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Late recurrence of ovarian cancer: a literature review and description of two cases

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Summary

Ovarian cancer is not the most frequent malignancy of female reproductive system, but it causes many deaths in women with this diagnosis. Mostly of the patients with ovarian cancer will have recurrence after first-line standard treatment containing surgery and chemotherapy. This article presents two cases with late recurrence in women with ovarian cancer; both were nine years after the first diagnosis and both were operated and received second-line chemotherapy. The authors reviewed medical literature with late recurrence of ovarian cancer.

Key words: Ovarian cancer; Late recurrence.

Introduction

Ovarian cancer is the world's fifth leading cause of cancer related death among women. This is mainly due to the biology of this cancer: a tendency toward asymptomatic spread in the peritoneum and lymphatic system. As a result, in nearly 75% of patients, the cancer is detected in the third and fourth stage of progression. Although complete remission after optimal cytoreduction and adjuvant chemotherapy is feasible in 80-85% of patients, the five-year survival rate in advanced stage disease does not exceed 30-50%, and in over 50-75% of patients, there is a recurrence of the neoplastic process [1-5].

Recurrence is observed in 80% of cases within the first two years of diagnosis, with the most common site being the peritoneal cavity. Less frequently, recurrence in the lymph nodes, liver, lungs or vagina may be observed [6-9].

Case Report

Case 1

A 54-year-old woman was diagnosed with ovarian cancer in March 2004. A total hysterectomy was performed in which the histopathologic examination confirmed *solid adenocarcinoma of the ovary G3* according to FIGO IC. The patient received six courses of treatment with the first-line chemotherapy regimen: intravenously paclitaxel 135 mg/m2 and cisplatin 75 mg/m2 every 21 days. The patient completed treatment with full remission of the neoplastic process (confirmed in abdominal and pelvic computed tomography (CT), abdominal ultrasound, and chest X-ray). Due to the patient being treated in another cancer unit, there was a lack of some clinical data, including the level of the CA 125 marker.

Nine years post-treatment, cancer recurrence was diagnosed. On abdominal ultrasound a mass of 50 mm diameter in the right iliac fossa and lymph nodes in the hepatic hilus with a diameter of 15 mm were discovered. The CA 125 level was 418.6 U/ml. On April 25, 2013 an omentectomy was performed, which confirmed the metastasis of a poorly differentiated tumor G3.

Histological evaluation comparing material collected in 2004 and 2013 confirmed that the changes in the greater omentum are in fact metastasis from the ovary. From May 2013, the patient received second-line chemotherapy: intravenous paclitaxel 175 mg/m2 and carboplatin (AUC 5.0) every 21 days. Due to poor tolerability (hematologic complications: anemia, neutropenia, thrombocytopenia), the planned six cycles of treatment were not administered (patient completed four courses).

Case 2

A 63-year-old woman was diagnosed with a malignant tumor of the ovary. A transvaginal ultrasound examination diagnosed a tumor with both cystic and solid components in the pouch of Douglas, with a diameter of 120 mm (CA 125 marker: 266.5 U/ml). During the surgical procedure performed on March 4, 2004, the uterus, both adnexa, and omentum were excised and approximately 3,000 ml of fluid was evacuated from the abdominal cavity. Papillary serous adenocarcinoma G3 of ovarian or tubal origin, FIGO III C was diagnosed histologically. From March 2004 to June 2004, the patient received treatment with first-line cytostatic agents: six courses intravenously of paclitaxel 135 mg/m2 and cisplatin 75 mg/m2 every 21 days. The chemotherapy was well tolerated. The patient completed the treatment with total remission, including clinical, marker (CA125: 4.1 U/ml) and imaging (CT, ultrasound, chest X-ray), which was confirmed during a second-look surgery performed on July 27, 2004.

Nine years after the completion of treatment, a recurrence of malignant disease was diagnosed: abdominal and pelvic CT (July 23, 2013) displayed a cluster of lymph nodes with a cross section of 25 x 22 mm near the left renal vessels running the length of the aorta to the left common iliac artery (CA 125 marker: 22.2 U/ml). The patient was monitored until April 2013 in outpatient care. In March 2013, a control CT found that the described enlarged lymph

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node cluster was infiltrating the lumbar muscles on the left side (52 x 28 mm). An axillary ultrasound revealed enlargement lymph nodes, which were removed surgically. Histopathologic examination determined an infiltration of a poorly differentiated tumor, *probably serous carcinoma G3*. In view of the ambiguity of the histopathologic evaluation, on May 13, 2013 a partial removal of the cluster of lymph nodes along the aorta was performed. The procedure was complicated by bowel obstruction, and during a laparotomy procedure on May 16, 2013, an anastomosis between the small bowel and the transverse colon was rendered. Histology confirmed a recurrence of cancer of the fallopian tube and ovary: *serous carcinoma G3*.

The patient received second-line chemotherapy: intravenous paclitaxel 175 mg/m2 and carboplatin (AUC 5.0), six courses of treatment every 21 days. In October 2013, after the cessation of treatment, complete remission of the neoplastic disease had been achieved [evaluated by abdominal ultrasound, chest X-ray, and the CA 125 marker (10.2 U/m)]. Currently the patient is receiving outpatient oncologic care.

Discussion

The incidence of recurrence is affected by many factors, such as: histological type, the stage of progression at the time of diagnosis, the degree of differentiation, the scope of surgery, the use of adjuvant therapy, and the sensitivity to platinum derivatives [9-11]. Depending on the time that has elapsed between the completion of the first-line treatment with platinum derivatives, and the appearance of recurrence of ovarian cancer, patients are divided into the following groups:

- Platinum resistant - recurrence occurs up to six months after completion of treatment with platinum.
- Partially platinum sensitive - recurrence occurs within six to 12 months after completion of treatment.
- Platinum sensitive - recurrence occurs more than 12 months after completion of therapy [6, 12, 13].

Among the studies of Robinson *et al.* [14] and Rauh-Hain *et al.* [15], it was concluded that patients who were additionally treated with bevacizumab within the standard treatment regimen of paclitaxel and platinum derivatives, cancer recurrence was in different anatomical sites: more often to the retroperitoneum, including the lungs and pleura, the central nervous system, the skin, and less commonly to the liver. This would explain the authors' concept pertaining to altered immunoregulation in the peritoneal cavity.

In many studies, it is emphasized that the recurrence of ovarian tumors appearing after more than two years after achieving complete clinical remission, have a different biology than those recurrences occurring up to two years from the completion of the first-line therapy. It is undisputable that the condition for diagnosing a case as a recurrence, and not as a second, independent tumor, is the confirmation of identical histological structures of the primary and the recurrent tumor [16, 17]. Nevertheless, it is observed that in some cases of ovarian cancer, clinical recurrences behave like new tumors and respond well to treatment with platinum derivatives. This observation also supports the hypothesis that some cases of late recurrent ovarian carcinoma are in fact subsequent primary peritoneal tumors, and not a consecutive pathological proliferation of dormant ovarian cancer cells. Another theory on late recurrence states that, the same carcinogen acting newly on different groups of cells may cause a tumor identical to the primary tumor [16]. The results presented by Buller *et al.* [17] on the study of late recurrence of ovarian cancer indicate that 77% of tumor cells treated as late recurrences, had a different genotype than the cells of the original tumor. Thus, the concept of "field cancerization" of the carcinogen, which originally affected the ovarian cells, was developed. In the same study, it was hypothesized that the incidence of late recurrence ovarian carcinoma, whose cells differ in clonality from the primary lesion, may be characteristic for families predisposed to malignant tumors. The case raises the suspicion that ovarian cancer of epithelial origin may change its histological picture with the progression of the cancer process. The likely hypothesis of multifocal epithelial neoplasia of the primary site, supports the development of tumors of epithelial origin in patients after prophylactic oophorectomy due to a positive family history and as a result of late recurrences in women treated for ovarian cancer [9, 18].

Frequently, the increasing concentration of CA 125 is the first sign of the recurrence of ovarian cancer. If there are no clinical signs of the disease, treatment of the recurrence based solely on the increasing marker does not prolong survival, while causing cytotoxic effects. The average time between the CA 125 concentration increase and the clinical or radiological recurrence is two to four months. The three parameters, (clinical and radiological recurrence, and the CA 125 marker) are good indicators to initiate treatment [1, 13, 19, 20]. There are many deciding factors to the treatment strategy, most importantly, tumor size and the breaks in platinum therapy [21, 22].

Due to the described diverse biology of tumors occurring as late recurrence ovarian cancer, and more frequently appearing in the form of singular changes rather than metastatic disease, the patient with late recurrence, is a good candidate to attempt complete cytoreduction of the changes during a secondary surgery. Surgical treatment as second-line therapy in recurrent ovarian cancer has good clinical results also in the case of recurrence of tumors with borderline malignancy [11].

It has been proven that in the case of late recurrence ovarian carcinoma, using a treatment regimen analogous to first-line therapy, the surgical treatment allows for radical removal of tumor foci. With aggressive chemotherapy, in the majority of patients, it is possible to achieve a favorable clinical outcome [17, 23]. Only in the case of borderline ovarian tumor recurrence, the response rate to chemotherapy is low [14]. If we assume that late recurrences of ovarian carcinoma are in actuality another primary tumor, it would explain the favorable response to treatment with platinum derivatives. By comparison, in

cases when tumor recurrence presented shortly after first-line chemical treatment was concluded, the tumors were resistant to platinum derivatives, because there was formation of cell clones resistant to the chemotherapeutic agent [19].

In the two presented cases on late recurrence, the histopathologic picture between the primary tumor and the recurrence did not differ. One of the patients completed chemotherapy with total clinical remission, depressed markers, and in the upcoming months requires only regular oncologic follow up care. Therefore, the presence of late recurrence ovarian carcinoma and the high probability of effective second-line treatment, justifies the practice of a longer and more intense monitoring of patients after the culmination of the first-line therapy [16]. Similarly, in borderline ovarian tumors, where the recurrence tends to appear at different intervals from the completion of the first-line therapy (even years late), there is a necessity, in the case of the diseased, for regular long-term monitoring of patients, including the performance of full pelvic examinations, ultrasound evaluation, and measurement of the concentration of the CA 125 marker in the serum [24].

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