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Case Report

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Solitary lymph-nodal para-aortic recurrence in a patient with High Grade Serous Ovarian Cancer

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Abstract

Ovarian cancer is the second most common cause of gynecologic cancer death. The most common histologic category of epithelial ovarian cancer is High Grade Serous Ovarian Cancer (HGSOC). The initial management usually involves appropriate staging and debulking surgery. Otherwise, patients with unresectable disease receive neoadjuvant chemotherapy, and then undergo Interval Debulking Surgery (IDS). However, even cases with complete clinical response often experience a recurrence. While the primary debulking surgery is the standard of treatment, the role of secondary debulking surgery for recurrent ovarian cancer is still debatable.

The most common sites of recurrences are pelvis and abdomen, whereas recurrence confined solely to lymph node is a rare event. Secondary cytoreductive surgery (SCS) for recurrent ovarian cancer presenting as isolated lymph node metastases has been associated with favorable long-term survival, although the resection of aortic metastatic lymph nodes could be related to severe intraoperative complications.

In this article, we report a case of a 72-year-old patient with an isolated lymph-nodal para-aortic recurrence with a history of primary debulking surgery for high grade serous ovarian cancer FIGO stage IV, four years before, followed by received adjuvant chemotherapy, and maintenance therapy. The patient presented with a lymph node relapse down the ileocolic artery and submitted to radical resection of the metastatic lymph nodes.

Key words: Ovarian cancer, recurrence, debulking

Introduction

Ovarian cancer ranks as the seventh most prevalent malignancy among women. The eighth most common cause of death from cancer, with survival rates below 45% over a five-year period.[1] Additionally, it is the second most common cause of gynecologic cancer death.[2]

Ovarian cancer is uncommon in women who are less than 40 years old, and the majority of malignancies in this age range, are germ cell tumors. Conversely, individuals above the age of 40 predominantly develop epithelial tumors, accounting for over 90% of cases. The likelihood of developing these tumors rises with age, reaching its highest point in the late 70s.

High Grade Serous Ovarian Cancer (HGSOC) is the predominant histologic category, representing more than 70% of all cases of Epithelial Ovarian Cancers (EOCs).[3] HGSOCs display papillary and solid growth patterns under microscopic examination. The cells are big and have a single nucleus, which shows pleomorphic nuclei with noticeable nucleoli and active cell division. The majority of HGSOCs occur randomly, however around 15% to 20% of women who are diagnosed with EOC have an inherited susceptibility to the disease due to mutations in the BRCA1 and BRCA2 genes.[4,5]

Despite being classified as ovarian, a significant percentage of high-grade serous tumors are currently believed to have their genesis in the fallopian tube.[6]

Despite recent technological advancements enabling more precise radiographic and laboratory diagnostic procedures, over 60% of ovarian cancer cases are still identified at an advanced stage. Given the elevated fatality rate associated with advanced stages of ovarian cancer, timely detection continues to be the primary determinant of prognosis. Regrettably, until nowadays there is still no public health screening program in place to promptly detect it. As a result, diagnosis frequently occurs during the advanced stages, leading to significant recurrence rates and typically low survival rates in this population.[7]

Surgery is mostly required for precise surgical staging, as it is documented using the International Federation of Gynecology and Obstetrics (FIGO) guidelines.[8] Additionally, surgery also serves a therapeutic purpose by removing visible disease. Treatment choices are determined by the stage and biology of the disease, and the results are influenced by the stage and histology.

Typically, the initial treatment involves appropriate staging and debulking surgery (involving bilateral sapling oophorectomy, abdominal hysterectomy) with the objective to resect all the areas of disease, ideally leaving no visible signs of disease [R0], and then administer adjuvant taxane/platinum combination chemotherapy. Alternatively, patients who are deemed unsuitable candidates for surgery due to severe disease have the option of undergoing Intermediate Debulking Surgery (IDS). This treatment approach involves administering neoadjuvant chemotherapy followed by debulking surgery.

However, even ovarian cancer with complete clinical response often experiences a significant recurrence rate.[3] Recurrence is present in approximately 25% of cases with early-stage illnesses and in over 80% of cases with more advanced stages.[3,9] The high rate of recurrence has been linked to the intrinsic resistance to chemotherapy.

Generally, the primary objective is to promptly identify recurring lesions, as this directly impacts the overall survival rate. NCCN guidelines advise scheduling follow-up appointments at intervals of 2-4 months during the initial 2-year period, and then at 6-month intervals for the subsequent 3 years, for patients with epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer. During each appointment, it is advisable to do a physical examination and determine the CA125 level or the appropriate tumor marker. Due to concerns about

the possibility of the condition returning, the patient underwent diagnostic imaging procedures, such as a CT scan or a PET scan.[10]

Patients who experience a recurrence within the first six months are classified as platinum resistant. In such cases, it is recommended to undergo single agent chemotherapy, such as taxol or liposomal doxorubicin, with or without the addition of bevacizumab. Alternatively, if a recurrence occurs after 6 months, patients are categorized as platinum-sensitive. In such cases, it is recommended to consider subsequent debulking surgery if complete removal of the tumor (R0) is possible, followed by chemotherapy.[3]

Case presentation

A 72-year-old woman first presented in July 2019 with abdominal pain and distension. The patient had three normal labors; from her family history she mentioned a brother with lymphoma, and underwent an open cholecystectomy. She had a history of type 2 diabetes, hypertension, autoimmune hypothyroidism and took metformin, gliclazide, allopurinol, levothyroxine, olmesartan/amlodipine, and alendronic acid. The diagnostic procedure consisted of a computerized tomography scan that showed gross ascites, peritoneal implants and a 3,8 cm mass in the left ovary, and tumor marker evaluations that revelead elevated levels of cancer antigen CA 125 (2222 U/mL) and CA 15-3 (533 U/ml). Furthermore, we performed an abdominal paracentesis and peritoneal fluid cytology indicated metastatic adenocarcinoma, and CA 125 was elevated (8150 U/ml) in the peritoneal fluid. Next step was a diagnostic laparoscopic surgery that revealed extended peritoneal carcinomatosis, ascites, diaphragmatic infiltration and omental cake with an overall Fagotti score=6. The peritoneal biopsy showed high grade serous cancer with immunohistochemical markers favoring female genital tract origin (p53/aberrant positive).

Treatment strategy began with the patient undergoing extended primary debulking surgery (PDS) including posterior pelvic exenteration with primary anastomosis, appendectomy, removal of peritoneal implants, implants of the abdominal wall, of the spleen, of gallbladder fossa, and trocar incision scars, round ligament of liver, omenectomy, and diaphragmatic stripping in September 2019. Histology showed high-grade serous ovarian carcinoma with positive ER, PAX-8, WT1, P53/aberrant involving both ovaries, omentum, mesoappendix, liver parenchyma and peritoneum (Stage IV, pT3c, Nx, M1).[8]

Afterwards, she received six cycles of adjuvant chemotherapy with carboplatin/paclitaxel from October 2019 to January 2020.

The patient was scheduled a follow up scheme for every 3 months the first two years[10] but at June 2022, she presented a relapse with multiple lymph node metastasis and received chemotherapy with carboplatin/paclitaxel and bevacizumab from July 2021 till November 2021, and followed a maintenance therapy scheme with olalaparib from December 2021 to May 2022.

In June 2022 she showed a slight rise of CA 125 (45,5 U/ml), and then the patient underwent CT scan that revealed a 5,3 x 3,2 cm mass in the right

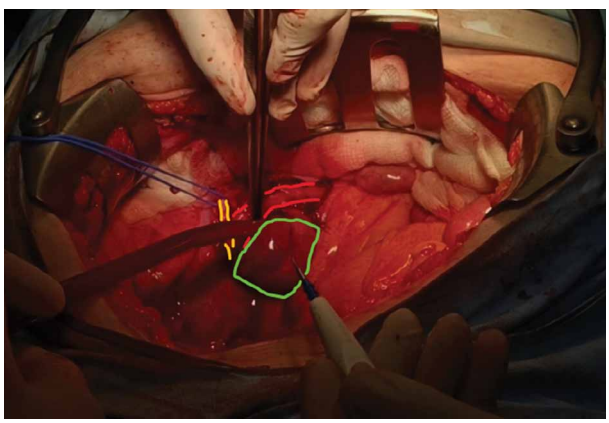

Figure 1. Lymph node mass (green border) prior to the onset of debulking. Mobilization of the right ureter (yellow border) and the common iliac artery (red border).

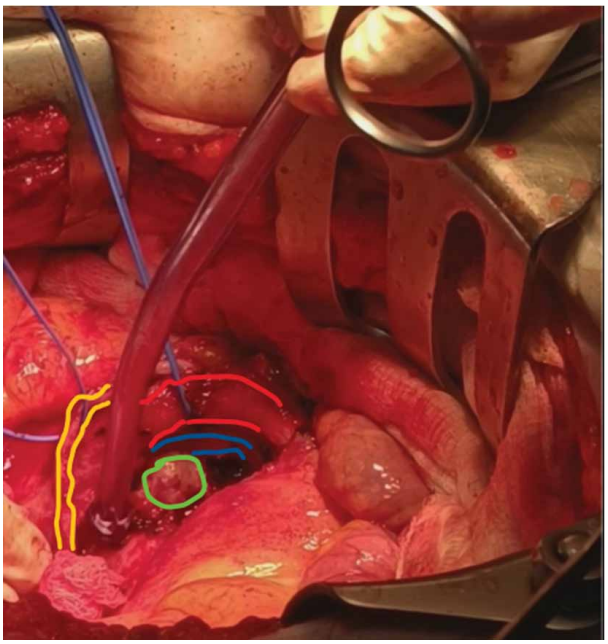

Figure 2. Lymph node mass (green border) following resection of the superficial lymph node group. Mobilization of the right ureter (yellow border), the common iliac artery (red border) and common iliac vein (blue border).

side of the root of mesentery with SUVmax=31,3. Oncologists decided to stop the maintenance therapy with opaparib and to start hormone therapy with letrozole because the histology showed ER positive serous ovarian cancer.

A secondary debulking open surgery with a para-aortic lymph-nodal radical dissection of the tissue down the superior mesenteric artery was performed in August 2022. At histological examination, the dissected lymph nodes were positive for metastasis, and the patient received 6 cycles of chemotherapy with carboplatin/gemcitavin.[3]

The third relapse was noted 7 months after the second one with detection of enlarged pelvic lymph nodes 30x17,5 mm in the contrast-enhanced CT and the tumor board suggested a different chemotherapy scheme with 16 cycles of chemotherapy with paclitaxel that the patient received until August 2023. In September 2023, the patient submitted to new imaging with positron emission tomography/computed tomography (PET/CT) revealed the involvement of two pelvic nodes (39 mm × 36 mm and 16 mm × 14 mm, respectively) down the right common iliac artery with no other positive sites. Tumor markers were not elevated with CA 125=23.6 U/ml, CA 15,3=67.7 U/ml, and CEA=1.07 U/ml. In addition, we performed contrast-enhanced CT that clearly identified these enlarged nodes, which we considered to be resectable.

After providing written informed consent, a debulking open surgery with a para-aortic lymph-nodal radical dissection of the tissue down the right common iliac artery. Bowel mobilization was initially performed due to extensive adhesions in the pelvic sidewall and the pouch of Douglas which was followed by mobilization of the right ureter which was adherent to the metastatic lymph nodes. The right common iliac artery and the anterior surface of the right common iliac vein were exposed. The metastatic lymph nodes were detected in the paraortic space resected, beneath the aortic bifurcation and in close relation to the right external iliac artery and vein; as shown in figure 1 & 2. The operative time during the surgical procedure was 180 min, and the estimated blood loss was 150 mL. No intraoperative or postoperative complications were noted.

Discussion

While primary cytoreductive surgery is the standard of care for advanced ovarian cancer in patients with resectable disease and good performance status, the role of secondary debulking surgery for recurrent ovarian cancer is still debatable.[11] The management of the relapse of the ovarian cancer is crucial because the median post-relapse survival is approximately 18 months,[12,13] and can be affected by the time from the end of platinum therapy and recurrence (platinum-free interval-PFI), and the pattern of the recurrence.[12]

More specifically, short duration of PFI is a negative prognostic factor for survival rate. Moreover, patients with diffuse abdominal carcinomatosis present an unfavorable prognosis compared with patients with discrete lesions, regardless the platinum-free-interval.[14] However, using non-platinum chemo or targeted therapy to prolong PFI in platinum intermediate recurrent ovarian cancer is not beneficial.[15,16]

The most common sites of relapses are pelvis and abdomen, whereas recurrence confined solely to lymph node is a rare event, accounting for 1-6%.[17,18] The treatment of choice for cases with isolated lymph node relapse (ILNR) has not been established yet in the literature due to heterogeneity of medical history and performance status of the patients, the evolution of chemotherapy agents, and the different sites of nodal disease among the cases. For instance, in a recent series of 79 patients, the treatment of ILNR included chemotherapy alone for 52 (65.7%) patients, surgery alone for 2 (2.5%) patients, the combination of surgery followed by chemotherapy for 17 (21.5%) patients and the combination of chemotherapy and radiotherapy for one patient (1.3%).[19] However, out of 135 patients in a different cohort study, 66 had an intraperitoneal relapse diagnosis, 30 had a retroperitoneal lymph node relapse diagnosis, and 39 had a combined site relapse diagnosis. Except for CA-125, which was considerably lower in the retroperitoneal recurrence group at diagnosis, at the conclusion of treatment, and at the time of recurrence, all groups had comparable clinical, pathological, and surgical aspects. Among the patients with ILNR 17 of them (56.7%) submitted primary surgery, while 13 of them (43.3%) interval debulking surgery after three cycles of neoadjuvant chemotherapy.[20] It is well mentioned that secondary debulking surgery in patients with paraaortic relapse includes high risks of iatrogenic vascular injuries due to their position posterior the major vessels.[18]

Recent study pointed out that ILNR show better prognosis than disease relapse in other sites resulting in a median post-recurrence survival (PRS) rate of approximately 37 months and an OS rate of 109 months.[21] The recent study demonstrated significantly higher rates of overall survival (OS) and post relapse survival (PRS) in the retroperitoneal recurrence group compared to the intraperitoneal and combined site recurrence groups. (OS: 93.07, 47.9 and 41.7 months, respectively, PRS: 68.57, 29.67 and 19.7 months, respectively).[20] By contrast, a retrospective analysis including 79 patients (5.2%) presented with ILNR, and 247 (16.4%) patients had isolated carcinomatosis recurrence (ICR) and concluded that ILNR is not associated with a favorable overall survival. The 3-year and 5-year OS rates in the ILNR group were 85.2% and 53.7% respectively, compared to 68.1% and 46.8 % in patients with ICR. The 3-year and 5-year overall survival rates following the detection of recurrence were 62.6% and 15.6% in the group of patients with incomplete lymph node resection (ILNR), and 44% and 15.7% in patients with incomplete chest resection (ICR).[19]

According to several studies high grade ovarian cancer with inactivation of BRCA1,2 or copy number gain of CCNE1 was associated with poor prognosis and chemoresistance.[22,23] Hollis et al. investigated the molecular typing of ILNR and did not identify enrichment of BRCA 1,2 or depletion of CCNE1 in comparison to extranodal relapse counterparts (24.4% vs 19.4% and 18.2% vs 22.6%, P = .865 and P = .900).[24] They also showed greater CD3þ and CD8þ cell infiltration in ILNR, indicating stronger tumor engagement by T cell populations, which may contribute to the more favorable course of disease.[24]

Concerning the management of ILNR, Gadduci et al. reported that patients who treated by secondary cytoreductive surgery plus chemotherapy presented longer median overall survival (>74.5 months), and PRS >74.5 months compared to the patients who received only chemotherapy 45.4 months, 20.8 months

respectively.[25] Bogani et al. evaluated the prognostic significance of complete lymphadenectomy in patients with ILNR. They compared 11 patients who had complete lymphadenectomy to 24 patients who had isolated bulky node resection and observed that there was no difference in overall survival (HR 0.98, 95% CI, 0.37–2.61). However, PRS was declined in those underwent complete lymphadenectomy (HR 0.41, 95% CI, 0.27–0.97).[26] Finally, a current review of the literature including 437 patients demonstrated that a combination of secondary debulking surgery plus adjuvant chemotherapy optimize the survival rate.[27]

Conclusion

Ovarian cancer presents significant challenges and necessitates the collaboration of various medical specialties. It is a highly stressful and regrettable condition for patients. Following primary treatment regimens, recurrences often occur, which are unpredictable and challenging. While the value of primary debulking surgery is unquestionable, there is ongoing debate over therapeutic choices for relapses.

Author contributions:

F.M., P.P contributed to conception and design. T.N., M.K. were responsible for overall supervision. P.V. drafted the manuscript, which was revised by V.D. All authors read and approved the final manuscript.

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