

## Case Report

## Extensive cutaneous metastases of ovarian cancer after prolonged response to liposomal doxorubicin ☆☆☆☆☆



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## Introduction

In 2012, an estimated 22,280 women were diagnosed with ovarian cancer and 15,500 died of the disease [1]. Approximately seventy-five percent of women diagnosed with ovarian cancer in the United States have stage III or more advanced disease at diagnosis. Although most patients respond to initial treatment, the rate of recurrence after initial treatment of ovarian cancer is as high as 65% to 75%. The most common site of recurrence is within the peritoneal cavity. In a postmortem study, Rose et al. evaluated the patterns of ovarian cancer metastasis and found that the most common sites of metastasis were the peritoneal cavity, paraaortic lymph nodes, large intestine, pelvic lymph nodes, and liver [2].

Ovarian cancer can metastasize by direct extension and transport throughout the peritoneal cavity and/or through lymphatic or hematogenous spread. Cutaneous metastases are rare, occurring in 1.9% to

5.1% of patients [3]. Cutaneous metastases are often a late manifestation of the disease and have a propensity to occur within previous surgical scars, although cases of cutaneous metastases to the limbs have also been reported. Cutaneous metastases most commonly manifest as small nodular lesions but can also manifest as herpetiform erythematous lesions and scarring plaques.

Treatment of recurrent metastatic ovarian cancer involves systemic chemotherapy with agents chosen on the basis of previously demonstrated platinum sensitivity or resistance. Pegylated liposomal doxorubicin (PLD) is a cytotoxic agent that has demonstrated efficacy in the treatment of recurrent platinum-sensitive and platinum-resistant ovarian cancer. In patients with platinum-resistant ovarian cancer, PLD as a single agent has shown a survival benefit nearly equal to what is observed with other cytotoxic agents but is associated with less toxicity. Given these findings and its relatively convenient dosing, PLD is often chosen as the preferred agent for patients with recurrent platinum-resistant ovarian cancer.

## Case

A 64-year-old woman was diagnosed with at least stage IA high-grade serous ovarian carcinoma following a laparoscopic bilateral salpingo-oophorectomy. The patient was subsequently referred to The University of Texas MD Anderson Cancer Center for further treatment. Initial evaluation by computed tomography (CT) demonstrated indeterminate subcentimeter liver lesions and a 1.8 cm lesion along the right external iliac vessels. As such, the patient was treated with six cycles of paclitaxel (175 mg/m<sup>2</sup>) and carboplatin (AUC = 5), which were completed in May 2006. She had no evidence of disease upon completion of therapy. The patient underwent BRCA testing which demonstrated no detectable mutations or large gene rearrangements.

Approximately 5 months after completion of therapy, CT revealed disease recurrence in the form of a 1-cm subcutaneous nodule involving the left rectus abdominus muscle and small peritoneal deposits within the pelvis and a lesion on the right external iliac vessels. The serum CA-125 level was 7.1 U/mL. Given that disease had recurred within 5 months of platinum-based therapy, the decision was made to treat the patient with single-agent PLD (40 mg/m<sup>2</sup>) every 28 days. The patient experienced an infusion reaction with the first cycle, and consequently the dose was reduced to 35 mg/m<sup>2</sup>. In October 2009, the patient had completed a total of 34 cycles of treatment with

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☆☆☆ Précis: Cutaneous metastases from ovarian cancer are rare and are associated with potentially severe morbidity. Such metastases present a clinical therapeutic challenge.

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PLD and requested a chemotherapy treatment break. Throughout the course of treatment with PLD, periodic CT had demonstrated a stable metastatic focus adjacent to the left rectus abdominus muscle. To evaluate whether this residual lesion was metabolically active, positron emission tomography (PET)-CT was performed before therapy was stopped. The focus was not fluorodeoxyglucose avid and thus was judged not to represent active disease. The CA-125 level was 11.4 U/mL. Chemotherapy was stopped, and the patient was placed on surveillance.

In April 2010, follow-up PET-CT revealed new metastases in the omentum and peritoneum. In May 2010, the patient underwent an exploratory laparotomy, total abdominal hysterectomy, omentectomy, splenectomy, resection of a right-sided pelvic wall mass, resection of anterior abdominal wall nodule, and optimal tumor-reductive surgery. The final pathology report after that surgery indicated high-grade serous carcinoma in the omentum and anterior abdominal wall nodule. In June 2010, PLD at 35 mg/m<sup>2</sup> every 28 days was reinitiated; the patient received an additional 8 cycles of this treatment.

In February 2011, PET-CT showed low-grade FDG uptake in a peritoneal nodule as well as new subcutaneous nodules that were too small to characterize. In March 2011, treatment was changed to letrozole 2.5 mg by mouth daily. The patient was treated with letrozole for 2 months. In May 2011, reassessment with PET-CT demonstrated progression of disease with enlargement of peritoneal implants and subcutaneous nodules. The CA-125 level was 166.6 U/mL. At that time, the patient was switched from letrozole back to PLD, but in July 2011, after the patient had received two cycles of this drug, PLD was discontinued because of a national drug shortage. The patient was subsequently treated with tamoxifen 20 mg twice daily. Two months later, she was changed to single-agent etoposide administered in 21-day cycles consisting of 50 mg by mouth for 2 weeks followed by a 1-week break.

After 2 months of treatment with etoposide, the patient noted progression of subcutaneous disease in the suprapubic region. In December 2011, etoposide was stopped, and the patient received 13 fractions of localized radiation at an outside facility. The CA-125 level at this time was 1133 U/mL (Fig. 1). After completion of radiation therapy, PLD was restarted. After the patient had received an additional four cycles of PLD, for a cumulative total of 48 cycles, PLD was stopped and single-agent paclitaxel (60 mg/m<sup>2</sup> weekly) was started because of concerns about radiation recall and progression of the abdominal wall and cutaneous disease. The patient received one cycle of paclitaxel. She had progression of disease and was then switched to a combination of cyclophosphamide and bevacizumab at an outside institution. She completed three cycles of this treatment and was noted to have progression of disease with extensive cutaneous involvement of the abdominal wall with multiple nodular and



Fig. 2. Cutaneous metastases on the abdominal wall in a patient with recurrent ovarian cancer.

ulcerative lesions on gross abdominal inspection (Fig. 2) and on PET-CT (Fig. 3). The wound care team at MD Anderson evaluated the patient's multiple and confluent abdominal wall lesions. Wound care specialists recommended daily cleansing of the wounds with saline followed by application of Xeroform and Aquaphor ointment to affected areas. The patient was referred to hospice care in August 2012. Two months after referral to hospice, she died.

**Comment**

Robinson et al. recently reported that in a series of 233 patients with recurrence after treatment for stage III ovarian cancer, only two patients (0.8%) had recurrence in cutaneous tissue [4]. Another group documented six cases of cutaneous metastases (0.9%) in 645 patients diagnosed with epithelial ovarian carcinoma [5]. The majority of these cutaneous recurrences were within previous laparotomy scars or drainage site scars. All studies of cutaneous metastases that were reviewed showed that such metastases from any visceral organ are associated with a very poor prognosis. Survival has been reported to be anywhere from 3 to 8 months after diagnosis of a cutaneous lesion in ovarian cancer.

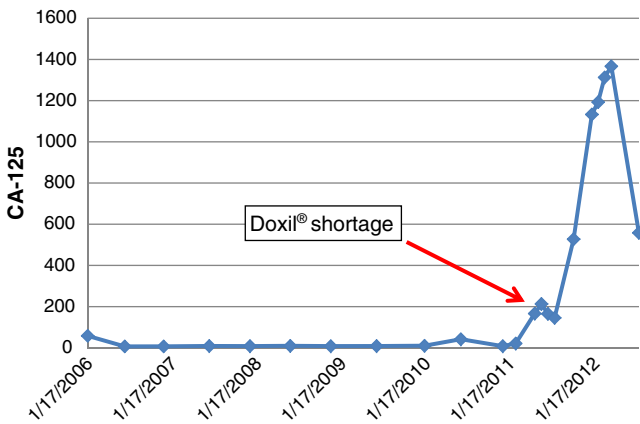


Fig. 1. CA-125 level over the course of the patient's treatment with various chemotherapy agents.

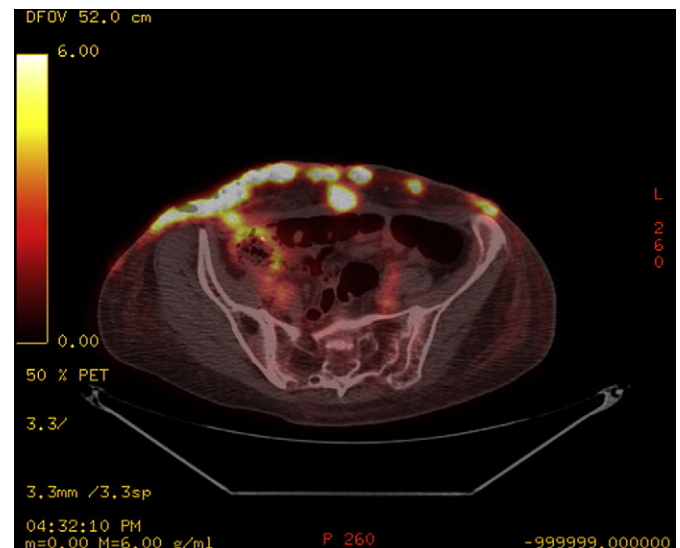


Fig. 3. Axial positron emission tomography image demonstrating fluorodeoxyglucose-avid lesions within the subcutaneous tissue of the lower abdomen.

The majority of patients with ovarian cancer eventually have a relapse, which is associated with poor long-term survival. Approximately 20% of patients with relapse have platinum-resistant disease.

PLD is a preferred treatment for such patients because it is among the non-platinum-based agents with the highest activity against recurrent platinum-resistant ovarian cancer. Etoposide is another agent with similar efficacy [6]. In the event that the patient cannot tolerate the cytotoxic nature of these drugs, hormonal agents such as letrozole and tamoxifen have proven effective in certain subtypes of platinum resistant disease [7,8]. However, the role of these agents, especially PLD, in the management of cutaneous metastases has not been fully evaluated.

Management of cutaneous metastases varies widely and remains a clinical challenge, especially if primary excision is not feasible because of the location or extent of disease. Previously evaluated systemic chemotherapies have had minimal effect. Earlier studies suggested that electrocoagulation, electron beam therapy, and phototherapy may be effective in treating cutaneous lesions. At present, the topical Toll-like receptor 7 agonist imiquimod and electrochemotherapy are being studied for treatment of cutaneous metastases. Imiquimod exerts its effects by activating local macrophages through its binding of toll-like receptor 7, which leads to release of pro-inflammatory cytokines that are responsible for the cytotoxicity of this drug [9]. Electrochemotherapy, historically used in the treatment of metastatic head and neck cancers, has been explored in the treatment of cutaneous disease in patients with chest wall recurrence of breast cancer. In electrochemotherapy, a local electrical current is applied to the lesion, which causes cellular membranes to become more permeable to the chemotherapy agent being used. In the case of bleomycin-based electrochemotherapy, the electric current increases permeability to the drug by 700-fold [10]. In a phase II study by Campana et al., bleomycin-based electrochemotherapy produced a complete response in 54% of the patients, and 81% of the patients were alive at 3 years [10]. However, it has been suggested that the aim of

electrochemotherapy in patients with extensive disease is to maintain stable disease. Limited data exist on the utility of this technology in patients with cutaneous metastases from ovarian cancer.

In conclusion, cutaneous metastases from ovarian cancer are rare and portend a poor prognosis. Management of cutaneous metastases remains a clinical challenge. Further studies evaluating the role of specific therapies are needed to guide treatment.

#### Conflict of interest statement

The authors of this paper have no conflicts of interest to declare.

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