

# A case of occult bowel perforation after a cycle of chemotherapy for advanced epithelial ovarian carcinoma

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## Summary

Occult bowel perforation is a rare complication in chemotherapy of advanced epithelial ovarian cancer (EOC). The authors present a case of a 75-year-old woman who had appendectomy due to suppurative appendicitis five years prior, that experienced an occult bowel perforation resulting in continuous decline of electrolytes after a single cycle of nedaplatin (NDP) and paclitaxel during neoadjuvant treatment of advanced EOC. To the authors' knowledge, this is the first reported case of an occult bowel perforation after neoadjuvant chemotherapy (NAC) for ovarian cancer. The complication was highly suggestive of a cell lysis mechanism for the perforation.

**Key words:** Advanced epithelial ovarian cancer; Occult bowel perforation; Electrolytes; Neoadjuvant chemotherapy; Nedaplatin; Cell lysis; CA 125.

## Introduction

Epithelial ovarian cancer (EOC) is the fifth most common malignancy among women and most ovarian cancers are only diagnosed after the disease has spread throughout the peritoneal cavity, when prognosis is poor [1]. More than 80% of these women with late-stage disease will die within five years. Approximately 75% of ovarian cancer patients are initially diagnosed with disseminated intra-abdominal disease and classified according to the International Federation of Gynecology and Obstetrics (FIGO) Stage III or Stage IV [2]. Treatment of ovarian cancer is based on the integration of surgery and chemotherapy [3]. Chemotherapy plays a major role in the adjuvant treatment and in the care of patients with advanced disease [4]. Primary chemotherapy with cytoreduction for advanced ovarian carcinoma has been controversial [5]. However, when clinicians think cytoreductive surgery as an initial step, it is not feasible or might entail excessive perioperative risk for the patient, and may then suggest the patient completes cytoreduction after three cycles of chemotherapy. The complications associated with chemotherapy are well known but bowel perforation is a rare event. There have been reports of bowel perforation in ovarian cancer patients with paclitaxel [6, 7]. In 2007, Carter and Durfee reported a case of bowel perforation with Stage III ovarian cancer after one cycle of adjuvant chemotherapy of carboplatin and paclitaxel; the patient was found to have bowel perforation on the fourth day after chemotherapy because of symptoms of acute peritonitis and identification by computed tomography (CT) scan [8]. Bowel perforation is a known complication associated with the use of bevacizumab [9] and in patients treated for gastrointestinal (GI) lymphomas [10-12]. In this case, occult bowel perforation was found intraoperatively which has not been reported before.

## Case Report

A 75-year-old woman, with 26 years of menopause, presented to the hospital with several months of abdominal discomfort, weight loss, and a large abdominal-pelvic mass. She denied urinary urgency and frequency, and minor GI symptoms, including abdominal distension, constipation, and smaller volume stools. She did not have hypertension or high blood sugar. Her past surgical history included significant appendectomy due to suppurative appendicitis at age 71. The mass was fixed and filled the pelvis. She was evaluated by CT scan and abdominal ultrasound (AUS), which both revealed a large cystic mass in the pelvis. AUS indicated no bladder invasion or hydronephrosis. Her CA-125 was 3,389 u/ml, CA-199, CEA, and hCG were normal. No palpable rectal involvement was noted during examination and urine and stool were normal. The mass was percutaneously biopsied under US guidance and pathology showed a poorly-differentiated adenocarcinoma consistent with an ovarian primary. The authors diagnosed an advanced ovarian carcinoma. With the patient's consent, the first cycle of chemotherapy was initiated one week after the initial diagnosis with nedaplatin (80 mg/m<sup>2</sup>) and paclitaxel (175 mg/m<sup>2</sup>) and dexamethasone (10 mg in the morning with chemotherapy, and 10 mg daily for two days), ondansetron was used to prevent vomiting. This patient was discharged the third day after chemotherapy. She had mild vomiting and was able to ingest a small amount of food from the sixth day after chemotherapy. She was provided with a supplement of electrolytes and nutritional support in the local community hospital. Vomiting stopped at the tenth day. She had no fever and did not complain of stomach ache. She returned at the 16<sup>th</sup> day following chemotherapy. Her electrolyte levels (Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Cl<sup>-</sup>) were low to normal; CA-125 level had dropped to 1,978 u/ml, AUS-measured size of the mass had not clearly decreased (Figure 1). Abdominal examination found that the mass was still fixed and there was no muscle tension. According to her weight, approximately half of her electrolytes were supplemented and potassium oral supplements were used. She could eat some food and the authors did not expect to find low electrolytes. However, some reviews found her electrolyte level was not stable; it always declined, even after oral electrolyte supple-

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Figure 1. — Radiologic image of the chest indicating diffuse shadows within the lung, leading to a suspicion of H1N1 infection.

ments and injection on the first day. She did not complain of stomach ache, diarrhea, or abdominal distention, could eat a little food, and her stools were normal. She had a 38.2°C fever that lasted for four hours then dropped to normal; her blood analysis indicated normal leukocytes. Upon patient consent, the authors decided to perform cytoreductive surgery and found extensive intestinal adhesions upon entrance into the abdomen. The adhesions were separated and found the mass originated from the right ovary; its upper pole reached the transverse colon without ascites. Metastasis to the greater omentum or other organs was not found. The authors did not touch the enlargement of the retroperitoneal lymph node. There were two sites ( $2 \times 3 \text{ cm}^2$  and  $2 \times 2 \text{ cm}^2$ ) of invasion of the mass into the bowel wall. After separation of the adhesions, two areas where the bowel was perforated were found. The mass and the bowel had formed sinuses, which were blocked because the mass' periphery was solid and its center was cystic and contained a large amount of foul-smelling fluid but the patient had no symptoms of acute peritonitis. The authors resected the mass and the perforated parts of the bowel (located in the ileum, with a total length of 20 cm) and performed direct anastomosis for the bowel. The pathologists confirmed the diagnosis of poorly-differentiated ovarian serous cystadenocarcinoma. Her postoperative course included two weeks of parenteral alimentation; after that, she could eat a small amount of food, did not feel abdominal distention, and her stools were normal. The patient was discharged on postoperative day 27. Her CA-125 dropped to 451 u/ml. She completed five further cycles of chemotherapy with nedaplatin and paclitaxel. After the third cycle, her CA-125 was normal. Currently, she is alive without disease 11 months after cytoreductive surgery and is undergoing further follow-up.

## Discussion

Adjuvant chemotherapy for early stage ovarian cancer is still controversial [3]. The standard care for patients with advanced ovarian cancer is maximal surgical cytore-

duction followed by systemic platinum-based chemotherapy and it is reasonable to expect a five-year survival for 40% and 20% of women diagnosed with ovarian cancer at Stage III and IV, respectively [3, 13]. Moreover, because most of recurrence after front-line surgical and medical therapies and secondary cytoreduction of surgery does not improve survival [14], further chemotherapy is required to treat relapse. Recently, a phase III randomized study compared primary cytoreduction followed by chemotherapy to neoadjuvant chemotherapy followed by interval debulking surgery in women with advanced ovarian cancer. No statistical difference in morbidity, mortality, or quality of life was found [5]. These results have stimulated a good deal of discussion between experts in this field. It is believed that upfront maximal cytoreduction is still the standard procedure, although further research should focus on how to select patients that cannot receive optimal cytoreduction and can benefit from a neoadjuvant strategy. Therefore, noninferiority of neoadjuvant chemotherapy followed by interval debulking surgery to primary debulking surgery followed by chemotherapy in patients likely to achieve optimal cytoreduction should be validated. A universally applicable clinical model that can predict which patients should undergo optimal cytoreduction remains elusive [15].

Over the years, experts and research groups have experimented with different combinations of drugs in order to improve the prognosis of ovarian cancer. Nedaplatin is a derivative of cisplatin that induces less nausea, vomiting, and nephrotoxicity. The authors found the combination of nedaplatin and paclitaxel had a beneficial effect on this patient, but this needs to be further investigated in other patients.

Bowel perforation is a rare and life-threatening complication of chemotherapeutic treatment of cancer. Spontaneous perforations of the small and large bowels have been reported during the treatment of various malignancies with chemotherapy alone (23%), in conjunction with corticosteroids (57%), and with corticosteroids alone (20%) [10]. The authors present a case of occult bowel perforation after a single cycle of treatment with nedaplatin and paclitaxel during neoadjuvant treatment of Stage III EOC. The mechanism underlying bowel perforation is uncertain, but it is thought to occur as a result of tumor necrosis with weakening of the bowel wall and poor wound healing that leads to bowel injury. Recently, bevacizumab, the first anti-angiogenesis molecule to demonstrate significant anti-cancer activity, has been used for the treatment of cancer, it inhibited the activities of vascular endothelial growth factor (VEGF), induced vasoconstriction, and resulted in ischemic injury [9, 16]. Patients with an intra-abdominal inflammatory process, such as diverticulitis, obstruction, tumor at the site of perforation, abdominal carcinomatosis or history of abdominal radiation might be at higher risk of bowel perforation [17-20]. Of course, most patients have obvious symptoms and need surgery immediately after bowel perforations; but if the patients electrolytes are not stable and no other reason is found, the authors think it might be the result of occult bowel perforation.





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