	RMS	Abdominal cavity
	Present case	20	Left SO	MCT, EC, YC, D	BEP	3 months	RMS	Pelvic, mediastinal

SO:Salpingoopherectomy; BSO: Bilateral salpingoophorectomy; MCT:Mature cystic teratoma; EC:Embryonal carcinoma; YS:Yolk sac; D:Dysgerminoma; IT: Immature teratoma; RMS:Rhabdomyosarcoma; SC:Squmaous carcinoma; CC: Choriocarcinoma; BEP: Bleomycin, Etoposide, Cisplatin; VAC:Vincristine, Actinomycin, Cyclophosphamide; FAMT: 5-Fluorouracil (5 FU) Cyclophosphamide, Mitomycin C, Chromomycin A; CI: Cisplatin, Ifosfamide; FR: Follow Refuse; DFS: Disease Free Survive; NR: Not reported

She was referred to medical oncology for further chemotherapy. She received 4 cycles of vincristine, actinomycin, and cyclophosphamide. At the latest follow-up at 24 months, she had no evidence of disease on PET-CT scan and abdominal ultrasound.

RESULTS

The pathologies of a total of 10 patients in the literature were evaluated. We assessed 11 cases, including our own case (Table 1). The mean age of the 11 patients was 27.36±16.39 years, with ages ranging between 6 and 65 years. Cystectomy, oophorectomy, salpingo-oophorectomy, and staging surgery were performed on the patients. Nine patients (81.8%) had rhabdomyosarcoma differentiated areas in primary pathology. Two patients (18.2%) did not have rhabdomyosarcoma differentiated areas in primary pathology. Ten patients (90.1%) received adjuvant chemotherapy, while one patient's adjuvant therapy status was not reported. The mean recurrence time was 10±8.94 years, ranging from 2 to 24 years. Reported areas of recurrence included retroperitoneal, peritoneal, pelvic, scapula, aortic bifurcation, abdominal cavity, and mediastinal area.

DISCUSSION

Malignant germ cell tumors are usually seen in the reproductive period, and their coexistence with pregnancy is more common (5). The rapid growth tendency of these lesions usually results in large masses that become symptomatic at an earlier stage, as seen in our patient. Mixed morphology is rarely observed (<1%), and the combination of histological subtypes determines the clinical behavior (9). Normal fetal outcome and long-term survival of the patient are the main goals of the treatment plan, which includes fertility-sparing surgery and adjuvant chemotherapy.

Diagnosis in the presence of mixed morphology is not straightforward due to the presence of various cell types. Immunochemistry usually contributes to the correct diagnosis, together with serum markers whenever possible (10). Histologically, dysgerminoma and endodermal sinus tumor are the most common subtypes of malignant mixed germ cell tumors (9,11). In our patient, dysgerminoma was accompanied by mature teratoma, embryonal carcinoma, and yolk sac tumor. Combined chemotherapy and surgery may achieve survival rates above 90% and protect reproductive potential (5,12,13). Our patient underwent conservative surgery (USO) together with chemotherapy, as in most of the reported cases (13-15). Surgical staging in our patient was performed due to the ongoing pregnancy, and all tissue biopsies obtained from the omentum and adjacent tissues were negative.

These heterogeneous tumors have the capacity to progress to higher or lower grades of differentiation, and sarcomatous differentiation of pathological subcomponents may result in a more aggressive clinical course with early recurrence and distant metastasis (3,16). Laboratory tests may be silent at the time of recurrence due to the

undifferentiated nature of RMS (13,21). Most of the reported cases had sarcomatous differentiation in their recurrent lesions, as seen in our case (Table 1). There were six recurrences in ten reported patients with RMS and mixed malignant germ cell tumors (13-18). In five of them, sarcomatous areas were detected in primary resection (13-16,21). Only Amada et al. reported a recurrent RMS without a sarcomatous nidus, similar to our patient. Early recurrence within six months was also similar to our patient (four months) (17). Normal levels of serum markers in our patient were also accepted as an indication of malignant transformation. Diagnostic imaging, including PET-CT scans, can be used for staging recurrent lesions and demonstrating local lymphatic metastasis or lung metastasis, which may indicate sarcomatous differentiation, as seen in our case.

Although conservative treatment with preservation of fertility may be achieved in ovarian malignant mixed germ cell tumors, more aggressive surgery and chemotherapy adapted to the new sarcoma diagnosis are vital elements of disease management after transformation (5,22-23). We suggest that close radiological follow-up, in the presence of normal blood tests, and a new chemotherapy regimen considering the RMS component, were responsible for the disease control obtained for more than two years despite early recurrence.

Our case demonstrates both the difficulties of obtaining the correct diagnosis and treatment of malignancy during pregnancy and the necessity for close follow-up in mixed malignant germ cell tumors of the ovary.

CONCLUSION

Although the prognosis of GCT depends on the clinical stage and location, the presence of a sarcomatous area in GCT is a factor indicating a more aggressive behavior. In patients with sarcomatous differentiation, the choice of chemotherapy may vary according to this component. It is important to determine the presence of the sarcomatous component in malignant germ cell tumors with detailed pathological examination. Additionally, close follow-up with radiological means is crucial to detect early recurrence and distant metastases as a result of sarcomatous transformation, as in our case.

Conflict of Interest
The authors have no conflicts of interest to disclose.

Funding Source
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