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Disseminated Intravascular Coagulation from Intraperitoneal Oxaliplatin for Appendiceal Carcinoma: A Case Report

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This is a case of a 65-year-old female diagnosed with appendiceal carcinoma, who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Profuse bleeding through the peritoneal drains, with hemodynamic instability, warranted a re-exploration on the fourth postoperative day. Intraoperatively, there was 500 mL of blood clots mostly on the right upper quadrant, diffuse muscle oozing along the previously-stripped right hemidiaphragm and right paracolic gutter, and a non-expanding hematoma on the right anterior abdominal wall. Bleeding parameters were checked postoperatively, and derangements pointing to a disseminated intravascular coagulation were noted. The patient was managed with multiple blood transfusions of packed red blood cells, fresh frozen plasma, platelet concentrates, and cryoprecipitate. Dexamethasone and tranexamic acid were given intravenously. The patient was discharged well on postoperative day 14 after clinical resolution of the bleeding. Eight days after discharge, however, patient succumbed to myocardial infarction.

Key words: disseminated intravascular coagulation, oxaliplatin, hyperthermic intraperitoneal chemotherapy

The conduct of hyperthermic intraperitoneal chemotherapy (HIPEC), after complete cytoreduction, has been reported to improve survival in patients with tumor dissemination confined to the abdomen. The intraperitoneal administration of chemotherapy allows for higher doses of chemotherapy to be given, with minimal systemic toxicity. Hyperthermia, on the other hand, allows for maximal tissue penetration.[1] This documented a case of a 65-year old female who underwent cytoreductive surgery (CRS) with HIPEC for appendiceal carcinoma who developed disseminated intravascular coagulation (DIC) from intraperitoneal oxaliplatin use. This manifested as intraperitoneal bleeding resulting in hemodynamic instability despite multiple blood transfusions.

The Case

A 65-year old female, Eastern Cooperative Oncology Group (ECOG) performance status 1, with no known co-morbidities and no previous surgery presented with a two-month history of anorexia, early satiety, increase in abdominal girth, and weight loss. She did not report of vomiting, or changes in bowel habits.

On initial consult, the patient was seen hemodynamically stable, with clinical findings of massive ascites. The presence of ascites precluded a more thorough abdominal examination on the patient.

The patient had a paracentesis done prior to her consult, with ascitic fluid studies showing no malignant cells or acid fast bacilli, and only a few lymphocytes and macrophages were identified. Both carcinoembryonic antigen (CEA) and CA-125 were elevated to 19.5 ng/ml and 103.9 U/ml, respectively.

A computed tomography (CT) scan of the abdomen revealed massive ascites with pockets of fluid at the left inguinal canal. In addition, the appendix was dilated to 2.1 cm with irregular wall thickening, primary consideration for which was a mucinous neoplasm. (Figure 1) A right ovarian mass measuring 2.8 cm × 2.3 cm, and omental caking were, likewise, seen. The patient was then presented at a multidisciplinary team (MDT) discussion, where a plan to perform CRS with HIPEC was arrived at.

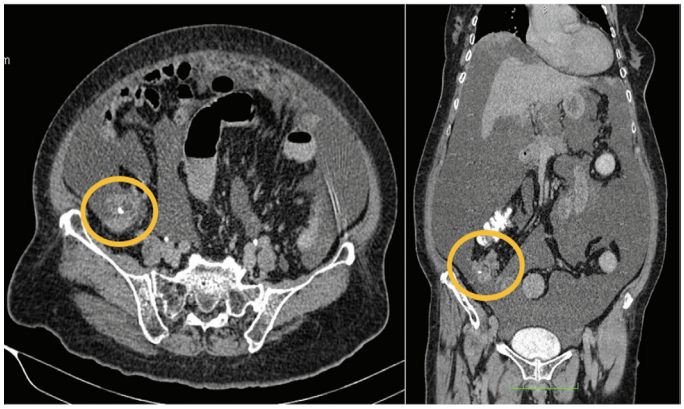

Figure 1. Abdominal CT scan with contrast showing massive ascites, insinuating into the subdiaphragmatic recesses, causing elevation of both hemidiaphragms. Encircled is the distended appendix measuring 2.1 cm (yellow circle) with irregular wall thickening and an appendicolith within its lumen.

She underwent evacuation of ascites; right hemicolectomy, with total omentectomy and splenectomy; total abdominal hysterectomy with bilateral salpingooophorectomy; selective peritonectomy that included stripping of the peritoneum of the bilateral hemidiaphragms through a midline laparotomy incision. Intraoperatively, 16 liters of serosanguinous ascites was drained. The appendix was noted to have been converted into a 2 cm x 3 cm complex mass. Multiple peritoneal implants were seen on the omentum, bilateral hemidiaphragms, hepatoduodenal ligament, anterior abdominal wall, both paracolic gutters, pelvis, and on the surface of the uterus and right ovary, with a peritoneal carcinomatosis index score of 11. Completeness of cytoreduction score 1 was achieved post-CRS. The impression during that time was an appendiceal carcinoma.

Hyperthermic intraperitoneal chemotherapy (intraperitoneal oxaliplatin 460 mg/m^2 at 41.5 to 42.5 degrees celsius for 90 minutes, intravenous leucovorin 20 mg/m^2, and intravenous 5-fluorouracil 400 mg/m^2) was then done. An ileostomy with distal mucus fistula was fashioned prior to closure of the abdomen. The total operative time was eight hours. The estimated blood loss was 1.3 liters; however, intraoperative blood transfusion was not warranted based on point-of-care blood testing done intraoperatively.

The patient's postoperative course was unremarkable until the fourth post-operative day, when there was note of bleeding from the intraperitoneal drains that warranted blood transfusion.

A decision to perform abdominal re-exploration was made as the patient had episodes of hypotension as low as systolic blood pressure of 70 mmHg despite resuscitation with fluids and blood products. Five hundred milliliters of blood clots mostly on the right upper quadrant, diffuse muscle oozing along the previously-stripped right hemidiaphragm and right paracolic gutter, and a non-expanding hematoma on the right anterior abdominal wall.

Upon checking the bleeding parameters, the observed derangements pointed toward DIC: low platelet count, elevated D-dimer concentration, and prolonged prothrombin time (PT).

The patient underwent multiple blood transfusions totaling 16 units packed red blood cells, 20 units fresh frozen plasma, 25 units platelet concentrate, and 10 units cryoprecipitate in a span of five days. She was also given dexamethasone and tranexamic acid. These were done to address the coagulopathy of the patient. The bleeding eventually resolved, and the patient was discharged well 14 days postoperatively.

The final histopathology of the patient revealed a poorly differentiated signet ring appendiceal carcinoma invading through the visceral peritoneum with lympho-vascular and perineural invasion. This also involved the periappendiceal lymph nodes, bilateral ovaries, serosa of the uterus, bilateral parametria, capsule of the spleen, perisplenic fat, and the peritoneum. All surgical lines of resection were negative for tumor.

Unfortunately, however, patient succumbed to myocardial infarction eight days after discharge.

Discussion

Primary appendiceal cancer is an uncommon malignancy of the gastrointestinal tract, accounting for 0.3 to 0.4% of all appendectomies. Signet ring carcinoma of the appendix is even rarer; seen in only approximately 4% of all appendiceal neoplasms. Often, the diagnosis is made only after the removal of the appendix. These are

commonly seen in the older population (mean age 58 years), with a 5-year survival rate of only 7%. For locally advanced resectable diseases, the standard treatment is CRS with HIPEC.[2]

The aim of CRS is to eliminate all macroscopic disease through a series of visceral resections followed by targeting any residual microscopic disease with intraperitoneal chemotherapy, exposing the peritoneal surfaces to high concentrations of chemotherapy with lower systemic toxicity.[1] This is primarily performed in cases of pseudomyxoma peritonei, appendiceal carcinoma, epithelial ovarian carcinoma, peritoneal sarcomatosis, peritoneal mesothelioma, colorectal cancer, gastric cancer, and pancreatic cancer. Major complications from this procedure range from 0 to 18%.[3]

The peritoneal cancer index (PCI) score is the most commonly used scoring system to evaluate the extent of the disease, which also determines prognosis. CRS and HIPEC do not seem to offer any survival benefit in patients with a PCI score of ≥17. In addition to PCI score, the completeness of cytoreduction (CC) score is used to measure the amount of macroscopic disease after CRS. Patients with CC-0 (no gross tumor) and CC-1 (tumor nodules <0.25 cm) are considered best candidates for HIPEC. This is based on the assumption that tumors less than 0.25 cm can be penetrated by the intraperitoneal chemotherapeutic regimen.[4]

In a study by Sugarbaker et al., hematologic (28%) and gastrointestinal (26%) complications were noted to be most commonly associated with CRS with HIPEC. Complications that were noted included neutropenia, sepsis, pleural effusion, respiratory insufficiency, thromboembolism, anastomotic leak, bowel perforation, fistula formation, intraabdominal abscess, and wound dehiscence.[5]

In PGH, for pseudomyxoma peritonei, adenocarcinoma from the appendix, colon, or rectum, the following regimen is used: mitomycin C 15 mg/m^2 and doxorubicin mg/m^2 intraperitoneally, with simultaneous administration of fluorouracil 400 to 800 mg/m^2 and leucovorin 20 mg/m^2 intravenously. However, this was modified due unavailability of mitomycin C during the peak of the pandemic. In some studies, among patients with peritoneal carcinomatosis from appendiceal neoplasms, oxaliplatin and irinotecan have been recently used.

Oxaliplatin is a third generation platinum complex.[6] High peritoneal and tumor oxaliplatin concentrations with limited systemic absorption is set at 460 mg/m^2 in 2 l/m^2 of 5% dextrose for HIPEC over a 30-minute perfusion.[7] Its mechanism of action relies on the formation of platinated DNA adducts resulting in the inhibition of DNA synthesis and repair, eventually causing apoptosis.[8] Nausea, vomiting, diarrhea, myelosuppression (particularly neutropenia and thrombocytopenia), mucositis, and reversible sensory neuropathies are the most frequently reported adverse effects. Hematologic toxicities are rarely reported.[9]

A few case reports described the occurrence of idiopathic thrombocytopenic purpura (ITP) and Evans syndrome, a rare autoimmune disorder causing anemia, thrombocytopenia, and neutropenia, upon infusion of oxaliplatin. There is even rarer incidence of emergent, life-threatening hematologic toxicities.[10,11] Although relatively rare in incidence compared to other adverse effects, in the PRODIGE 7 Trial, it was reported that hematologic complications are significantly higher among patients who received HIPEC in addition to CRS than those who underwent CRS alone.[12]

The exact manner how the tendency to DIC occurs is yet to be ascertained. Certain hypotheses have been formulated, and based on these, it can be the activation of both an immune-mediated, and an inflammatory mechanism. It is believed that antibody-drug immune complexes are formed to target receptors in the red blood cells and/or platelet membranes. At the same time, pro-inflammatory cytokines are released thereby causing constitutional systemic symptoms.[11,13,14,15,16] Steroid therapy, as was done for this patient, may be given to attenuate the risk of these adverse reactions.[17]

In the case presented, the patient had experienced bleeding that warranted a re-exploration with the suspicion of bleeding coming from the operative site. Initially, a systemic cause of the bleeding was not highly considered since there were no other areas of bleeding, save for the intraperitoneal bleeding seen from the Jackson-Pratt drains. The only identified source was bleeding from the muscles at the subdiaphragmatic area.

Upon checking of the bleeding parameters, it was noted that the patient had a low platelet count, an elevated D-dimer concentration, and a prolonged prothrombin time (PT). All these factors lead to the diagnosis of a disseminated intravascular coagulation (DIC). Had the intraperitoneal use of oxaliplatin been suspected to be a cause of bleeding, an earlier work-up for DIC could have been done. This, possibly, may have averted a re-laparotomy.

In a case report by Kurian, et al., DIC was also observed in a patient with a prior history of hypersensitivity to intravenous oxaliplatin. The patient presented with gross hematuria and ecchymoses of the upper extremities. The patient was managed conservatively with supportive care and was discharged after four days.[9] Unlike the previous patient, the patient currently being presented had a longer and complicated hospital stay due to the complexity of the operation done. In addition, CRS by itself was not highly considered as the cause of the patient's DIC, as there were no signs of sepsis that could predispose the patient to develop it. As of writing, this may be the first reported case of DIC from intraperitoneal infusion of oxaliplatin.

Learning Points

Oxaliplatin, although commonly used to treat malignancy, should be used with caution. Disseminated intravascular coagulation, although not often seen with its use, should be suspected if patients present with bleeding either in the postoperative site or other distant areas, and derangements in laboratory parameters after oxaliplatin perfusion. Further investigation to rule out other factors that might have caused bleeding should also be done. Health care providers need to be aware of its adverse effects, even the less common ones, as these have potentially fatal consequences, if not detected and addressed early.

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