Case Report

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

# Late Jejunal Perforation after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Patients with Peritoneal Carcinomatosis

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**Abstract**

**Objective:** Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment strategy that improves survival in selected patients with peritoneal carcinomatosis. However, gastrointestinal complications remain a major source of morbidity. This report aims to present a case of late-onset spontaneous jejunal perforation following CRS and oxaliplatin-based HIPEC and to discuss possible underlying mechanisms. **Case Presentation:** A 55-year-old male patient diagnosed with appendiceal mucinous adenocarcinoma and extensive peritoneal carcinomatosis underwent CRS followed by oxaliplatin-based HIPEC at 42.5 °C for 30 minutes. The early postoperative course was uneventful, and the patient was discharged. On postoperative day 19, the patient was readmitted with fever and abdominal pain. Imaging revealed jejunal perforation accompanied by an anastomotic leak. Emergency laparotomy was performed, including resection of the perforated jejunal segment and creation of an end jejunostomy. No tumor implants or intraoperative injury were identified at the perforation site. **Discussion:** Gastrointestinal perforations after HIPEC are most commonly reported in the early postoperative period, whereas late spontaneous perforations are rare. Despite the short half-life of oxaliplatin, mechanisms such as peritoneal drug sequestration, hyperthermia-induced subclinical tissue injury, impaired fibroblast function, and delayed wound healing may contribute to late perforation. Current literature provides limited data addressing these mechanisms. **Conclusion:** Late-onset jejunal perforation following CRS and HIPEC is a rare but serious complication. This case highlights the potential long-term gastrointestinal effects of intraperitoneal oxaliplatin administered under hyperthermic conditions. Further experimental and clinical studies are warranted to better understand these mechanisms and to optimize patient safety.

**Keywords:** Peritoneal carcinomatosis, cytoreductive surgery, HIPEC, oxaliplatin, jejunal perforation

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## 1. Introduction

Peritoneal carcinomatosis (PC) is a clinical condition observed in advanced stages of gastrointestinal, gynecological, and primary peritoneal malignancies and significantly affects prognosis. Among gastrointestinal cancers, appendiceal tumors and colorectal

cancers represent the leading causes of peritoneal carcinomatosis. In recent years, it has also been shown that selected gastric cancers may benefit from this treatment approach [1].

The aim of cytoreductive surgery (CRS) is the resection and excision of all intraabdominal structures in such a way that no macroscopic malignancy remains. Intraperitoneal chemotherapy administered following surgery aims to achieve microscopic cytoreduction after macroscopic cytoreduction. Through intraperitoneal administration, therapeutic concentrations can be achieved within the peritoneal cavity using lower doses of chemotherapeutic agents, thereby providing similar efficacy with fewer systemic side effects. The pharmacokinetic activity of intraperitoneal chemotherapy is greater than that of systemic intravenous chemotherapy [2].

Hyperthermia enhances the effectiveness of intraperitoneal chemotherapy by increasing peritoneal blood flow, augmenting cytotoxicity, inhibiting DNA repair mechanisms, and influencing the tumor microenvironment.[3] Therefore, intraperitoneal chemotherapy is recommended to be administered at high temperatures (≥40°C), where thermal chemosensitization is maximized, and it has been suggested that the treatment should be maintained for at least 30 minutes. However, a definitive consensus on this issue has not yet been reached [4].

The temperatures achieved during HIPEC treatment may also result in adverse effects. These adverse effects may be systemic due to the chemotherapeutic agent or may include mechanically induced effects such as thermal bowel injury and acute renal failure caused by increased temperature. In addition, intraabdominal abscesses and pleural effusions may also be observed [5,6].

Although drug selection, dosage, and administration have largely been standardized across centers, successful outcomes require appropriate patient selection, complete cytoreduction, perioperative intraperitoneal chemotherapy, and postoperative systemic chemotherapy, all applied within a multidisciplinary approach. Correct patient selection combined with aggressive surgery and intraperitoneal chemotherapy leads to prolonged survival and enables a potentially curative approach for this patient group, which otherwise has a very poor natural course [7].

Another factor determining treatment efficacy and complication rates is the choice of chemotherapeutic agent. Various studies have demonstrated that oxaliplatin is more effective in patients with colorectal cancer, whereas mitomycin-C is considered safer compared to oxaliplatin [8].

Due to the aggressive surgical procedures and cytotoxic chemotherapeutic agents administered at high intraabdominal temperatures, gastrointestinal anastomotic leaks and jejunal–ileal perforations, particularly in the early postoperative period, have been reported in some studies, even though certain agents are considered relatively safe. In patients who did not undergo HIPEC, the average time to leakage has been reported as 5 days, whereas it has been reported as approximately 10 days after HIPEC. This difference has been attributed to the effects of cytotoxic agents and to targeted tissue injury at the sites of tumor implants affected by these agents [9,10]. According to alternative viewpoints, spontaneous perforation may result from trauma inflicted during excision of luminal organ implants during surgery [11].

Although Bekhor et al. reported a study describing bowel content fistulization occurring even beyond 90 days postoperatively, there are no studies providing detailed information regarding the nature, etiology, and timing of such perforations [12]. In this report, we aimed to present a spontaneous jejunal perforation observed on postoperative day 19 in a patient operated on in our clinic for appendiceal mucinous adenocarcinoma. No tumoral implants or perioperative injury were identified in the perforated segment.

However, data regarding delayed gastrointestinal complications following HIPEC remain limited, particularly concerning the underlying mechanisms of late-onset bowel perforation.

**Figure 1. Contrast enhanced CT scan image during emergency room application**

## 2. Case Presentation

A 55-year-old male patient who presented to our clinic was found to have findings compatible with appendiceal mucinous cancer and widespread intraabdominal metastatic lesions on diagnostic evaluation, and surgical treatment was planned. The patient underwent appendectomy, total colectomy, omentectomy, ileorectal anastomosis, cholecystectomy, splenectomy, hepatoduodenal lymph node dissection, peritonectomy, diaphragmatic stripping, followed by HIPEC using oxaliplatin at a dose of 460 mg/m², administered at 42.5 °C for 30 minutes with a perfusion rate of 200 mL/min.

Although early postoperative follow-up revealed a subileus condition, this resolved, and the patient was discharged on postoperative day 10. The patient was readmitted on postoperative day 19 with high fever (38.4 °C) and abdominal pain. On admission to the emergency department, bile-stained discharge from the wound site was observed, suggesting enteric leakage. Contrast-enhanced abdominal CT was performed immediately and demonstrated free air and intraabdominal fluid collections consistent with jejunal perforation. Based on these findings, the patient was taken for emergency laparotomy without delay (Figure 1).

Intraoperatively, a perforation was identified 80 cm distal to the ligament of Treitz, along with leakage at the ileorectal anastomosis in the upper rectum. After intraabdominal lavage, the perforated rectal area was repaired, and the perforated jejunal segment was resected together with a 20-cm segment, followed by exteriorization as an end jejunostomy on the anterior abdominal wall (Figure 2). Wound dehiscence (eventration) was noted, and skin suturing was performed. Postoperatively, the patient was mobilized early, and nutritional management was arranged. The patient was discharged in good condition on postoperative day 20 following the second operation.

Histopathological examination of the resected jejunal segment confirmed the absence of tumor infiltration at the perforation site and revealed fibrinosuppurative exudation consistent with perforation-related inflammation.

**Figure 2**. **Perforated jejunal segment fistulized to the skin**

## 3. Discussion

In advanced-stage cancers related to appendiceal mucinous adenocarcinoma and in pseudomyxoma peritonei, aggressive cytoreductive surgery combined with simultaneous HIPEC represents one of the most important treatment options due to its favorable impact on prognosis [13]. A patient-centered, multidisciplinary approach forms the foundation of treatment. Among patients undergoing CRS and HIPEC, the most commonly reported gastrointestinal complications include anastomotic leakage, bowel perforation, bowel loop obstruction, and evisceration [9,12].

Temperatures exceeding 42 °C may cause late-term damage to the intestinal mucosa through various mechanisms [14]. However, the patient reported here on postoperative day 19 represents a different clinical scenario. The half-life of oxaliplatin has been reported to range between 29 and 40 minutes in various studies. Given this duration, prolonged intraperitoneal drug activity would not be expected. This phenomenon may be secondary to sequestration of the drug within the peritoneal cavity, indirect effects of drug-induced DNA damage, or early tissue injury that subsequently becomes septic [15].

Experimental studies conducted in rats undergoing colonic anastomosis have demonstrated adverse effects of chemotherapeutic agents used in HIPEC; however, no statistically significant differences were observed among cisplatin, doxorubicin, mitomycin-C, and oxaliplatin. Nevertheless, compared to control groups in which

chemotherapeutic agents were not used, impaired wound healing was demonstrated by reduced tissue hydroxyproline levels [16].

Considering wound healing and anastomotic healing timelines, collagen synthesized by fibroblasts in standard tissues and by both fibroblasts and smooth muscle cells in intestinal tissue plays a critical role [17]. No studies have been identified in the literature investigating the relationship between fibroblast production from smooth muscle cells and intraperitoneal HIPEC administration. Furthermore, there are no studies evaluating the effects of oxaliplatin on hydroxyproline levels in colonic anastomotic healing across different postoperative time periods.

Histopathological evaluation of the resected jejunal segment demonstrated transmural edema and fibrinosuppurative exudation without evidence of tumor infiltration at the perforation site. Immunohistochemical staining (PanCK) was negative, further supporting the absence of epithelial tumor involvement. These findings strengthen the hypothesis that the perforation was not related to tumor implantation but rather to non-neoplastic mechanisms.

The present case is particularly noteworthy due to the absence of tumor involvement or direct surgical injury at the perforation site, suggesting a potential role of chemotherapy-induced tissue vulnerability under hyperthermic conditions.

## 4. Conclusion

To the best of our knowledge, there are no studies in the literature investigating the relationship between intraperitoneal HIPEC administration and fibroblast differentiation originating from smooth muscle cells. Although several experimental studies have evaluated the effects of oxaliplatin on colon anastomosis healing through hydroxyproline levels, studies systematically examining different postoperative phases of anastomotic healing remain limited.

The perforation observed in our patient suggests that oxaliplatin may influence anastomotic healing through alternative biological mechanisms and raises the possibility of potential long-term mechanical effects. Experimental models evaluating colon anastomosis healing at different postoperative time points, including the assessment of fibroblast differentiation from abdominal midline tissues and smooth muscle cells, may help clarify these potential mechanisms.

In addition, the impact of the elevated temperatures used during HIPEC on wound healing and anastomotic integrity should be further investigated in experimental studies. If similar clinical findings are observed in other patients or meaningful results are demonstrated in experimental models, certain clinical considerations regarding the intraoperative use of oxaliplatin at high temperatures may need to be revisited. Furthermore, advanced experimental studies investigating the long-term effects of oxaliplatin may provide valuable insights.

For these reasons, we believe that the case presented here may contribute to the understanding of potential mechanisms underlying these findings and holds scientific value.

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