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Small Bowel Perforation in Non-Squamous Non-Small Lung Cancer after Bevacizumab Therapy: A Case Report

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Abstract
Background: *Bevacizumab-associated gastrointestinal perforation reported incidence is less than 1%, with a mortality of 15-20%.*
Case presentation: *Herein, we report a 75-year-old male was diagnosed with metastatic non-small cell adenocarcinoma of the left lung. Fifteen days after the first cycle of chemotherapy (carboplatin, paclitaxel, and bevacizumab), the patient experienced abdominal pain. A fluid collection10 x 4 cm adjacent to small bowel loops containing air was noted on the computed tomography. Unfortunately, the percutaneous drainage of the collection was not feasible, and the patient underwent exploratory laparotomy. Intraoperatively, an enterectomy with side-to-side anastomosis due to necrosis and perforation of the bowel wall, and drainage of the intra-abdominal abscess were carried out.*
Conclusion: *Bevacizumab-associated gastrointestinal perforation is a potentially fatal complication. Its diagnosis could be challenging due to immunosuppression. The management is complex and requires a multidisciplinary approach that engages surgeons, interventional radiologists, and oncologists.*
Keywords: *Bevacizumab; non-squamous non-small cell lung cancer; gastrointestinal perforation; complications; management.*

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I. Introduction

Bevacizumab (Bev), a recombinant human monoclonal antibody that deactivates vascular endothelial growth factor (VEGF), is widely used in the treatment of locally advanced or metastatic colon cancer, cervical cancer, non-squamous non-small cell lung cancer (non-squamous NSCLC), and glioblastoma multiforme (1). In non-squamous NSCLC, Bev combined with other chemotherapeutic agents prolongs overall survival and improves progression-free survival and response rate (2, 3).

Generally, Bev is well-tolerated with acceptable toxicity. The typical side effects include hypertension and proteinuria. Other rare complications encompass epistaxis, gastrointestinal bleeding, pulmonary bleeding, arterial or venous thrombosis, and delayed wound healing (4, 5).

One potentially fatal complication is Bev-associated gastrointestinal perforation (BAP), which has a high mortality. The reported incidence of BAP is less than 1%, with a mortality of 15-20%. The most typical site of perforation is the large bowel, followed by the small intestine and stomach. Although several theories have been proposed to explain the development of BAP, the exact mechanism remains unclear (6, 7).

Diagnosis of BAP is challenging as typical symptoms and signs of gastrointestinal perforation might be absent due to immunosuppression. The optimal management of BAP is complex and requires a multidisciplinary approach that engages surgeons, interventional radiologists, and oncologists (1).

II. Case presentation

A 75-year-old male was diagnosed with metastatic non-small cell adenocarcinoma of the left lung with bilateral lung metastases two months ago. He was scheduled for palliative chemotherapy containing carboplatin, paclitaxel, and bevacizumab. Fifteen days after the first cycle of chemotherapy, the patient appeared to the emergency department with a six-day history of abdominal pain localized in the left upper quadrant associated with vomiting and diarrhea. No history of fever, constipation or urinary complaints was noted. The patient

reported that a private doctor administered acetaminophen/codeine phosphate/caffeine and butylscopolamine bromide three days ago without alleviation of the symptoms.

His vital signs were as follow: T: 38 OC, heart rate 90 beats/minute, respiratory rate 17 breaths/minute, blood pressure 158/90 mmHg, SatO2 94% Physical examination disclosed a distended abdomen with local peritonitis in the left upper quadrant. There was ubiquitous tenderness to palpation. Laboratory studies revealed elevated white blood cells (14.73 K/UI), neutrophils 84%, erythrocyte sedimentation rate 60 mm/hr, C-reactive protein 458 mg/L, and LDH (325 U/L). A contrast-enhanced computed tomography of the abdomen was performed and showed a well-defined fluid collection 10 x 4 cm adjacent to small bowel loops containing air.

The patient was admitted to the surgical department for observation. Parenteral fluid substitution and antibiotics were commenced. The following day surgeons consulted with interventional radiologists concerning the fluid collection. Percutaneous drainage of the fluid collection was not feasible according to interventional radiologists, and therefore an exploratory laparotomy was decided. Intraoperatively, small bowel perforation and an intra-abdominal abscess due to necrosis of the bowel wall were diagnosed. An enterectomy of almost 15 cm of small bowel with side-to-side isoperistaltic anastomosis and drainage of the intra-abdominal abscess were carried out. The patient recovered uneventfully, and he was discharged on the eighth postoperative day. Histological examination revealed areas of complete necrosis of the small bowel wall next to seemingly healthy bowel parts. In the ischemic parts, there was thrombosis of the intramural blood vessels. The patient suffered diffuse ischemic necrosis of a healthy small bowel while on bevacizumab-containing chemotherapy.

III. Discussion

Bevacizumab (Bev) is a recombinant human monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). VEGF is overexpressed by several malignant tumors and promotes tumor angiogenesis. It is involved in tumor proliferation, invasion, and metastasis. It is also correlated with recurrence and prognosis, and therefore its deactivation is essential for treatment (8). BEV is widely used in combination with other chemotherapeutic agents in treating colon cancer, cervical cancer, non-squamous non-small cell lung cancer (non-squamous NSCLC), and glioblastoma multiforme (1, 6, 7).

In advanced or metastatic non-squamous NSCLC, the combination of Bev with carboplatin and paclitaxel or cisplatin and gemcitabine is more effective than conventional chemotherapy (7). The addition of Bev to carboplatin and paclitaxel resulted in prolonged overall survival by two months from 10.3 to 12.3 months (2), while the addition to cisplatin and gemcitabine improved progression-free survival and response rate (9). However, it did not improve overall survival, possibly due to the high use of efficacious second-line therapies (3).

Bev displays acceptable toxicity. The most typical adverse effects include hypertension and proteinuria. Other rare complications encompass epistaxis, gastrointestinal bleeding, pulmonary bleeding, arterial or venous thrombosis, and delayed wound healing (4, 5, 10, 11). Pulmonary bleeding can be either minor mucocutaneous hemorrhage or significant hemoptysis. Major hemoprysis was linked with squamous cell histology, tumor necrosis and cavitation, and the tumor's location in the vicinity of major blood vessels (11).

A rare but potential fatal side effect is Bev-associated gastrointestinal perforation (BAP), which has a high mortality. This catastrophic complication has been noted in several malignancies, including colorectal, pancreatic, NSCLC, breast, and ovarian cancers (7, 12). The reported incidence of BAP is less than 1%, with a mortality of 15-20% (1, 2, 6, 13). The most typical perforation site is the colon, followed by the small intestine and stomach (6). Several mechanisms have been proposed to elaborate the development of BAP:

1. Thrombosis and vasoconstriction of the mesenteric veins might lead to bowel ischemia.
2. Necrosis of the intramural tumor may result in the weakening of the bowel wall.
3. It is known that VEGF affects bowel wall proliferation and healing via microcirculation, protection from nitrous oxide, prostacyclin activity, and normal platelet function.

Therefore, the deactivation of VEGF by Bev might impair intestinal healing after chemotherapy-related damage, which in turn can make intestinal mucosa vulnerable to ulcers and BAP. Nonetheless, the exact mechanism by which gastrointestinal perforation happens remains unclear (7, 14).

In a randomized phase III study, Tamiya et al. evaluated clinical predictors of BAP in non-squamous NSCLC. The authors concluded that BAP was correlated with deteriorating performance status during the first cycle of chemotherapy, grade $\geq$3 diarrhea, grade $\geq$2 stomatitis, and febrile neutropenia (7). Diagnosis of BAP is challenging as the patients might be asymptomatic due to immunosuppression. Alternatively, the patients could present with acute abdomen due to peritoneal contamination, pneumoperitoneum, hemoperitoneum, or intra-abdominal abscess (1).

The management of patients with BAP is complex and requires a multidisciplinary approach that engages surgeons, interventional radiologists, and oncologists. The optimal control depends on the time of presentation, the condition of the patient, and the patients' goals and wishes. Medical management and

percutaneous drainage might be successful in cases of intra-abdominal abscess. However, patients frequently require surgical intervention, including bowel resection with or without diversion (1).

IV. Conclusion

Bevacizumab is a recombinant human monoclonal antibody that deactivates vascular endothelial growth factor. It is widely used to treat locally advanced or metastatic colon cancer, cervical cancer, non-squamous non-small cell lung cancer, and glioblastoma multiforme. A rare but potentially catastrophic adverse effect is bevacizumab-associated gastrointestinal perforation. The reported incidence is less than 1%, with a mortality of 15-20%. The most typical site of perforation is the large bowel, followed by the small intestine and stomach. The diagnosis of bevacizumab-associated gastrointestinal perforation might be challenging due to immunosuppression. The patients could be asymptomatic or present with acute abdomen due to peritoneal contamination, pneumoperitoneum, hemoperitoneum, or intra-abdominal abscess. Managing these patients is complex and requires a multidisciplinary approach that engages surgeons, interventional radiologists, and oncologists. The optimal management depends on the time of presentation, the condition of the patient, and the patients' goals and wishes.

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1. Tepelenis K: Study conception and design, drafting of manuscript.
2. Tepelenis N: Study conception and design, drafting of manuscript.
3. Stefanou SK: Literature search and acquisition of data.
4. Stefanou CK: Literature search and acquisition of data.
5. Kefala MA: Analysis and interpretation of data.
6. Galani V: Analysis and interpretation of data.
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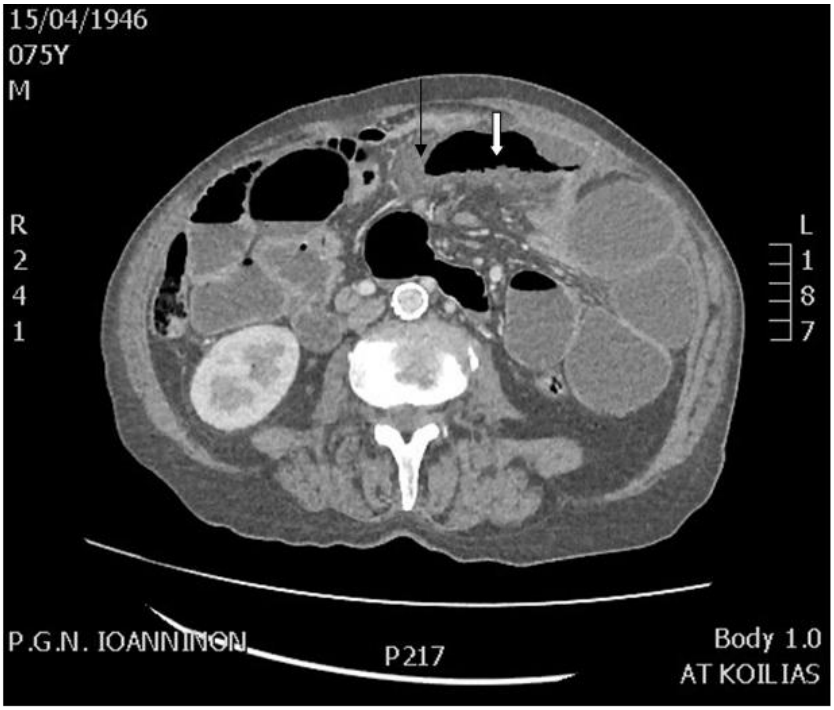

Figure 1: Computed tomography of the abdomen: A well-defined fluid collection 9.4 x 4 cm (black arrow) adjacent to small bowel loops containing air (white arrow).

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