Medical and Research Publications
International Open Access

Case Report **Journal of MAR Case Reports (Volume 5 Issue 3)**

Metastatic Gastric Cancer Simulating a Primary Ovarian Cancer Presenting During Pregnancy. A Case Report

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Received Date: May 09, 2022

Published Date: June 01, 2022

Abstract

The most likely metastatic tumors mimicking primary ovarian tumors are those of the gastrointestinal, pancreatic, or biliary tract, and endocervical adenocarcinomas. The same state of pregnancy can mask its presentation secondary to obstruction by the gravid uterus, gastrointestinal symptoms typical of pregnancy such as nausea, vomiting and abdominal distension. We present a case of a 38-year-old patient diagnosed with stage IIIB endometrioid adenocarcinoma at 15 weeks of gestation. Treatment was started with chemotherapy and the pregnancy continued until 35.0 weeks due to data of fetal distress. Uterine atony occurs during the surgical procedure, so it was decided to perform an obstetric hysterectomy. During the procedure, a right adnexal mass is observed which was reported by pathology as endometroid carcinoma. At the end of the puerperium, she is readmitted to complement the surgical approach with laparoscopic ovarian cytoreductive surgery where metastatic intestinal-type adenocarcinoma was found and a gastric biopsy was performed of a vegetative lesion in the cardia reporting a poorly differentiated invasive adenocarcinoma in gastric mucosa, clinical stage IV. We rectified our diagnosis of ovarian cancer as Krukenberg tumor. We carry out a review of the literature on what has been reported so far on the treatment and prognosis of this rare disease and its presentation during pregnancy.

Keywords: *Krukenberg, chemotherapy, pregnancy, ovarian tumors.*

Abbreviations

FIGO; International Federation of Gynecology and Obstetrics,

IUGR; Intrauterine growth restriction,

CT; Computed Tomography,

MRI; Magnetic Resonance Imaging,

AFP; Alpha-Feto-Protein,

HCG; human chorionic gonadotrophin,

HE4; human epididymal protein 4.

Introduction

Cancer incidence linked with pregnancy goes around 0.02%-0.1%. **[**1**]** The most frequent types of cancer during pregnancy are breast cancer (40%), lymphoma (12%), and cervical cancer (10%). **[**2**]** Ovarian cancer stays up as the fifth most diagnosed malignancy during pregnancy even though it may be hard to diagnose, due to the physiologic changes associated with pregnancy, we must keep in mind the odds of malignancy in ovarian masses. **[**3**]**

Most of annexal masses during pregnancy are functional or benign and they are often an incidental finding in the ultrasound test when the patient goes to the prenatal care appointments. Ovarian tumor incidence comprehends between 2.4-5.5%, within this, approximately 5% of cases are malignant tumors. **[**4**]** Approximately 10-15% of these cases are presented as acute abdominal pain secondary to ovarian. torsion, being the this the most common and serious complication of ovarian tumors during pregnancy and usually occurs between 8-16 weeks of gestation. Tumor rupture is a rare complication.**[**5**]**

Due to the low incidence, the assessment and decision making in patients with cancer during pregnancy is complicated. In general terms, is preferred to give oncologic treatment instead of ending the pregnancy, because it has been demonstrated no improvement in the prognosis. **[**6**]** Nevertheless, many experts refuse to treat an oncologic patient who choose to continue with the pregnancy because of the potential toxicity of chemotherapy. The physician must individualize the management according to the patient, if she wants to keep with the pregnancy, the gestational age, the pathologic report, and the clinical stage.**[**7**]**

In all the cases they must have a multidisciplinary treatment given by an obstetrician, oncologic surgeon, clinical oncologist, and hematologist. Thus, giving the correct diagnosis is fundamental to treat the disease. It`s important to keep in mind that late diagnosis may affect the psychological and social environment between the baby and the mother. We present a case of an invasive poorly differentiated adenocarcinoma in gastric mucosa metastatic to the ovary simulating a primary ovarian cancer.

Clinical case

A 38-year-old patient, gravida 2 abortion 1 (GIIAI) coursing her second pregnancy, with no other personal history of interest for the case. Her current condition began at 15 weeks of gestation with nausea, exacerbated and associated with acute abdominal pain. She attends to another hospital where left ovarian tumor with rupture data was diagnosed by pelvic ultrasound. An urgent exploratory laparotomy was practiced, they reported the presence of hemoperitoneum of approximately 1000 milliliters and decided to perform left oophorectomy which was sent to pathology with a histopathological report of moderately differentiated adenocarcinoma compatible with primary ovarian cancer.

She arrived at our institution for the first time at 17.3 weeks of gestation for review of pathology slides and establish management. Final diagnosis is established by pathology as endometrioid adenocarcinoma with squamous differentiation grade 3 (poorly differentiated) with necrosis of 5% of the tumor surface analyzed and focal lymphovascular invasion. The immunohistochemistry was reported positive for CK7 and negative for WT1, PAX8 and P53. A diagnosis of stage IIIB endometrioid adenocarcinoma with squamous differentiation of the left ovary was established according to the International Federation of Gynecology and Obstetrics (FIGO) classification.

During pregnancy she received 6 chemotherapy cycles with carboplatin and paclitaxel. Her pregnancy continues with no complications. Follow-up with growth curve and Doppler velocimetry is maintained until week 34.4 where fetal weight is reported in percentile 1 with Doppler velocimetry without alterations, for which it is diagnosed with intrauterine growth restriction (IUGR) type I. At 35.0 weeks of gestation, cardiotocographic monitoring was performed, observing data of fetal distress with recurrent and prolonged late decelerations, so it was decided to terminate the pregnancy and a caesarean section was performed.

Surgical procedure is started identifying friable tissues and with difficult differentiation of tissues until obtaining by Kerr-type caesarean section, a single live newborn weighing 1909 grams, with Apgar score 8/9 and Silverman 1. Next, uterine atony occurs with no response to conservative management and with data of hemorrhage infiltration in the myometrium, so we decided to perform a hysterectomy. Otherwise, a right ovarian mass of approximately 10 centimeters was identified, with a necrotic appearance and torsion of the ovarian pedicle (Fig. 1). We performed right oophorectomy and the tissue was sent to the pathology department for the definitive examination.

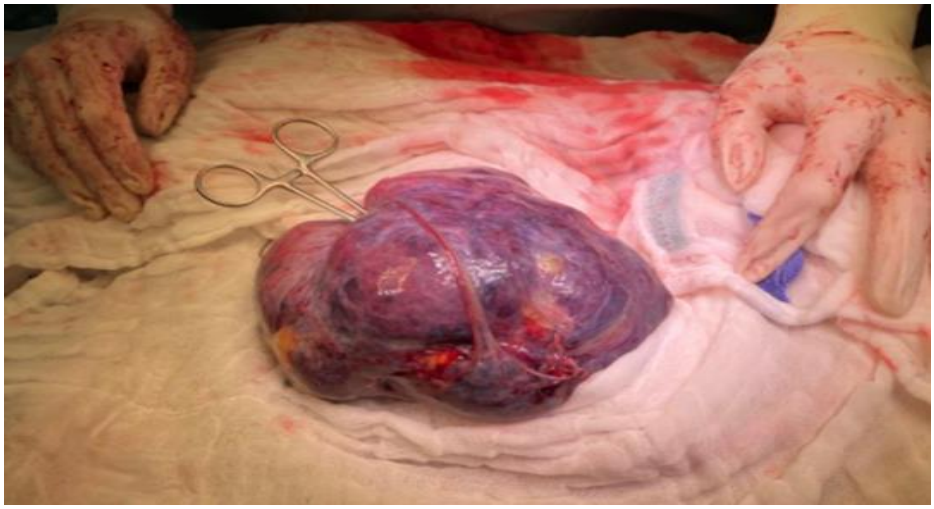

Figure 1: Right ovarian mass of approximately 10 centimeters, with a necrotic appearance and torsion of the ovarian pedicle.

The surgical procedure was ended 6 hours later. During the immediate postoperative period, the patient is admitted to the Critical Medicine service, where she remains under surveillance for approximately 48 hours with adequate clinical evolution and is discharged home after 4 days without incident. The histopathological study reported moderately differentiated endometrioid carcinoma with squamous differentiation of the right ovary, without capsular invasion, with lymphovascular invasion. The uterus was negative for neoplasia.

At the end of the puerperium, she was readmitted to complete the surgical approach with laparoscopic ovarian cytoreductive surgery. Peritoneal lavage was performed for cytological study, biopsy of peritoneal implants, appendectomy and omentectomy. The histopathological result of peritoneal lavage was positive for adenocarcinoma. Peritoneal biopsies report implants of moderately differentiated adenocarcinoma, cecal appendix with a focus of moderately differentiated adenocarcinoma, product of omentectomy with implant of moderately differentiated adenocarcinoma and two lymph nodes negative for neoplasia. According to the immunophenotype (CK7, CK20, CDX-2 positive) (Fig. 2) it is supported that they were metastatic focus of an intestinal-type adenocarcinoma, for which a gastric biopsy was performed by endoscopy, observing vegetating lesion in the cardias (Fig. 3), reporting poorly differentiated invasive adenocarcinoma invasive in gastric mucosa, clinical stage IV.

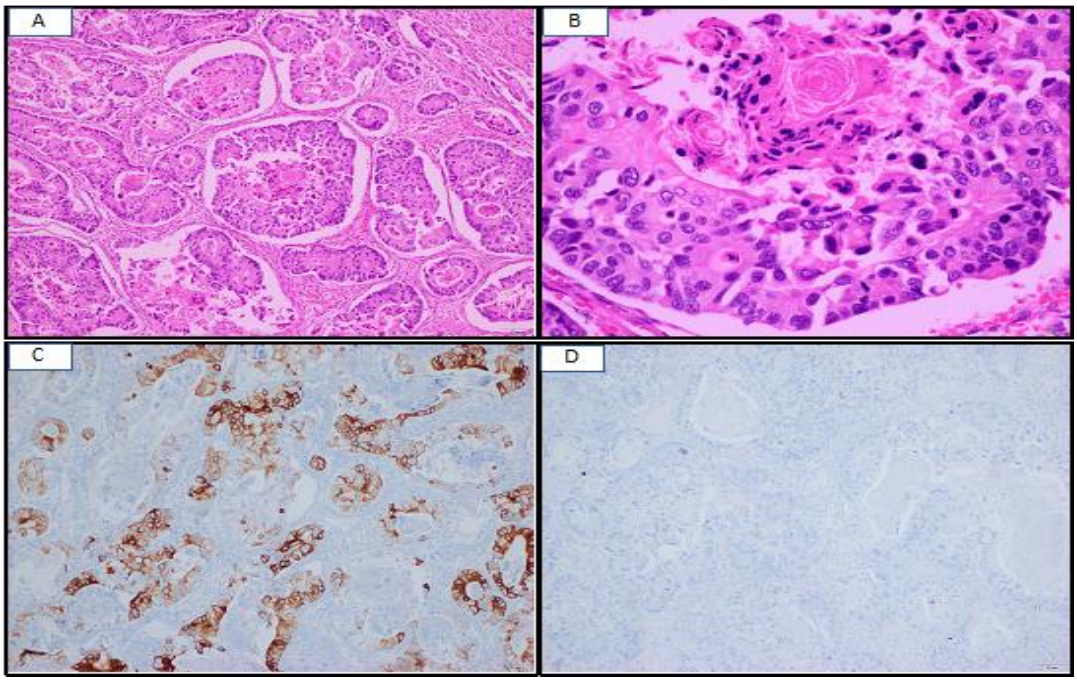

Figure 2: Histopathological results of right ovary (A) Hematoxylin and eosin stain 10x. (B) Hematoxylin and eosin stain 20x. (C) Positive focal immunohistochemistry for monoclonal antibody CK7 (D) Negative immunohistochemistry with monoclonal antibody PAX-8.

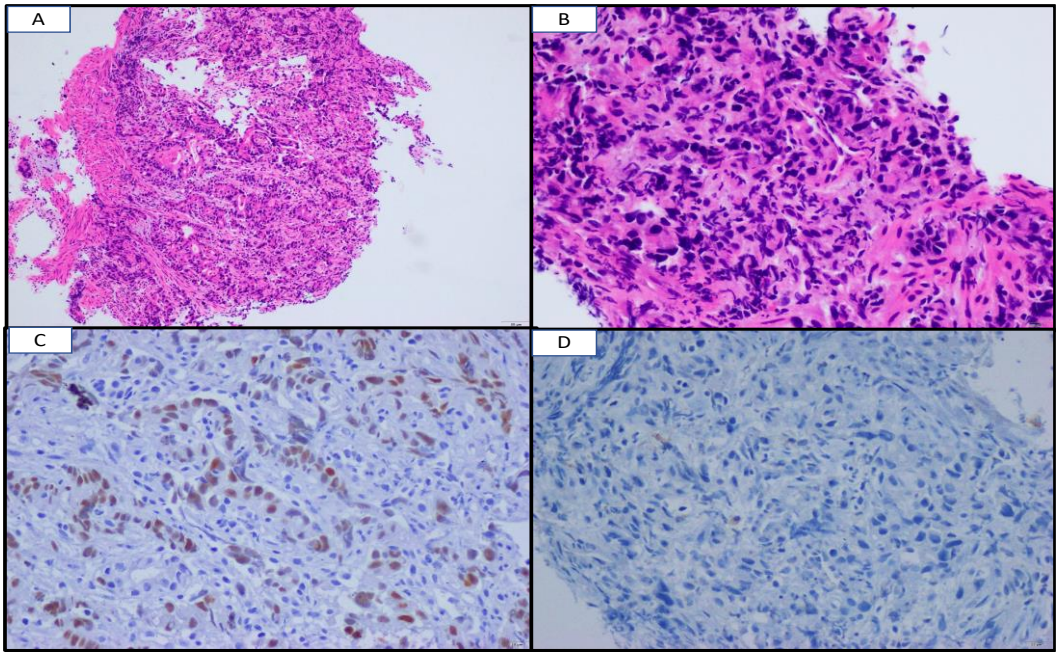

Figure 3: Tumoral gastric tissue. (A) Hematoxylin and eosin stain 10x. (B) Hematoxylin and eosin stain 10x. 20x. (C) Positive nuclear immunohistochemistry with monoclonal antibody for CDX-2. (D) Negative immunohistochemistry with monoclonal antibody MUC5 AC.

Discussion

Cancer cases diagnosed during pregnancy have been increasing because nowadays, women tend to postpone motherhood to older ages.8 Most women with ovarian cancer which complicates pregnancy want to maintain pregnancy and preserve fertility, a situation that is in turn encouraged by late childbearing and low birth rates.4 In the absence of large prospective and randomized studies or cohort studies, it is difficult to know how to manage these patients and to create reference standards for optimal management.

Most patients with ovarian cancer do not present specific symptoms or signs, making this entity difficult to diagnose early in pregnancy. Ultrasound is the study of choice for the evaluation of ovarian masses in pregnancy.**[**7**]** Computed tomography (CT) and magnetic resonance imaging (MRI) can be useful when ultrasound is inconclusive, however, it must be remembered that CT expose the fetus to radiation.6 MRI is useful in the differential diagnosis of benign and malignant tumors, as well, to help select patients who are candidates for surgical treatment. **[**1**]** The use of biochemical markers such as CA 125 are not useful since they are normally elevated in pregnancy **[**7**]**, as are other markers such as alpha-feto-protein (AFP) and human chorionic gonadotrophin (HCG) in the case of germ cell tumors, reserving its use for monitoring and evaluation of therapeutic response.

However, there are other markers such as human epididymal protein 4 (HE4), which does not rise physiologically in pregnancy and can be used for both diagnosis and monitoring of ovarian cancer.**[**6**]**

In general terms, oncological treatment is preferred over pregnancy termination or elective preterm birth, since pregnancy termination has not been shown to improve prognosis and prematurity can have a negative impact on neonatal development, not so exposure to chemotherapy. **[**3**]** In early stages, surgical treatment can be planned after 16 weeks of gestation and chemotherapy can be administered from the second trimester as would be normally indicated in non-pregnant patients. In advanced stages of the disease, when complete cytoreduction surgery is not possible, neoadjuvant chemotherapy should be administered. **[**7**]**

Administration of systemic therapy must follow certain guidelines, including the following:

(1) The medical oncologist must treat the mother and protect the fetus.

(2) The use of chemotherapy is not allowed in the period of organogenesis (first trimester) due to the high risk of miscarriage and congenital malformations.

(3) Chemotherapy can only be given in the second and third trimesters.

(4) Endocrine therapy should be avoided.

(5) Tyrosine kinase inhibitors or monoclonal antibodies are not recommended due to lack of evidence. **[**9,10**]**

Regarding surgical treatment, the management of an adnexal mass diagnosed during pregnancy creates a dilemma for gynecologists. It is difficult to discriminate malignant ovarian neoplasms from functional cysts or benign ovarian tumors. If an adnexal mass is larger than 6 cm, has a complex structure, ascites, or persists after 16 weeks of gestation, surgical management is critical to obtain a final histologic diagnosis and rule out malignancy. **[**11**]** This is recommended during the second trimester to decrease the risk of miscarriage, torsion, rupture, or late diagnosis of malignancy. **[**4**]** Once malignancy is confirmed, surgical staging of these curable entities is crucial to determine if adjuvant chemotherapy is required, especially in pregnant patients. The staging procedure is ideally recommended between 14-22 weeks of gestation **[**3**]** and includes wash cytology, ipsilateral salpingo-oophorectomy, peritoneal biopsies, and omentectomy. Examination of the fornix and pelvis is often suboptimal, due to limited uterine manipulations to avoid premature uterine contractions. **[**2**]**

The goal of ovarian cancer treatment during pregnancy is to achieve a better oncological prognosis while preserving fetal viability. **[**12**]** The reported risks associated with chemotherapy depend mainly on the gestational age and the dose of the antineoplastic agents used. **[**13**]** Administered during the second trimester may increase the risk of preterm premature rupture of membranes, intrauterine growth restriction and preterm delivery. Platinum therapy is recommended since it is not associated with

teratogenic effects and no differences in obstetric and neonatal outcomes have been observed with taxane-based treatment. [6] Thus, the first line of treatment for epithelial ovarian cancer during pregnancy consists of a combination of platinum derivatives and paclitaxel. It is important to mention that to avoid neonatal myelosuppression and maternal hematological toxicity, the last cycle of chemotherapy should be administered at least 3 weeks before birth. [7]

Even though at the beginning our patient was diagnosed and treated as an ovarian cancer, the histologic and immunohistochemical findings of the cytoreductive surgery strongly suggested a primary gastric tumor, strongly suggesting a Krukenberg tumor.

Krukenberg tumor, originally described in 1896, represents 1-2% of ovarian tumors. [14] This tumor during pregnancy is even rarer given that the incidence of gastric cancer in women of reproductive age is 0.4 – 0.5%. [14,15] Initially, it was described as a tumor originating from the ovarian stroma with mucoid degeneration and signet ring cells, however, this definition has been expanded to include all metastatic glandular carcinomas to the ovary from different sites. [16,17] These types of tumors are almost always metastases from a gastrointestinal primary [18], with gastric cancer being the most frequent primary origin (76%), followed by intestine (11%), breast (4%) and appendix (3%). [18,19]

There have been few cases reported with this condition and even fewer during pregnancy. Persistent gastrointestinal symptoms, as well as physiological and hormonal changes during pregnancy, tend to mask the presentation of a Krukenberg tumor, making its diagnosis a challenge for the physician. [4,14] The presence of "signet ring" cells indicates that the primary tumor is of gastrointestinal origin, however, although the presence of these cells was not reported in our case, positive immunohistochemistry for CK7 and CK20 (characteristic of gastropancreatobiliary origin) support Krukenberg's diagnosis. [14]

Something important to mention, is thar our patient had no risk factors for gastric cancer given her age (95% of gastric cancers occur in patients over 50 years of age), with no history of H. Pylori infection, and denied smoking. In addition, she did not present symptoms suggestive of gastric malignancy such as dysphagia, and her gastrointestinal symptoms were associated with what was expected during pregnancy. Despite undergoing multiple ultrasounds, no other abnormalities were detected until the time of cesarean section and cytoreductive surgery.

Previously in the literature, visualization of the ovaries during obstetric ultrasounds has been suggested in order to detect any alteration early. [1,14] Given that most patients undergo at least 2-3 ultrasounds during pregnancy, it could be a useful measure to implement in daily practice. Similarly, Jaspers et al.20 suggest performing a diagnostic endoscopy in patients with epigastric symptoms in the second trimester, especially associated with hemoptysis or weight loss. In general, maternal survival in cases of Krukenberg tumors is very poor, with 1-year, 2-year, and 5-year survival rates of 45.6%, 45.6%, and none after 5 years, respectively. [17]

The pregnancy was the major obstacle in the clinical assessment of this case. The abdominal symptoms were considered pregnancy-related. Also, due to the pregnancy the ovarian cytoreductive surgery can´t be done at the moment of diagnosis. Due to the rarity of the disease and the non-specific presentation, it would be necessary to carry out a compilation of studies to unify the information described until now or to carry out prospective studies to determine the optimal treatment and management of patients. pregnant women complicated with this disease.

Conclusion

The morphology of primary and secondary neoplasms of the ovary has always been a point of discussion with overlapping features that can make it a challenge for clinicians to diagnosed, especially when de metastatic disease is due to an occult primary involving one or both ovaries.

Even though ovarian cancer in pregnancy is rare, adnexal ultrasound is mandatory when scanning during the first trimester to rule out the presence of associated fallopian or ovarian masses.

On the other hand, Krukenberg's tumor diagnosed in pregnancy is an uncommon situation that raises both diagnosis and medical management issues. More clinical experience might be needed to clarify what would be an appropriate strategy in the management of pregnant women with malignant ovarian tumors, including Krukenberg tumors.

Acknowledgments

We would like to thank all participants, for dedicating their time and energy to take part in this case report.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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