Case report

Hyperthermic intraoperative thoracoabdominal chemotherapy for stage IVB epithelial ovarian carcinoma

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1. Background

Epithelial ovarian cancer (EOC) is the most lethal malignancy in Western countries. Most patients present with advanced disease and synchronous peritoneal metastases (PM), with poor prognosis (Pavlov et al., 2009). The optimal management for patients with newly diagnosed, primary stage III EOC, is a combination of systemic chemotherapy with interval cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (Auer et al., 2020). Hyperthermic intrathoracic chemotherapy (HITHOC), a palliative targeted surgical therapy for patients with malignant pleural effusion, has also been reported, with acceptable morbidity and overall survival benefit (Zhou et al., 2017; Dattatri et al., 2019). A combination of HIPEC and HITHOC, hyperthermic intraoperative thoracoabdominal chemotherapy (HITAC), has been described recently for concomitant peritoneal and pleural disease, but only in patients with pseudomyxoma peritonei and peritoneal mesothelioma. It is associated with high morbidity, but acceptable survival and low intrathoracic recurrence (Sugarbaker et al., 2012). We herein present the case of a 48-year-old patient with stage IVB EOC, who presented with PM and refractory unilateral pleural effusion, who successfully underwent surgical management with CRS and HITAC.

2. Case presentation

This is the case of a 48-year-old woman who presented with rapidly progressive shortness of breath due to a right pleural effusion of unknown origin. Her medical record was remarkable for well-controlled asthma and previous vaginal hysterectomy for pelvic prolapse. Computed tomography imaging (CT) revealed an important right pleural effusion suspicious of malignancy, but without macroscopic disease, with bilateral complex adnexal masses and PM, including visible implants on diaphragmatic domes, small bowel mesentery and omentum (Fig. 1). A subsequent positron-emission tomography–CT was also positive for enlarged mediastinal lymph nodes. CA-125 level was 724 IU/mL. The diagnosis of EOC was confirmed at pleural cytology. The patient was subsequently given 3 cycles of neoadjuvant chemotherapy (NACT) combining paclitaxel and carboplatin (TC), during which she required several thoracenteses for symptoms relief. Follow-up imaging reported response to treatment, with complete regression of the hypermetabolic supra-diaphragmatic lymph nodes and partial regression of the right pleural effusion with persistent pleural thickening, but without visible implants. Intraabdominal response was also reported, with a decrease in size of the adnexal and mesenteric implants. CA-125 level decreased to 140 IU/mL. The case was discussed at...
ge gynecologic oncology reports 34 (2020) 100654
2

multidisciplinary tumor board. It was decided to proceed with surgical management if a complete peritoneal CRS was feasible, but to perform video assisted thoracoscopic surgery (VATS) first to assess the presence of pleural disease. Subsequent HIPEC would be performed if microscopic-only disease was found and full-thickness diaphragmatic resection was required, as pleural CRS for macroscopic disease was judged unreasonable. HIPEC only would be performed if VATS was negative. Signed informed consent was obtained from the patient, who understood the experimental nature of this procedure.

The patient was brought to the operating room one week later. A right-sided VATS was performed first, which revealed diffuse pachypleuritis compatible with sequelae of miliary pleural implants on the inferior parietal pleura. The visceral pleura was macroscopically normal. Frozen sections of the inferior parietal pleura were positive for microfoci of malignant cells. An exploratory laparotomy was performed after. The peritoneal cancer index (PCI), a tool used to assess the extent of PM throughout the peritoneal cavity, was 24, with extensive disease on the parietal peritoneum and in the pelvis, but spared colon and small bowel. A completeness of cytoreduction (CC) score of 1 (remnant tumor of less than 0.25 cm) was deemed feasible, with acceptable surgical risks and morbidity. In the absence of macroscopic disease on the pleura, it was decided to proceed with CRS of the abdominal compartment with HITAC. The CRS included a posterior exenteration (bilateral salpingo-oophorectomy, partial vaginal resection, low anterior resection and complete pelvic peritonectomy), selective parietal peritonectomies, bilateral diaphragmatic dome peritonectomies, appendectomy, cholecystectomy, supramesocolic omentectomy, electro-evaporation of small bowel mesenteric implants, as well as selective pelvic and para-aortic lymphadenectomy. An 8 cm implant on the right diaphragmatic dome required a full-thickness resection, which was not immediately repaired (Fig. 2). A closed-technique HITAC was then performed. The inflow tube was placed in the pelvis, and the outflow tube was inserted through the right pleural cavity (Fig. 3). Temperature probes were placed at the four quadrants of the abdomen. Carboplatin (AUC 10) in normal saline solution, with a perfusion volume of 2L/m², at a target temperature of 42 °C for 90 min, was introduced, with maintained ipsilateral lung ventilation. After completion of HITAC, a non-progressive, 15 cm subcapsular liver hematoma was observed and managed with liver packing. The right diaphragmatic dome defect was closed primarily. Total length of the surgery was 12 h and estimated blood loss was 1150 mL. The patient remained in the intensive care unit for 8 days following surgery.

Fig. 1. Computed tomography (CT) imaging at initial presentation (A) Significant right pleural effusion. (B) Peritoneal metastases on the right diaphragmatic dome (arrow). (C) Complex right ovarian mass (arrow). (D) Peritoneal metastases on the omentum (arrow).

Fig. 2. Right diaphragmatic dome deficit of 8 × 10 cm following cytoreductive surgery, left open to allow chemotherapy circulation during hyperthermic intraoperative thoracoabdominal chemotherapy.
Gynecologic Oncology Reports 34 (2020) 100654

3. Summary and conclusion

This case illustrates the challenges related to the treatment of patients with advanced EOC and pleural disease. Despite being the most common metastatic site of stage IV EOC, the accuracy rate of pleural cytology for suspicious effusions remains low and management can be complex (Escayola et al., 2015). In this case, the patient was initially given NACT, since stage IVB patients benefit from it and response to treatment is a good prognostic factor (Tajik et al., 2018). However, despite good response to treatment outside of the pleural space, the patient remained symptomatic because of a refractory pleural effusion. Since the patient was young and motivated, with proven platin-sensitive, surgical management options were explored.

The administration of HITHOC has been described in recent literature as a targeted palliative therapy for patients with refractory primary and secondary pleural metastases, and is usually combined with CRS of the pleural compartment. Pharmacokinetic studies on HITHOC cohorts report that high concentrations of intrapleural drugs may be achieved using this technique, with tissue penetration up to 4 mm (Zhou et al., 2017). However, in a recent study by Sugarbaker et al. (Sugarbaker et al., 2012) comparing the systemic absorption rates of mitomycin C with HIPEC, HITHOC and HITAC, the absorption rate of HITHOC was significantly lower after 90 min (41%), while HIPEC (75%) and HITAC (67%) rates were comparable. The same study reported similar data with doxorubicin regimens. In this case, the patient presented with microscopic-only disease on the parietal pleura, which was responsible for the refractory pleural effusion. Without visible disease in the pleural space on preoperative imaging, but with macroscopic infiltration of the right diaphragmatic dome, it was believed to be secondary to full-thickness diaphragmatic involvement with PM rather than pleural carcinomatosis. This suspicion was confirmed at VATS, where no disease was found on the visceral and parietal pleura, except on the diaphragm. HITAC seemed to be the best option, with good systemic absorption and optimal lavage of the abdominal compartment, while addressing the pleural space. Without the need for full-thickness diaphragmatic resection, HITAC would not have been performed.

The administration of HITAC is associated with additional challenges compared to HIPEC, especially for the anesthesia team. Blood loss, fluid shifts and temperature extremes may be more difficult to manage (Solanki et al., 2019). Nephrotoxicity can also be an issue (Dattatri et al., 2019). Carboplatin HIPEC has been demonstrated to be safe and effective in the treatment of EOC (Mikkelsen et al., 2019) and was our agent of choice, as it reduces this risk compared to other agents such as cisplatin (Colombo et al., 2016). Otherwise, few adjustments were made to the institution’s HIPEC protocol in order to perform HITAC. Regarding chemotherapy dose, Sugarbaker et al. (2012) demonstrated that adjustments are not necessary with HITAC. It was also decided to use the same volume of perfusion than for HIPEC, but to maintain ipsilateral lung ventilation in order to induce an intermittent negative-pressure and enhance circulation of chemotherapy through the pleural compartment. The outflow tube was positioned in the pleural space, but close to the diaphragmatic defect, as the diaphragmatic pleura was the main region to cover with chemotherapy outside the abdomen. It also allowed to avoid circulation problems and retained chemotherapy inside the thorax.

This case was approached with a curative intent despite being stage IVB initially. Although the patient did experience early recurrence at the thoracic level, we believe that this procedure was justified, as she is now disease-free in the abdomen and oligometastatic in the thorax. Also, because of the recurrent right pleural effusion and persistence of disease at this level, we think that the patient would not have tolerated palliative chemotherapy for long without the procedure.

In conclusion, although this is the first case reporting such an approach for this etiology, CRS with HITAC seems to be a reasonable and feasible option in fit patients for short-term control of advanced EOC and full-thickness diaphragmatic infiltration with pleural effusion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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None.

Patient consent

Written informed consent was obtained from the patient for publication of this case-report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

All authors contributed to the conception and design of the study, as well as critical review of the article and final approval for publication. Alexandre Brind’Amour and Elizabeth Tremblay managed the acquisition, analysis and interpretation of data and wrote the article. Lucas Sideris is guarantor of the project.

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