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REVIEW/DERLEME

Infiltrative Type Mucinous Ovarian Cancer Diagnosed During Pregnancy, A Case Report and Literature Review

Gebelikte Teşhis Edilen İnfiltratif Tip Müsinöz Tip Yumurtalık Kanseri, Vaka Raporu Ve Litertür Derlemesi

Celal Akdemir[1], Ali Onur Arzık[1], Zeliha Öcal[2], İlayda Gercik Arzık[3], Şimal Çoban[4], Özlem Özdemir[5], Ayhan Gül[1], Muzaffer Sancı[6]

[1] Izmir City Hospital, Department Of Gynecologic Oncology, Izmir, Türkiye
[2] Tepecik Education and Research Hospital, Department of Gynecology And Obstetric, Izmir, Türkiye
[3] Izmir City Hospital, Department of Perinatology, Izmir, Türkiye
[4] Izmir City Hospital, Department of Pathology Izmir, Türkiye
[4] Izmir City Hospital, Department of Medical Oncology Izmir, Türkiye
[5] University of Health Sciences İzmir, Faculty of Medicine, İzmir, Türkiye

ABSTRACT

The incidence of ovarian malignancies during pregnancy is rare and is estimated to be approximately 1:10,000 to 1:50,000 in pregnant women. In this case report, we present a rare case of infiltrative type mucinous ovarian cancer in pregnancy. A 38-year-old patient, who was referred to our clinic with the diagnosis of adnexal mass in the 12th gestational week, underwent right oophorectomy and was diagnosed with infiltrative mucinous ovarian cancer on pathology, was offered an individual treatment plan considering the available literature and her own expectations. Termination of pregnancy and cytoreductive surgery were recommended to the patient.

Keywords: Pregnancy, Ovarian Cancer, Mucinous Ovarian Cancer

ÖZET

Gebelik sırasında yumurtalık malignitelerinin görülmesi nadirdir ve gebe kadınlarda yaklaşık 1:10.000 ila 1:50.000 oranında görüldüğü tahmin edilmektedir. Bu olgu sunumunda literatürde ender görülen gebelikte saptağımız infiltratif tip müsinöz over kanseri olgusunu sunuyoruz. 38 yaşında, 12. gebelik haftasında adneksiyal kitle tanısıyla kliniğimize sevk edilen, sağ ooferektomi uygulanan ve patoloji sonucunda infiltratif tip müsinöz over kanseri teşhisi konulan hastaya mevcut literatür ve kendi beklentileri dikkate alınarak bireysel tedavi planı sunuldu. Hastaya gebeliğinin sonlandırılması ve sitoredüktif cerrahi yapılması önerildi.

Anahtar Kelimler: Gebelik, Yumurtalık Kanseri, Müsinöz Tip Yumurtalık Kanseri

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Correspondence: Celal Akdemir, Izmir City Hospital, Department Of Gynecologic Oncology, Izmir, Türkiyee. E-mail: akdemircelal@gmail.com

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INTRODUCTION

The incidence of adnexal masses in pregnancy has been reported to range from 0.15 to 5.7%, with the majority of cases being benign (1). The occurrence of ovarian malignancies during pregnancy is exceedingly uncommon, with an estimated frequency of 1:10,000 to 1:50,000. (2).The majority of these tumors are histopathologically classified as germ cell tumors, while there have been reports of epithelial ovarian malignancies occurring in pregnant women at a rate of 1:12,000 to 1:50,000 (3).

Given that the majority of data pertaining to the diagnosis and treatment of ovarian carcinoma during pregnancy is derived from retrospective studies and case reports in the literature, the subsequent follow-up process remains unclear(4).

In the case of adnexal masses observed during pregnancy, surgical intervention may be indicated if the mass is deemed to have the potential for rupture or torsion, or if the mass is classified as malignant.

Patients with significant early-stage malignant disease should be treated surgically, and the patient should have a final staging according to the pathology or frozen histopathology report. During pregnancy, staging procedures may include infracolic omentectomy, appendectomy, pelvic-peritoneal biopsies, and lymph node dissection, in addition to other procedures as indicated. In cases of advanced epithelial ovarian cancer, termination of pregnancy should be considered when diagnosed in the first half of pregnancy. Biopsy or adnexectomy should be performed in patients who express a desire to maintain pregnancy, followed by platinum-based chemotherapy. In these cases, residual chemotherapy during pregnancy and cytoreductive surgery should be planned after delivery, as surgery to define the disease cannot be performed (5).

In this case report, we aimed to present a case of mucinous ovarian carcinoma with infiltrative stromal invasion pattern detected during pregnancy and to share our experience with this rare disease diagnosed during pregnancy.

CASE PRESENTATION

A 38-year-old patient with a history of three previous cesarean deliveries was referred to our institution with a diagnosis of an adnexal mass in pregnancy at 12 weeks of gestation. It was determined that the adnexal mass was initially identified at the sixth gestational week, and the patient was subsequently referred to our facility due to abdominal distension and discomfort during follow-up. On ultrasound examination, a fetus with a positive fetal heartbeat was observed in the uterine cavity, which was 11+6 weeks old according to CRL (crown-rump length) measurement. No evidence of fetal malformation was identified. Additionally, ultrasound imaging revealed a dense cystic lesion with internal echogenicity measuring approximately 25 cm, presumed to originate from the right ovary and occupy the pelvic region. (Image 1) Laboratory analysis of the patient's blood parameters indicated elevated levels of CA125 (11.3 U/mL), CA19-9 (14.7 U/mL), and CEA (0.9 µg/L).

The mass is suspicious for malignancy in the non-contrast magnetic resonance image of the patient under evaluation. The patient, who described symptomatic pain, underwent right oophorectomy at the 14th week under spinal-epidural anesthesia with mini laparotomy without disruption of cyst integrity. Following the frozen pathology report, which indicated borderline mucinous carcinoma, omentum

biopsy and multiple peritoneal biopsies were obtained. Intraoperatively, pelvic and paraaortic lymph nodes were found to be normal.

No postoperative fetomaternal complications were observed

The final pathology of the patient was reported as mucinous carcinoma with intact capsule, no neoplastic cells on the surface and infiltrative invasion pattern with the tumor limited to a single ovary. Figo (The International Federation of Gynecology and Obstetrics) Stage 1A CK7(+), CK20 focal (+), CDX2(+), p16(-), PAX8(-) (Image 3)

For the evaluation of the gastrointestinal system, the patient underwent endoscopy and colonoscopy during the postoperative period, both of which were reported as normal. The case was discussed in a multidisciplinary meeting involving gynecologic oncology, perinatology, and medical oncology. The patient was provided with detailed information regarding the potential poor prognosis and risks associated with the aggressive course of the infiltrative subtype. Current literature was reviewed and personalized according to the patient's expectations, leading to the recommendation for termination of the pregnancy followed by cytoreductive surgery. The patient accepted this option, and termination was performed at 19 weeks of gestation. Approximately four weeks post-termination, the patient underwent cytoreductive surgery, which included hysterectomy, left unilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissection, infracolic omentectomy, and appendectomy. During the operation, the lymph nodes in the para-aortic region were found to be fixed and bulky. The lymph node dissection in this area was performed in collaboration with the cardiovascular surgery department. (Image 4) In the final pathology report, carcinoma metastasis was observed in the omentum and para-aortic lymph nodes (14/15). The patient, who underwent maximal cytoreduction, was recommended for adjuvant chemotherapy.

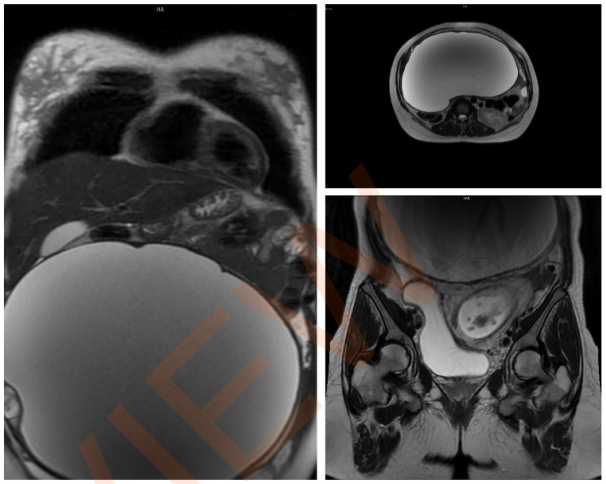

Figure 1. Preoperative Magnetic Resonance İmaging (MRI) Evaluation

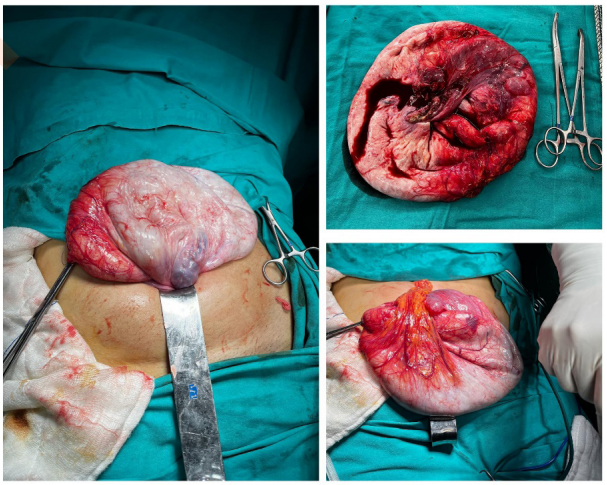

Figure 2. Appearance Of The Mass During The Operation

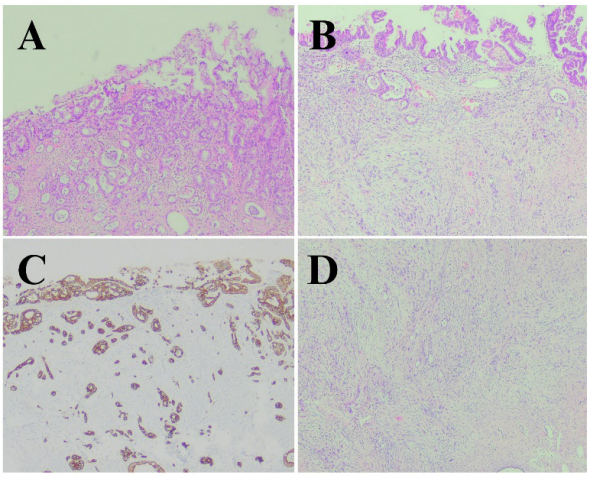

Figure 3. Postoperative Pathological Evaluation 3A: Infiltrated Glandular Structures Under Well-Differentiated Mucinous Areas 3B: Infiltrative Pattern Starting Right Under The Surface. 3C: Tumor Cells And The Pattern İs More Evident With The Cytokeratin 7 İmmunohistochemistry 3D: Destructive Stromal İnvasion

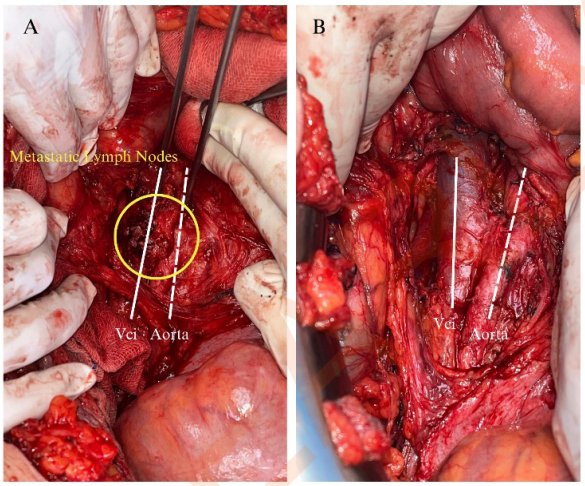

Figure 4.Before And After Bulky Lymph Node Dissection İn The Paraaortic Region

DISCUSSION

The therapeutic management of adnexal masses in pregnant women is complicated by the necessity of assessing both maternal and fetal well-being simultaneously. The diagnosis of ovarian cancer during pregnancy presents a number of challenging dilemmas. Ovarian cancer represents the second most prevalent gynecological malignancy diagnosed during pregnancy, preceded only by cervical cancer.[5]

Its occurrence during pregnancy is infrequent, with estimates indicating a frequency of approximately 1 in 10,000 to 1 in 50,000 pregnancies.[2] Malignant ovarian tumors are more frequently reported in primigravidas, and the majority are diagnosed at an early stage through routine ultrasound examinations.

Given its high sensitivity in characterizing the morphology of adnexal masses, ultrasound is the optimal diagnostic tool during pregnancy. Specific ultrasonographic findings may be indicative of the differentiation between benign and malignant lesions. Malignant lesions often present with specific ultrasound features, including thick or irregular septations, mural nodules, solid or papillary components, and increased vascularity. While ultrasound provides sufficient information regarding the risk of malignancy in masses during pregnancy, magnetic resonance imaging (MRI) can serve as a useful secondary imaging modality for characterizing large masses, gastrointestinal-related conditions, and tubo-ovarian abscesses. Magnetic resonance imaging (MRI) examinations can be safely performed in pregnant patients during the second and third trimesters. Furthermore, they can be utilized to assess extragonadal spread in cases of potential malignancy (6).

Tumor marker levels are useful for distinguishing between benign and malignant tumors. CA-125 is secreted by 80-90% of epithelial ovarian tumors. However, in pregnancy, it is widely accepted that tumor markers do not contribute to the diagnosis because of their physiological increase. Inhibin, HCG, and α-fetoprotein may be elevated in the context of germ cell, sex cord stromal ovarian tumors or fetal abnormalities

(7).

Minimally invasive surgery or open laparotomy are acceptable surgical approaches in pregnant women with adnexal masses. It is imperative to avoid cyst rupture during surgical resection. The objective of mass resection operations in which pregnancy is preserved is to alleviate maternal symptoms and to provide a pathological diagnosis.

In 2014, the World Health Organization (WHO) defined mucinous ovarian cancers according to the growth pattern. The WHO subdivided these cancers into two categories: the expansile subtype and the infiltrative subtype (8). Expansile invasion in comparison to mucinous carcinomas, mucinous carcinomas with infiltrative invasion are more frequently identified in advanced stages and are associated with a poorer prognosis. Expansile-invading mucinous carcinomas exhibit clinical behavior similar to that of mucinous borderline tumors. In contrast, infiltrative mucinous carcinomas are associated with a highly aggressive clinical course and increased mortality. The infiltrative subtype is closely associated with higher rates of recurrence, peritoneal spread, and lymph node involvement (9,10,11).

Mucinous ovarian carcinomas are usually detected at an early stage; 83% are detected at stage I, while 17% are diagnosed at stage II or advanced stages (12).

Current management of all epithelial ovarian cancers, including mucinous ovarian cancers, is surgical staging for early disease and cytoreductive surgery followed by platinum-based chemotherapy for advanced disease. The most commonly used regimen for mucinous ovarian carcinomas is the combination of carboplatin and paclitaxel, which is the standard protocol for all epithelial ovarian cancers. Mucinous ovarian carcinomas have been shown to be less responsive to platinum-based chemotherapy compared to other subtypes of epithelial ovarian carcinoma (13).

Although adjuvant chemotherapy has been demonstrated to reduce the risk of recurrence in early-stage serous carcinomas, the benefit of chemotherapy in early-stage mucinous cancers remains uncertain. In a retrospective study by Nasioudis et al. on the efficacy of chemotherapy in early-stage mucinous carcinomas, no significant difference was observed in survival rates between patients who received chemotherapy and those who did not, when the cancers were classified as Stage 1A/1B or 1C. The researchers concluded that the option of adjuvant chemotherapy should be considered on an individual basis and discussed with patients, given the current lack of evidence (14). While the majority of mucinous ovarian cancers diagnosed at an early stage have a favorable prognosis following surgical intervention, patients with advanced mucinous ovarian carcinoma exhibit exceedingly low survival rates. This may be attributed to the absence of efficacious standard chemotherapy protocols, the intrinsic resistance of the cancer to conventional platinum-based chemotherapy, and the histologic and mutational differences from other epithelial ovarian cancers (15). In a meta-analysis comprising data from seven different studies, it was found that the risk of mortality in patients with advanced-stage mucinous ovarian carcinoma is more than twice that of patients with serous epithelial ovarian carcinoma (16).

Mucinous ovarian carcinomas can often be morphologically confused with other metastatic tumors, particularly gastrointestinal adenocarcinomas. Several clinical algorithms

based on the size and laterality of the lesions have recently been found to be sensitive in predicting the primary origin of mucinous ovarian carcinomas. In patients aged 20 to 40, unilateral large masses (>10 cm) have been identified as significant indicators of mucinous ovarian carcinoma(17).

Immunohistochemistry and genomic profiling are utilized to differentiate mucinous ovarian carcinomas from other mucinous adenocarcinomas. The typical immunohistochemical profile of primary mucinous ovarian carcinomas is characterized by CK 7 expression, with variable positivity for CK 20, CDX2, ER, and PgR. Conversely, PAX8, WT1, and SATB2 are typically negative. Immunohistochemical analysis of the our patient's tissue samples revealed positive staining for CK7, CK20, CDX2, and negative staining for PAX8 and p16.

Due to the similar pathological and molecular characteristics of mucinous ovarian carcinomas and gastrointestinal tumors, retrospective studies have found that patients with mucinous ovarian carcinoma benefit from empirical gastrointestinal chemotherapy regimens (18). A randomized study (mEOC/GOG 0241) comparing the combination of capecitabine and oxaliplatin to that of carboplatin and paclitaxel exists in the literature regarding the treatment of mucinous ovarian carcinomas. Although the study was terminated early due to the rarity of mucinous ovarian cancers, the data obtained from the enrolled patients did not show a statistically significant difference in progression-free survival and toxicity profiles between the treatment arms (19).

The reasons for the refractoriness of traditional platinum-based chemotherapy regimens in mucinous ovarian cancers remain uncertain due to the rarity of the disease and the lack of comprehensive studies.

In early-stage expansile mucinous carcinomas, peritoneal staging combined with fertility-sparing surgery that preserves the uterus and contralateral ovary is considered an acceptable approach. However, in infiltrative mucinous carcinomas, lymph node metastasis has been reported in 17% to 30% of cases, even in early stages (20).

The safety of chemotherapy during pregnancy depends on gestational age, mechanism of action, and dosage. Exposure to chemotherapy during the first trimester increases the risk of significant malformations, miscarriage, and fetal loss. During the first trimester, exposure can lead to teratogenic effects, including cardiac defects and neural tube defects, among various organ malformations (21).

The second and third trimesters are crucial for fetal organ maturation, neurological development, and fetal growth(22). Exposure to chemotherapy during these periods has been associated with intrauterine growth restriction and preterm birth. Data on the long-term effects of intrauterine chemotherapy exposure remain insufficient (23).

Mucinous ovarian cancers diagnosed during pregnancy are reported to be quite rare in the literature(24,25,26). In a case report from 2012, a patient diagnosed with FIGO Stage IA mucinous ovarian carcinoma underwent unilateral salpingo-oophorectomy at 6 weeks of gestation and wished to continue her pregnancy. At 39 weeks, she underwent metastasectomy and cesarean delivery due to a recurrence indicated by a 12 × 11 cm mass between the bladder and uterus. Following surgery, the patient received neoadjuvant chemotherapy and was subsequently diagnosed with FIGO Stage IIIC.

While the clinical course of the reported case shares similarities with that of our patient, our patient exhibited disease progression with omental and paraaortic lymph node metastases over a much shorter period (70 days) (FIGO Stage IA > FIGO Stage IIIB).

The treatment of mucinous ovarian carcinomas during pregnancy remains a significant challenge due to limited experience and knowledge, as well as concerns regarding fetal effects. Delaying the management of suspected malignant adnexal masses in pregnant women until after delivery may result in delays in treatment, disease progression, and subsequent worsening of maternal prognosis. While conservative treatment may be an acceptable option for early-stage ovarian carcinomas during pregnancy, the aggressive nature of infiltrative mucinous ovarian carcinomas necessitates the implementation of individualized treatment strategies tailored to the patient.

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