EJGO European Journal of Gynaecological Oncology

Ovarian clear cell carcinoma recurrence presenting as subcutaneous nodules

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Summary

Skin metastasis is a rare form of ovarian carcinoma spread and is associated with widespread disease and a poor prognosis. The authors present a case of a patient, with a past history of ovarian clear cell carcinoma, who presented with subcutaneous nodules as the first sign of recurrent metastatic disease.

Key words: Ovarian cancer; Ovarian clear cell carcinoma; Skin metastasis; Subcutaneous nodule; Case report.

Introduction

Ovarian cancer is associated with the highest mortality rate of all gynaecological malignancies in developed regions of the world and is the eighth most common type of cancer world-wide [1]. Epithelial ovarian cancers account for 90% of ovarian cancers. Ovarian clear cell carcinoma is a distinct subtype of epithelial ovarian cancer and often presents as a pelvic mass at FIGO Stage I or II disease [2-3]. Unfortunately ovarian clear cell carcinomas are associated with higher rates of recurrence and subsequent higher mortality rates compared with other epithelial ovarian cancers [4].

Epithelial ovarian cancers generally metastasise by direct seeding of the peritoneal cavity. Extra-peritoneal metastases occur in less than 40% of patients and in these cases, metastases to pleura, lung, and liver are well-recognised sites of distant ovarian cancer spread [5-6]. Subcutaneous nodules are a rarely encountered site of distant metastasis, occurring in about 3.5% of epithelial ovarian cancers [5]. The majority of subcutaneous metastases occur as a single nodule at the level of the umbilicus, known as the Sister Mary Joseph nodule, which is thought to occur secondary to direct peritoneal spread [5].

Subcutaneous metastases from solid tumours occur at a rate of 10%, most frequently from breast cancer and melanoma [7]. The diagnosis of subcutaneous metastases is commonly associated with extranodal metastatic disease and a poor prognosis [7]. In ovarian cancer, the median survival time from diagnosis of skin metastasis is nine months [7].

The authors present a case of a woman who presented with multiple anterior abdominal wall subcutaneous nodules confirmed to be metastatic ovarian clear cell carcinoma, and discuss the clinical implications of this finding.

Case Report

A 46-year-old female patient presented with a left ovarian mass, which was an incidental finding on a routine general examination. At the time of initial diagnosis, there was a large complex cystic mass arising from the left ovary on computerised tomography (CT). The Ca125 level was within the normal range at 20 U/ml. The patient underwent a total abdominal hysterectomy and left salpingo-oophorectomy, left pelvic lymph node dissection, and left para-aortic node sampling. She had previously had a right salpingo-oophorectomy. She was diagnosed with FIGO Stage 1C1 ovarian clear cell adenocarcinoma based on comprehensive staging. The left ovarian cystic mass was densely adherent to the pelvic peritoneum, pelvic side wall, uterus and rectum, and ruptured intraoperatively. Peritoneal washings were negative and there was no evidence of lymph node spread (0/11 lymph nodes positive). She was managed postoperatively with six cycles of chemotherapy with carboplatin and paclitaxel and no radiotherapy. A CT scan postoperatively demonstrated no evidence of distant metastases.

Four years after the initial diagnosis, the patient presented with intermittent abdominal pain and mild abdominal distension. A restaging CT demonstrated a left pelvic sidewall mass, which was confirmed to be ovarian clear cell carcinoma by fine needle biopsy. This was initially managed with three cycles of carboplatin and six weeks of radiotherapy. The carboplatin was ceased after the third cycle due to an anaphylactoid reaction. The following year a positron emission tomography (PET)-CT scan demonstrated that the left pelvic sidewall mass had increased in size. This was managed surgically, with a laparotomy, removal of an omental nodule, and division of adhesions. After a period of nine months, the patient presented with persistent vague abdominal symptoms, however a PET scan demonstrated no evidence of disease recurrence and the Ca125 level remained within the normal range.

At age 52, two months after this PET scan, and five years after the initial diagnosis, the patient noted a number of "lumps" in her abdominal skin and on examination there were multiple subcutaneous nodules in the anterior abdominal wall. A magnetic resonance imaging (MRI) scan demonstrated five new subcutaneous

Revised manuscript accepted for publication June 29, 2015

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVII, n. 4, 2016
doi: 10.12892/ejgo3176.2016

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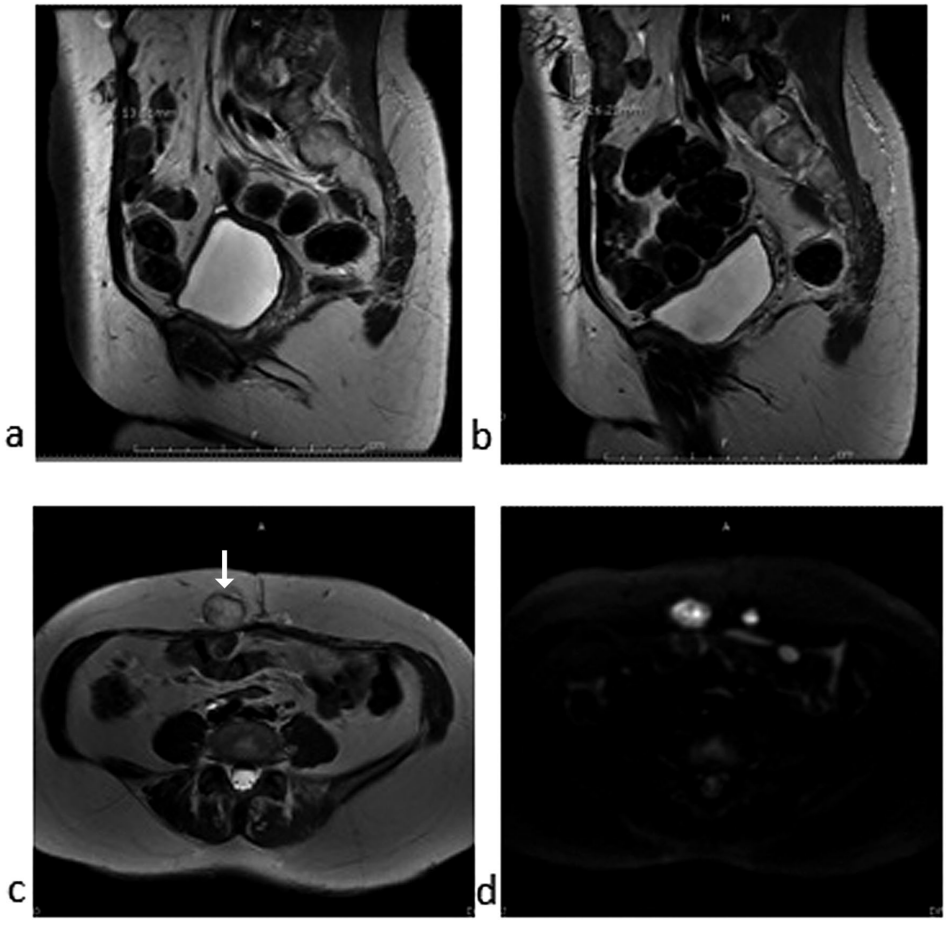

Figure 1. — a), b), c) MRI images demonstrating five new subcutaneous nodules in the anterior abdominal wall. The largest nodule is to the right of the midline scar below the umbilicus in the subcutaneous fat, indicated with the arrow. There are four left-sided smaller nodules. d) In diffusion weighted imaging (DWI) all of the nodules demonstrate restricted diffusion and enhancement.

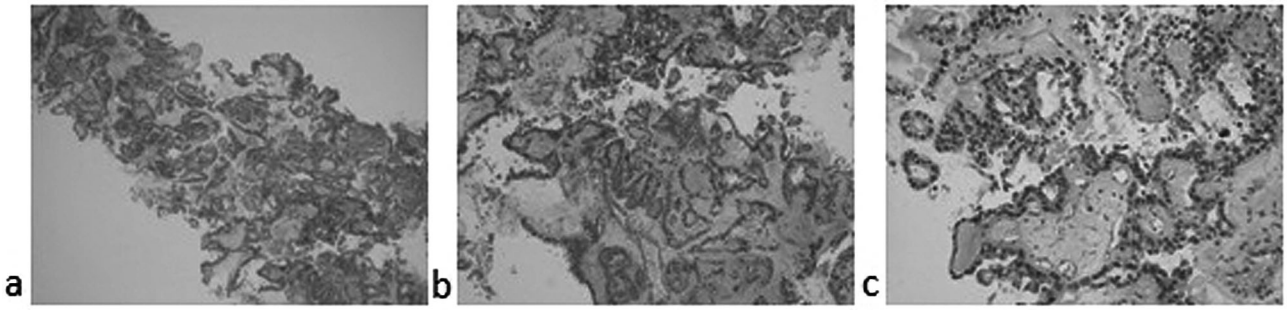

Figure 2. — Histopathology of subcutaneous nodule demonstrating features consistent with ovarian clear cell carcinoma, including Hobnailed appearance of tumour cells, cytoplasmic clearing, eosinophilic stromal cores in papillae, and papillary and glandular architecture. Haematoxiline and Eosin staining. Magnification a) ×5; b) ×10; c) ×20.

nodules (Figure 1), confirmed to be metastatic ovarian clear cell carcinoma on fine needle biopsy (Figure 2). A repeat PET scan demonstrated widespread metastatic disease in the liver and omentum. The Ca125 level was 193 U/ml. The patient was treated with two cycles of carboplatin and gemcitabine chemotherapy. A CT scan following these two cycles demonstrated progression of disease and the Ca125 level had risen to 2,400 U/ml; and therefore the chemotherapy regime was changed to liposomal doxorubicin. At the time of this report, the patient had received six cycles of chemotherapy with liposomal doxorubicin. The Ca125 had fallen to 300 U/ml and a CT scan demonstrated stable disease.

Discussion

Ovarian cancer is associated with the highest mortality of all gynaecological cancers [8]; and therefore gaining a greater understanding of the pathophysiology of ovarian

cancer is of upmost importance. Ovarian clear cell carcinomas, a subtype of epithelial ovarian cancers, typically present early in the disease process, however disease recurrence is common and often fatal [2]. Metastasis from ovarian cancer occurs predominantly by direct extension into the peritoneal cavity and dissemination via the peritoneal fluid [9]. Studies have found that approximately 30-38% of patients with epithelial ovarian cancer develop distant metastases [5-6]; and the presence of distant site metastases, including liver, lung, and pleural are associated with poor prognosis. As discussed in this paper, distant metastases to skin are very rare [5].

The pathophysiology contributing to skin metastases remains unclear. The majority of cases reporting skin metastases detail nodules in surgical sites and laparoscopic port sites, suggesting direct seeding may be an important factor [5, 10]. This case study details five subcutaneous nodules in the anterior abdominal wall, not associated with a surgical incision site. A recent case study has also presented the finding of subcutaneous nodules in the chest wall associated with metastasis from epithelial ovarian cancer [11]. This suggests that direct peritoneal spread may not be the only factor contributing to metastases to skin and likely lymphatic or haematogenous spread may be involved. Previous studies have shown that lymphatic invasion of ovarian tumours is associated with metastases to lymph nodes, small bowel, lung, and liver [12]. Further investigation is required to identify the underlying mechanism contributing to subcutaneous metastases from ovarian carcinoma.

Skin and other distant metastases occur at late stages and are associated with disseminated disease, as was the finding in this case. Management options at this late stage are unclear; however palliative approaches have been suggested to be appropriate [5, 13]. Surgical resection of the subcutaneous nodules has also been proposed to increase survival time [14]; although this may not be suitable in the setting of widespread disease [13].

Oncologists should be aware of subcutaneous nodules as a presentation of ovarian cancer recurrence and investigate any new development of subcutaneous nodules accordingly.

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