Clinical Case Report

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Two independent incidences of skin metastases in the umbilicus and abdominal wall in ovarian serous adenocarcinoma

A case report and review of the literature

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Abstract

Rationale: Advanced ovarian cancer is usually associated with intra-abdominal metastases and while it commonly spreads directly to the omentum, intestine, liver, or other organs, it can also metastasize through the lymphatic channels and the hematogenous pathway. With an increasing number of invasive operations being performed with chemoradiotherapy, the incidence of extra-abdominal metastases has risen. Nevertheless, ovarian cancer with skin metastases is quite rare.

Patient concerns: We report a case of ovarian cancer with two independent incidences of skin metastases in the umbilicus and abdominal wall.

Diagnoses: The patient was a 67-year-old woman who was diagnosed with ovarian cancer stage IIIC and underwent cytoreductive surgery. A solitary brown cauliflower-like metastatic lesion, approximately $6 \times 5 \times 4$ cm was identified in the umbilicus area two years after primary surgery. During tumorectomy, intraoperative exploration revealed that while the tumor was located close to the peritoneum, there was no penetration.

Interventions: The patient recovered well and received multiple rounds of chemotherapy. Ten months later, the patient presented with skin lesions located on the abdominal wall that grew rapidly and spread from the lower abdomen wall to the bilateral waist and femoral skin. These lesions were multiple, ulcerated, rough heliotrope plaques that produced a foul-smelling faint yellow liquid. Biopsy analysis revealed skin metastasis of poorly differentiated serous adenocarcinoma.

Outcomes: The patient was treated with chemotherapy but died 3 months after the skin metastasis occurred for the second time.

Lessons: Ovarian cancer with skin metastasis is a rare condition with poor prognosis. Pathological diagnosis of early skin lesions is essential for ovarian cancer patients and that systemic and local disease should be treated with surgery or palliative therapy in order to provide patients with the best chances of survival. Tumorectomy is appropriate when lesions are isolated and when the patient's performance status is good. However, systemic therapy including chemotherapy and radiotherapy should be considered when skin lesions are associated with severe intro-abdominal disease.

Abbreviations: CA125 = carbohydrate antigen 125, DWI = diffusion-weighted imaging, ER = estrogen receptor, FIGO = International Federation of Gynecology and Obstetrics, KPS = Karnofsky Performance Status, MRI = magnetic resonance imaging.

Keywords: abdominal wall metastasis, extra-abdominal metastasis, ovarian cancer, skin metastases, umbilicus metastasis

1. Introduction

Most ovarian cancers are in their advanced stages when first diagnosed and accompanied by pelvic organs metastases, which is the most common route of ovarian cancer metastasis. Ovarian cancer can also metastasize through the lymphatic channels and the hematogenous pathway. The incidence of ovarian cancer associated with skin metastases is rare and ranges from 1.9% to 5.1%.[1–4] Several metastatic patterns are known to exist: isolated cutaneous nodule, multiple cutaneous nodules, inflammatory metastasis, and cicatricial plaques.[5] Typical umbilical metastatic nodules are known as Sister Joseph's nodule, which often represents advanced gastrointestinal tract and ovarian malignancy with a poor prognosis.[6] In this report, we described the case of a patient with ovarian cancer who suffered 2 independent incidences of skin metastases in the umbilicus and abdominal wall within an interval of 10 months.

2. Case presentation

Ethical approval was obtained from Ethics Committee of Qilu Hospital, Shandong University. Informed consent was obtained

Editor: Mauro Alaibac.

This work was supported by key research and development project of Shandong Province Science and Technology Development (2015GSF118068).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:49(e9118)

Received: 6 July 2017 / Received in final form: 14 November 2017 / Accepted: 15 November 2017

http://dx.doi.org/10.1097/MD.0000000000009118

from the patient for publication of this case report and any accompany images.

The patient was a 67-year-old woman who complained of abdominal distension and was admitted to our hospital in July 2013. Examination revealed massive ascites, smears of which confirmed the presence of cancer cell. Serum carbohydrate antigen 125 (CA125) was 1527 U/mL. The patient's medical history and family history were of no significance. The patient received 2 cycles of neoadjuvant chemotherapy with paclitaxel (175 mg/m^2), cisplatin (75 mg/m^2), and interleukin-2 (3 MIU); each administered via a single intraperitoneal injection. When the patient's CA125 level fell to within the normal range (8th October 2013), we carried out an exploratory laparotomy, including complete hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, and cytoreductive surgery for pelvic metastases. Histopathological analysis revealed bilateral ovarian serous adenocarcinoma and omental tissue metastatic adenocarcinoma (Fig. 1A) of International Federation of Gynecology and Obstetrics stage IIIC. The patient refused to accept adjuvant therapy and an elevated CA125 level was detected 1 year after surgery. Consequently, the patient received chemotherapy with paclitaxel (175 mg/m^2) and carboplatin with AUC (5 mg/mL/min) for 10 cycles.

In October 2015, a solitary brown cauliflower-like excrescence was found in the umbilicus area. That was $6 \times 4 \times 5$ cm in size.

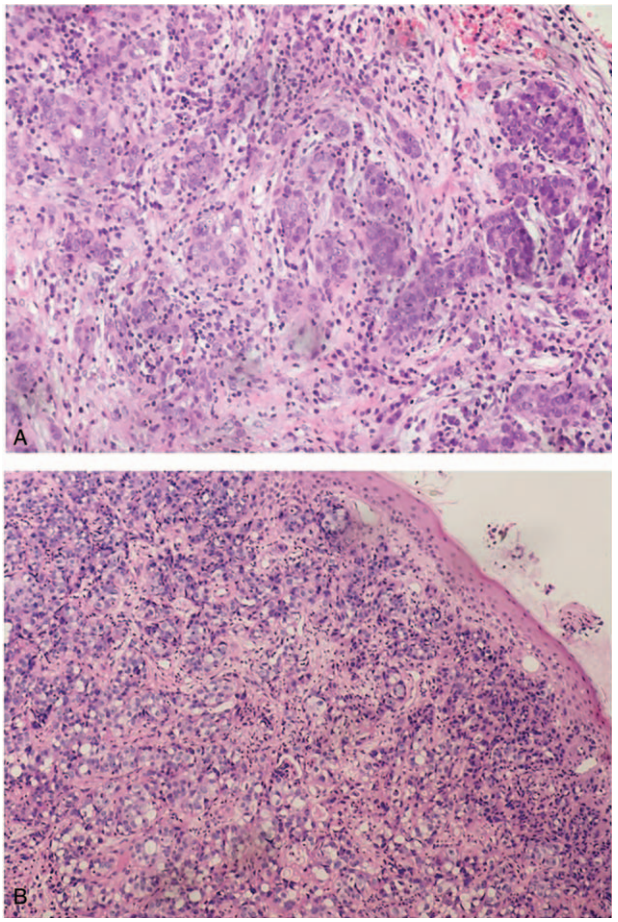

Figure 1. Images of pathological tissue slices (original magnification, ×40). A, Histopathology shows ovarian serous adenocarcinoma after primary surgery. B, A biopsy shows skin metastasis with poorly differentiated serous adenocarcinoma.

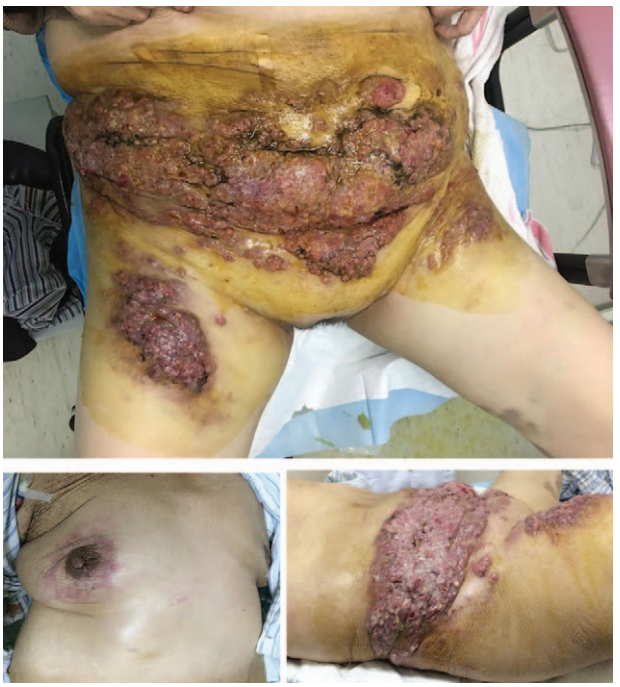

Figure 2. Skin lesions located on the abdominal wall that grew rapidly and spread from the lower abdomen wall to the bilateral waist and femoral skin, and were multiple, ulcerated, rough heliotrope plaques up to 30×10 cm in size releasing a foul-smelling faint yellow liquid. There were multiple, nodular, erythematous lesions, up to 2 cm in size located on the right breast.

The patient's serum CA125 was 928.3 U/mL and there was no evidence to suggest metastasis in the peritoneum or elsewhere. Tumorectomy was performed on 23rd October 2015. Intraoperative exploration revealed that the tumor was located close to the peritoneum but did not penetrate. The bowel surface was smooth, and biopsy of the parietal peritoneum did not show any obvious metastasis in the abdominal cavity. Histopathological analysis showed that the umbilicus area was associated with subcutaneous metastatic serous adenocarcinoma. The patient received multiple rounds of intravenous chemotherapy after tumorectomy, including cyclophosphamide, pharmorubicin, and cisplatin (1 cycle), ifosfamide and epirubicin (5 cycles), and docetaxel and capecitabine (1 cycle).

In August 2016, 10 months after the skin tumorectomy, the patient again presented with skin lesions located on the abdominal wall that grew rapidly and spread from the lower abdomen wall to the bilateral waist and femoral skin. These lesions were multiple, ulcerated, rough heliotrope plaques up to 30×10 cm in size and released a foul-smelling faint yellow liquid. There were multiple, nodular, erythematous lesions, up to 2 cm in size, located on the right breast skin. The patient complained of pain, exudation, and itching (Fig. 2). The biopsy revealed skin metastasis of poorly differentiated serous adenocarcinoma (Fig. 1B) and the CA125 level was 1099 U/mL. Magnetic resonance imaging of the abdomen and pelvis showed multiple metastases in the abdominal wall and bilateral femoral skin, right costicartilage, gluteus muscle, and pelvic cavity (Fig. 3). Because of severe exudation, we were forced to change dressings every other day. The patient received chemotherapy with carboplatin and pemetrexed disodium for 1 cycle. Unfortunately, on 23rd November 2016, 3 months after the second skin metastases, the patient died of multiple organ failure.

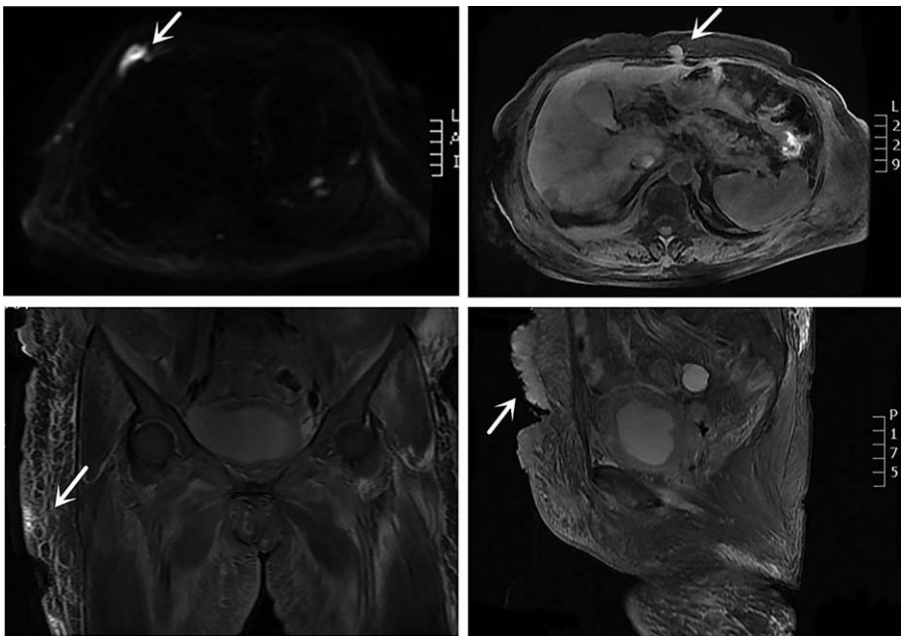

Figure 3. Magnetic resonance imaging (MRI) scan of the abdominal and pelvis shows multiple metastases in the abdominal wall and bilateral thigh skin, right costicartilage, and pelvic cavity (arrows). Lesions showed hyperintensity on diffusion-weighted imaging (DWI).

3. Discussion

Ovarian cancer with extra-abdominal metastasis is rare and accounting for approximately 3% of metastatic site of ovarian cancer. The skin is the fourth common site of extra-abdominal metastases in ovarian cancer; other sites include the pleura, lungs, brain, lymph nodes, and bone.[4,7] Several theories have been put forward to explain the occurrence of skin metastases in ovarian cancer. These include direct invasion from underlying growth, accidental implantation of tumor cells during surgical procedures (iatrogenic), and the contiguous extension of tumor cells throughout the lymphatic root.[8] In some cases, direct invasion of ovarian cancer can occur through surgical scars. Literature also shows that cancer can also progress to the skin and metastasize through the hematogenous and lymphatic pathway.[5,8–22] We present an overview of the current literature relating to ovarian cancer with skin metastasis in Table 1. The most common metastatic site of ovarian cancer is the umbilicus area. It also called Sister Joseph's nodule .[6] Yoon et al.[9] reported a case of mucinous cystadenocarcinoma ovarian cancer that metastasized to the left shoulder and scalp in Korea. In another study, Matsui et al[16] presented a Japanese patient with serous adenocarcinoma ovarian cancer who grew a soft mass, 5 cm in diameter, in the right occipital region of the scalp 29 months after the original diagnosis of ovarian cancer. Nasal metastasis as a first symptom of ovarian cancer has also been reported.[22] In addition, ovarian cancer can metastasize to the skin of the chest and breast, back, vulvovaginal area, arms, and thighs.

Skin lesion can be isolated or multiple and skin metastases can occur coincident with the diagnosis of advanced ovarian cancer, or occur during the postoperative period as the disease progression. Several metastatic patterns have been identified: isolated cutaneous nodule, multiple cutaneous nodules, inflammatory metastases, and cicatricial plaques.[5] Cormio et al[4] conducted a research studying involving 162 patients with epithelial ovarian cancer and concluded that the significant risk factors for the development of skin metastases are tumor stage, grade, and lymph node involvement; stages III and IV ovarian cancer are more likely to develop skin metastasis.

Cheng et al[7] performed a retrospective study involving 20 cases of ovarian cancer patients with extra-abdominal metastases and 645 cases of ovarian cancer patients without extra-abdominal metastases and found that some risk factors may be associated with extra-abdominal metastases. The important prognostic factors associated with survival are Karnofsky Performance Status, sensitivity of primary chemotherapy, metastatic site, and systemic therapy after the diagnosis of extra-abdominal metastases.

The prognosis of ovarian cancer with skin metastasis remains poor. Dauplat et al[1] reported that the median time interval between the diagnosis of ovarian cancer and skin metastasis was 12 months (range, 1–41 months). However, the overall survival time after the diagnosis of skin metastasis from ovarian cancer was 4 months (range, 2–65 months) in Cormio et al's case series.[8] The most important prognostic factor associated with survival is the interval time between the diagnosis of ovarian cancer and skin metastases. Data showed a better survival (mean, 9.7 months) in patients who had an umbilical metastasis detected before definitive treatment of the primary tumor,[23] compared with those who had an umbilical metastasis detected after definitive treatment of the primary tumor. Biopsy pathology provides strong evidence to diagnose skin metastasis associated with ovarian cancer. It is worth mentioning that skin metastasis of ovarian cancer should be included in the differential diagnosis of pilomatrical carcinoma. Immunohistochemistry can reveal expression of estrogen receptor, progesterone receptor, keratin 7, and CA125 in the gland-forming elements of tumors.[10] PAX8 expression may be a particularly useful marker to discriminate metastatic ovarian cancers from other primary adnexal cancers and help provide guidance for treatment and prognosis.[24]

There is no treatment criterion for ovarian cancer with skin metastases. The option of therapy depends on the patient's general condition, the location of the metastases, and the history of

Table 1

Review of the literature of ovarian carcinoma with skin metastasis.

Author and year (refs)	Country	Case no	Age	Pathological type (n)	Stage (FIGO)	S. 1	Lesion site	Lesion form	Therapy	Interval, mo	S. 2	Outcome
Yilmaz 2006[5]	Turkey	1	69	Serous papillary carcinoma	IV	24	Lower abdominal wall and upper leg	Multiple nodules; 1–2 cm	CT	36	4	dead
Cormio 2003[8]	Italy	9	52.8	Serous papillary cystoadenocarcinoma (7)	III(5)	NA	NA	0.5–3 cm	CT (5)	23.4±12	4	Dead (8)
				Endometrioid carcinoma (1)	I(2)				CT+surgery (4)			Still alive (1)
				Mucinous carcinoma (1)	IV(2)							
Kim 2010[9]	Korea	1	30	Mucinous cystadenocarcinoma	NA	72	Left shoulder and scalp	A nodule; 2 cm	CT	72	NA	Still alive
Lalich 2010[10]	US	1	31	Endometrioid adenocarcinoma with squamous differentiation	II	NA	Left upper arm, left axilla, and abdomen	Multiple nodules; 6 cm	Surgery	0	1	Dead
Kothiwala 2015[11]	India	1	50	Serous cystadenocarcinoma	IC	48	Chest, breast, and abdomen	Multiple nodules; 1–2 cm	CT	48	NA	NA
Woopen 2012[12]	Germany	1	64	Serous-papillary adenocarcinoma	NA	2.5	Laparotomy scar area	Erysipelas like	CT	NA	9	Dead
Charalampidis 2016[13]	Greece	2	34	Serous papillary carcinoma	III	24	Chest, abdomen and extremities	Multiple nodules; 0.5–2 cm	CT	24	12	Dead
			64	Serous papillary carcinoma	II	84	Back	Isolated nodule; 1.9 × 1.8 cm	RT	120	24	Still alive
Wiechert 2012[14]	US	1	54	High-grade endometrioid adenocarcinoma	IIC	12	Inguinal fold and the vulvo-vaginal area	Multiple erythema and maculopapule	CT+RT	36	10	Dead
Kim 2012 [15]	Korea	1	60	Serous papillary adenocarcinoma	IIIC	42	Right thigh and inguinal areas	Multiple erythematous; 2 cm	CT+surgery	12	6	Dead
Matsui 2002 [16]	Japan	1	64	Serous adenocarcinoma	IIC	13	Right occipital region of scalp	Soft mass; 5 cm	CT+RT	29	12	Dead
Demirci 2010[17]	Turkey	1	43	Serous papillary cystadenocarcinoma	IIIC	8	Extensive suprapubic region to the umbilicus	Multiple ulcerated erythematous; 4 cm	RT	72	NN	Still alive
Tsai 2006 [18]	Taiwan	2	72	Serous cystadenocarcinoma	IIIC	96	Umbilical area	1.5 cm	CT	NA	22	Still alive
			44	Endometrioid ovarian cystadenocarcinoma	IIC	36	Umbilical area	3 cm	CT	NA	12	Still alive
Achimas-Cadariu 2015[19]	Romania	1	49	Micropapillary serous ovarian carcinoma	IIIC	21	Chest, bilateral breast skin, vulva, lower abdomen and limbs.	Multiple mass	CT	21	2	Dead
Traiman 1994 [20]	Brazil	1	37	Serous papillary cystadenocarcinoma	III	NA	Lower abdominal wall	20 × 20 cm	CT+RT+surgery	72	72	NA
Schonmann 2003 [21]	Israel	1	48	Ovarian serous carcinoma	IIIC	24	Abdominal skin, extremities, and the gluteal skin	Multiple erythematous vesicular	CT	NA	2	Dead
Antonio 2016 [22]	Portugal	1	58	Ovarian cystadenocarcinoma	IV	NA	Left nasal ala	A nodule; 1 cm	CT	NA	3	Dead

S. 1: disease-free survival (months). Interval: time interval between first surgery and skin metastasis. S. 2: survival after skin metastasis (months). Outcome: patient's outcome until article published.
CT = chemotherapy, FIGO = International Federation of Gynecology and Obstetrics, NA = not available, RT = radiotherapy.

previous treatments. Control of the abdominal disease remains a major problem in the management of patients with ovarian cancer.[11] It is appropriate to perform surgical resection when cutaneous metastasis is isolated, and the patient's general condition and life expectancy should be evaluated. For extensive cutaneous metastases, palliative therapy is usually the most appropriate because the skin lesions are typically associated with intra-abdominal lesions.[15] It has been reported that electrocoagulation or external radiotherapy may be effective for local control with less pain, hemorrhage, and infection, but these approaches are also limited in the treatment of systemic disease.[17,25]

Existing literature shows that the median interval after skin metastasis was 13.7 months (range, 1–72 months) in the Table 1. The longer the interval between first surgery and skin metastasis, the longer the patient survives. Our patient suffered 2 independent incidences of metastases in the umbilicus and abdominal wall within an interval of 10 months. The first skin lesion was isolated to the cutaneous nodule and did not penetrate the peritoneum. Tumorectomy has proved to be an effective treatment for this kind of lesion. To our knowledge, the second incidence of metastasis in this case was the first to present with such extensive metastatic lesions with such severe intra-abdominal metastases. However, the patient ultimately died from the progression of ovarian cancer.

4. Conclusion

In conclusion, ovarian cancer with skin metastasis is a rare condition with poor prognosis. The learning we can draw from this case is that the pathological diagnosis of early skin lesions is essential for patients with ovarian cancer and that systemic and local disease should be treated with surgery or palliative therapy to provide patients with the best chances of survival. Tumorectomy is appropriate when lesions are isolated and when the patient's performance status is good. However, systemic therapy including chemotherapy and radiotherapy should be considered when skin lesions are associated with severe intra-abdominal disease.

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