Gynecologic Oncology Reports 24 (2018) 48–50

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Advanced ovarian cancer treated in pregnancy and detected by cell-free DNA aneuploidy screening

Christina N. Cordeiro Mitchell[a,*], Tricia Murdock[b], Amanda N. Fader[c], Rebecca L. Stone[c]

[a] Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Ovarian cancer
Chemotherapy in pregnancy
Cancer in pregnancy
Cell free DNA screening
Fetal aneuploidy screening
Noninvasive prenatal testing

1. Introduction

Cancer affects approximately one in 1000 pregnancies. Three to six percent of antepartum adnexal masses typically detected during routine obstetrical ultrasounds are malignant. Germ cell ovarian malignancies are most common, followed by stromal and epithelial cancers (Cordeiro & Gemignani, 2017). About one third of women have extra-ovarian spread at diagnosis (Blake et al., 2015).

As more women delay childbearing, the incidence of ovarian cancer in pregnancy may increase. This warrants greater understanding of the optimal treatment of this complex condition. Additionally, the utilization of cell-free DNA (cfDNA) screening for fetal aneuploidy has dramatically increased among women over 34. Careful interpretation of test results is of utmost importance, as false positive abnormal fetal aneuploidy screening results can signify occult malignancy. Here, we present a case of high grade serous ovarian cancer detected by cfDNA fetal aneuploidy screening six weeks prior to the clinical diagnosis of stage IVA disease.

2. Case

A 40-year old woman with a history of fibroids and infertility presented to us at 33 weeks gestational age with stage IVA high grade serous ovarian cancer. The patient conceived via in vitro fertilization (IVF) without preimplantation genetic screening. During her first trimester, five-centimeter complex right ovarian cysts appeared stable over serial ultrasounds. Cell-free DNA screening for fetal aneuploidy at 10 weeks was positive for monosomy 13 and other non-test chromosomal aneuploidies. After counseling that this was likely a false positive, the patient did not pursue confirmatory testing. Anatomic and growth sonograms were normal. At 15 weeks, the patient developed dyspnea and the ovarian cysts had doubled in size.

During an admission for symptomatic ascites and pleural effusions one week later, diagnostic laparoscopy revealed carcinomatosis. An omental biopsy demonstrated high-grade serous carcinoma with papillary features (CK7, WT-1, and p16 diffusely positive; estrogen receptor focally positive; progesterone receptor moderately positive; p53 aberrant/null pattern), concordant with thoracentesis cytology. The patient initiated intravenous carboplatin monotherapy on a three-week cycle.

The patient's CA-125 levels declined from 1039 U/mL to 24 U/mL after three cycles of carboplatin. However, she noted a new growth at her supraumbilical port site, which grew through a fourth cycle. CA-125 rose to 135 U/mL. Paclitaxel was added to her fifth cycle, due to disease progression manifesting as enlarging port site metastases.

After receiving betamethasone at 32 weeks, she transferred care to our institution. Imaging revealed carcinomatosis and large abdominal wall port site metastases. At 34 2/7 weeks, she underwent a Cesarean section, total hysterectomy, bilateral salpingo-oophorectomy, peritonectomy, omentectomy, splenectomy, cholecystectomy, portal lymphadenectomy, appendectomy, ablation of liver serosal implants, abdominal wall resection and generalized cytoreductive surgery to no gross residual. Her estimated blood loss was six liters, necessitating a massive transfusion protocol. She was admitted to the intensive care

* Corresponding author at: 10753 Falls Road, Pavilion 2, Suite 335, Lutherville, MD 21093, USA.
E-mail address: cmitch66@jhmi.edu (C.N. Cordeiro Mitchell).

https://doi.org/10.1016/j.gore.2018.03.006
Received 5 February 2018; Received in revised form 12 March 2018; Accepted 17 March 2018
Available online 23 March 2018

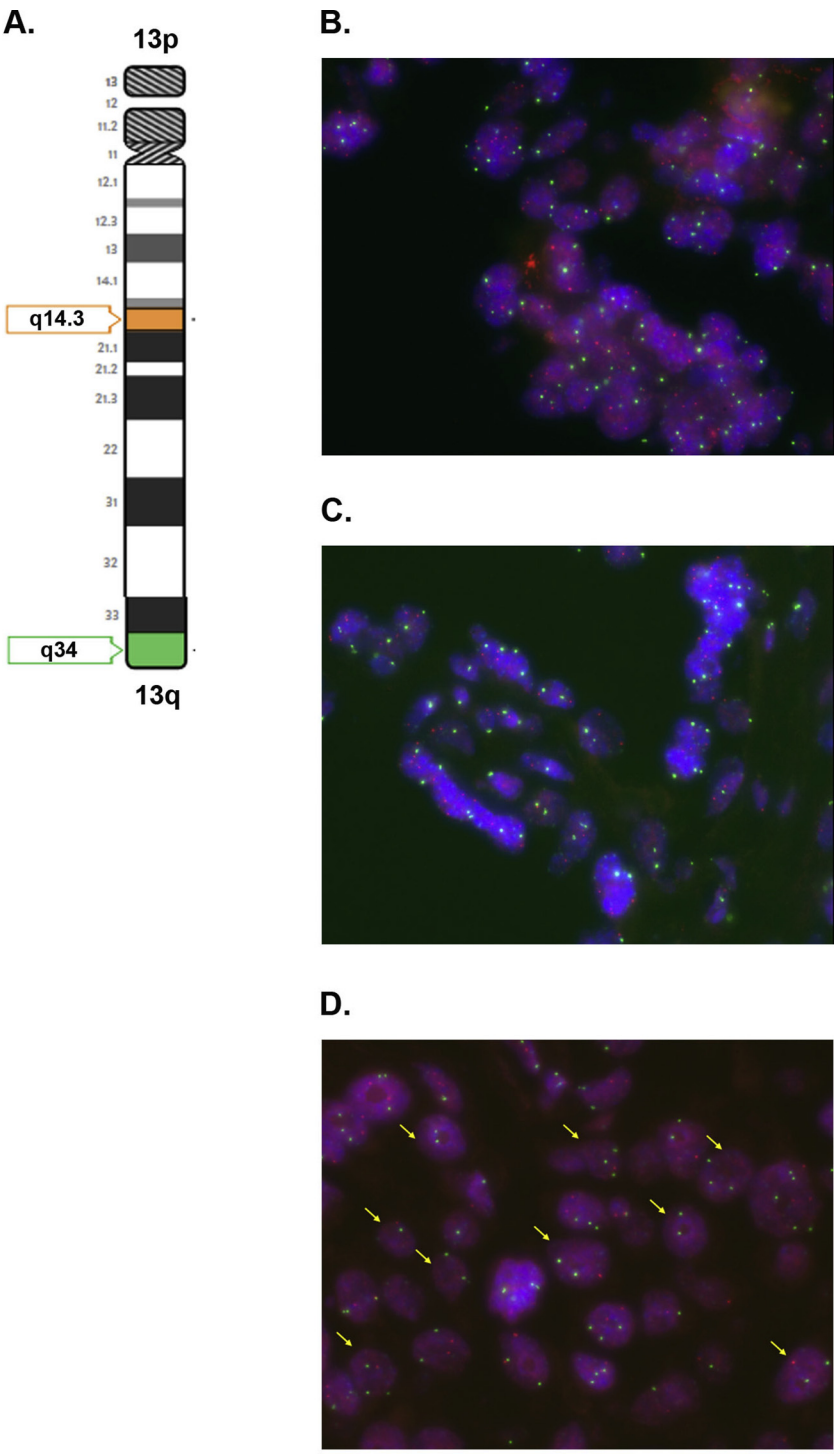

Fig. 1. (A) Dual-probe FISH analysis using two probes for different loci on chromosome 13 (red 13q14.3 and green 13q34). The red probe for 13q14.3 is close to the tumor suppressor retinoblastoma gene. (B and C) Normal control and placental tissue from the present case showing 2 red and 2 green signals per cell, consistent with chromosome 13 diploidy. (D) Tumor tissue from the present case showing loss of red signal(s) in some tumor cells (yellow arrows), indicating possible deletion in 13q14. Circulating tumor DNA with this deletion was detected by the patient's abnormal fetal aneuploidy screen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

unit, stabilized and transferred to the postpartum unit two days later. Her postoperative course was uncomplicated and she was meeting discharge milestones by postoperative day seven.

At the time of this report, the patient has had a nine-month disease-free interval following completion of adjuvant chemotherapy with carboplatin and paclitaxel. Genetic testing for hereditary ovarian cancer was negative. However, FoundationOne® (Foundation Medicine, Inc., Cambridge, MA) tumor testing was positive for homologous recombination deficiency.

The patient's infant was initially admitted to the neonatal ICU for respiratory support and subsequently to the nursery for hyperbilirubinemia and poor feeding. She was discharged to home on day of life 15 and is meeting developmental milestones at one year.

Histopathologic evaluation of the placenta demonstrated no tumor involvement. To determine whether the cfDNA result of monosomy 13 was due to placental mosaicism or tumor-derived cfDNA, fluorescence in situ hybridization (FISH) was performed on placental and tumor tissue using probes for 13q14.3 and 13q34 (Fig. 1A). Loss of 13q14.3 signal in the tumor, but not the placenta, confirmed that the genomic imbalance identified in the cfDNA screen originated from the tumor (Fig. 1B–D).

3. Discussion

This report describes a case of stage IV epithelial ovarian cancer in pregnancy that was complicated by disease progression marked by bulky port site metastases on carboplatin monotherapy necessitating interval Cesarean cytoreduction. Abnormal cfDNA aneuploidy screening preceded her cancer diagnosis by six weeks. This case demonstrates that a discordance between abnormal fetal aneuploidy screening and other fetal testing may signify occult malignancy. It also emphasizes the importance of managing ovarian cancer in pregnancy according to clinical practice guidelines, including neoadjuvant carboplatin/paclitaxel chemotherapy followed by complete cytoreductive surgery postpartum.

To our knowledge, this is the first report of a false-positive fetal aneuploidy screen heralding a diagnosis of ovarian cancer during pregnancy. The large placental contribution to plasma DNA in pregnancy (12.1–41%) is the basis for using cfDNA for fetal aneuploidy screening (Sun et al., 2015). False positive results can result from placental mosaicism, co-twin demise, maternal chromosomal mosaicism, DNA copy-number variants, maternal organ transplantation and maternal malignancy (Bianchi et al., 2015). In cases of malignancy, apoptotic cancer cells are thought to be released into circulation as cfDNA. Since placental mosaicism can result in a false positive cfDNA aneuploidy screen (Mardy & Wapner, 2016), FISH testing for 13q14.3 and 13q34 in placental and tumor tissues was retrospectively performed. This revealed that the monosomy 13 was tumor-specific, indicating that the cfDNA screen detected a tumor-derived monosomy 13, rather than isolated placental mosaicism.

Sun et al. (Sun et al., 2015) reported a case of a patient with follicular lymphoma associated with gross abnormalities on cfDNA testing. To quantify the occurrence of occult cancer in the setting of false positive cfDNA test results, Bianchi et al. (Bianchi et al., 2015) examined 125,426 cfDNA samples from asymptomatic pregnant women undergoing aneuploidy screening. Among 3757 (3%) of patients with abnormal results, ten were diagnosed with occult cancer. Maternal cancers were most often associated with multiple aneuploidy results (Bianchi et al., 2015).

This and the present case underscore the necessity of considering a diagnostic procedure when prenatal screening reveals multiple aneuploidies, due to a 20–44% risk of maternal cancer with multiple, as opposed to isolated, aneuploidies (Cohen et al., 2018). Further studies of cfDNA results in pregnancy-associated cancers may better characterize the utility and predictive value of abnormal cfDNA results in detecting malignancy, thereby improving maternal care. Furthermore, this technology may ultimately provide a means for early noninvasive cancer screening and/or diagnosis in high-risk women. Plasma tests to detect cell tumor DNA (ctDNA) using a combination of protein and genetic biomarkers to create a mutant DNA tumor template screening platforms are on the horizon for gynecologic malignancies (Cohen et al., 2018). However, cfDNA aneuploidy testing is not restricted to screening based solely on high-risk tumor templates. Multiple abnormal aneuploidy results should alert the care provider to a possible underlying malignancy.

In pregnancy, most ovarian malignancies are diagnosed early and are of non-epithelial origin. Therefore, data on the management of advanced stage epithelial ovarian cancer in pregnancy are largely derived from case reports (Cordeiro & Gemignani, 2017). In currently reported cases (n = 5), visible disease at initial surgery was confined to the ovaries and omentum, platinum-based doublet chemotherapy was effective, and interval surgery was limited to Cesarean section and completion staging (Cordeiro & Gemignani, 2017; Ramos et al., 2013; Modares Gilani et al., 2007). The present case is unique in that the patient presented with stage IVA disease with carcinomatosis, progressed during treatment with carboplatin monotherapy, and required extensive cytoreduction at time of Cesarean hysterectomy to achieve no gross residual.

Because advanced ovarian cancer in pregnancy is rare, most practitioners have limited experience with managing this condition. As a result, inconsistencies in care can occur (Cordeiro & Gemignani, 2017). However, in 2013, the European Society for Medical Oncology (ESMO) published principles for the management of ovarian cancer in pregnancy, including referral to a center with expertise, management with a multidisciplinary team, and the use of the same chemotherapy protocols prescribed to non-pregnant patients (Peccatori et al., 2013). Presently, neoadjuvant paclitaxel plus carboplatin is recommended for epithelial ovarian cancer in the second and third trimesters, based on cooperative phase III trials and observational studies showing no significant long-term adverse impact on children exposed in utero after the first trimester (Cordeiro & Gemignani, 2017; Peccatori et al., 2013).

Initiation of single agent carboplatin, as opposed to doublet carboplatin/paclitaxel, may have negatively impacted disease control in this case. It is also theoretically possible that this patient's fertility treatment contributed to her large disease burden–perhaps oocyte retrieval precipitated dissemination. Although we do not suppose that this patient's disease could have been diagnosed earlier, nor prevented, this case warrants caution for providers performing oocyte retrievals in the setting of abnormal ultrasounds.

In conclusion, the present case documents a unique case of an abnormal cfDNA first trimester screen resulting from occult ovarian cancer in pregnancy, retrospectively confirmed by molecular analysis of paired tumor and placenta DNA. Prompt recognition of cfDNA screens with multiple aneuploidies and/or associated with findings such as complex adnexal masses, has the potential to improve cancer outcomes in pregnancy. Referral of women with ovarian cancer in pregnancy to institutions with expertise in managing this condition can further optimize care. Historically, the prognosis of patients diagnosed with epithelial ovarian cancer during pregnancy has been comparable with age- and stage-matched non-pregnant patients. However, this will only continue if guideline-adherent care is practiced in pregnancy. Clinical practice guidelines from the Society of Gynecologic Oncology (SGO) and the National Comprehensive Cancer Network (NCCN) for managing women diagnosed with cancer during pregnancy are needed to ensure safe and high-quality care.

Conflicts of interest

The authors have no conflicts to disclose.

References

Bianchi, D.W., Chudova, D., Sehnert, A.J., Bhatt, S., Murray, K., et al., 2015. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. JAMA 314 (2), 162–169.

Blake, E.A., Kodama, M., Yunokawa, M., Ross, M.S., Ueda, Y., Grubbs, B.H., Matsuo, K., 2015. Feto-maternal outcomes of pregnancy complicated by epithelial ovarian cancer: a systemic review of literature. Eur. J. Obstet. Gynecol. Reprod. Biol. 186, 97–105.

Cohen, J.D., Li, L., Wang, Y., Thoburn, C., Afsari, B., et al., 2018. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science 359 (6378), 926–930 Feb 23.

Cordeiro, C.N., Gemignani, M.L., 2017. Gynecologic malignancies in pregnancy: balancing fetal risks with oncologic safety. Obstet. Gynecol. Surv. 72 (3), 184–193.

Mardy, A., Wapner, R., 2016. Confined placental mosaicism and its impact on confirmation of NIPT results. Am. J. Med. Genet. C. Semin. Med. Genet. 172 (2), 118–122.

Modares Gilani, M., Karimi Zarchi, M., Behtash, N., Ghaemmaghami, F., Mousavi, A.S., Behnamfar, F., 2007. Preservation of pregnancy in a patient with advanced ovarian cancer at 20 weeks of gestation: case report and literature review. Int. J. Gynecol. Cancer 17, 1140–1143.

Peccatori, F.A., Azim, H.A., Orecchia, R., Hoekstra, H.J., Pavlidis, N., Kesic, V., Pentheroudakis, G., on behalf of the ESMO Guidelines Working Group, 2013. Cancer, pregnancy, and fertility: esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 24 (vi160–70).

Ramos, J.R., Roma, E., Palomar, L., Poveda, J.L., 2013. Paclitaxel and carboplatin treatment for advanced ovarian cancer during pregnancy. Chemotherapy 59, 344–345.

Sun, K., Jiang, P., Chan, K.C., Wong, J., Cheng, Y.K., et al., 2015. Plasma DNA tissue mapping by genome-wide methylation sequencing for noninvasive prenatal, cancer, and transplantation assessments. Proc. Natl. Acad. Sci. U. S. A. 112 (40), E5503–12.