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Case Report
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Delayed Anastomotic Leakage After Bevacizumab Therapy in Rectal Cancer Patient: A Case Report

Rektal Kanserli Hastada Bevacizumab Tedavisi Sonrası Gecikmiş Anastomoz Kaçağı: Olgu Sunumu

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Abstract: Surgery, chemotherapy, and targeted agents play crucial roles in the treatment of colorectal cancer (CRC). Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor used in metastatic CRC, has been associated with delayed wound healing, potentially increasing the risk of anastomotic leakage. In this case, a 71-year-old patient who underwent low anterior resection for rectal cancer developed delayed anastomotic leakage 26 months after surgery. Imaging revealed a presacral abscess and a collection communicating with the intestinal lumen, and surgical exploration confirmed anastomotic dehiscence. A diverting colostomy was performed, and the patient remained stable in the postoperative period. This case highlights that bevacizumab therapy can impact anastomotic integrity even in the late postoperative period, emphasizing the need for prolonged and careful follow-up in such patients.
Keywords: Colorectal cancer, anastomotic leak, bevacizumab

Özet: Kolorektal kanser (KRK) tedavisinde cerrahi, kemoterapi ve hedefe yönelik ajanlar önemli rol oynar. Bevacizumab, metastatik KRK'de kullanılan bir VEGF inhibitörüdür ancak yara iyileşmesini geciktirerek anastomoz kaçağı riskini artırabilir. Bu olguda, rektum kanseri nedeniyle düşük anterior rezeksiyon yapılan 71 yaşındaki bir hastada, ameliyattan 26 ay sonra gecikmiş anastomoz kaçağı gelişmiştir. Görüntülemelerde presakral apse ve bağırsak lümeni ile bağlantılı koleksiyon saptanmış, cerrahi eksplorasyonda anastomoz ayrışması görülmüştür. Hastaya saptırıcı kolostomi açılmış ve postoperatif dönemde stabil seyretmiştir. Bu vaka, bevacizumab tedavisinin geç dönemde bile anastomoz bütünlüğünü etkileyebileceğini göstermekte ve bu hastaların uzun süreli dikkatli takibinin gerekliliğini vurgulamaktadır.
Anahtar Kelimeler: Kolorektal kanser, anastomoz kaçağı, bevacizumab

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1. Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy worldwide in both men and women. The rising incidence of colorectal malignancies remains a significant public health concern, as CRC continues to be a leading cause of cancer-related mortality globally (1). For localized disease, preoperative radiotherapy is recommended for stage II/III rectal cancers. However, in approximately 20% of cases, synchronous metastases are present at diagnosis, necessitating primary tumor resection followed by first-line chemotherapy. Moreover, even after curative surgical resection of the primary tumor, metastatic recurrence occurs in approximately 40% of cases, at which point systemic chemotherapy followed by possible surgical resection is advised (2).

Despite advancements in surgical techniques and perioperative rehabilitation, anastomotic leakage remains a rare but feared surgical complication with potentially catastrophic consequences for the patient (3). Anastomotic leakage is defined as a disruption of intestinal wall integrity at the colorectal or coloanal anastomotic site, leading to a pathological communication between the intraluminal and extraluminal compartments (4). The incidence of anastomotic leakage and dehiscence in colorectal surgery varies, reaching up to 35% in some cases. Factors such as surgical technique, bowel integrity, anastomotic tension, comorbid conditions, and the use of medications that impair healing significantly contribute to the risk of anastomotic leakage (5).

Over the past decade, survival rates for unresectable and recurrent CRC have improved significantly due to the development of cytotoxic agents such as fluorouracil (5-FU), irinotecan, and oxaliplatin, as well as molecularly targeted therapies, including VEGF and epidermal growth factor receptor (EGFR) inhibitors (6). Despite their promising benefits, these treatments require thorough investigation of their impact on postoperative complications, particularly anastomotic leakage after colectomy (7).

Bevacizumab has been reported to cause adverse events such as arterial thrombosis, bleeding, and gastrointestinal perforation. Additionally, limited studies have suggested that bevacizumab therapy increases the risk of anastomotic leakage in rectal cancer patients undergoing low anterior resection (8). Here, we present a case of delayed anastomotic leakage occurring approximately 26 months after low anterior resection in a rectal cancer patient.

2. Case Presentation

A 71-year-old male patient presented with complaints of abdominal distension, pain, constipation, and hematochezia. The patient had no known chronic illnesses, and laboratory tests revealed no abnormalities. To investigate the etiology, thoracic and abdominal computed tomography (CT) was performed, revealing circumferential, irregular, mass-like thickening of the rectal wall. Additionally, mesorectal fascia showed infiltration with fatty tissue stranding and pathologically enlarged lymph nodes, the largest measuring approximately 9 mm.

Colonoscopy identified a broad-based polypoid lesion in the cecum and an ulcerovegetative mass completely encircling the lumen at the 3 cm level of the rectum. Biopsies confirmed adenomatous changes with low-grade dysplasia in the cecal polyp and adenocarcinoma in the rectal lesion. Pelvic magnetic resonance imaging (MRI) showed a circumferential tumor affecting a 5-5.5 cm segment of the distal rectum, beginning approximately 1 cm from the anorectal angle. The tumor was protruding into the intraluminal space and extended into the perirectal fat tissue, particularly at the 2 to 6 o'clock position. The deepest invasion was measured at approximately 4 mm, classifying the lesion as T3. The patient was subsequently planned for neoadjuvant therapy, receiving 50.4 Gy (1.8 Gy x 28 fractions) of radiotherapy, followed by surgery.

After obtaining informed consent, the patient underwent low anterior resection, hand-sewn coloanal anastomosis at approximately 3 cm from the anal verge, using non-absorbable monofilament sutures, and ileocecal resection with ileocolonic anastomosis for the cecal lesion. Intraoperatively, the anastomotic site appeared well vascularized, with no evidence of tension or ischemia. A protective loop ileostomy was created proximal to the ileocolonic anastomosis. The patient had an uneventful postoperative course, tolerated oral intake, and was discharged in good condition. Final pathology confirmed a moderately differentiated adenocarcinoma, staged

as pT3N0, located below the peritoneal reflection, and the patient was referred to medical oncology for adjuvant treatment.

Follow-up imaging and colonoscopy revealed no abnormalities, and the ileostomy was closed at 16 months postoperatively. This extended interval was due to the patient undergoing prolonged adjuvant chemotherapy and close surveillance imaging, which delayed surgical candidacy. However, approximately nine months after ileostomy closure, the patient presented to the emergency department with a deteriorated general condition. CT revealed a presacral collection, surrounding the anorectal level by more than 180 degrees and containing fluid, air, and fecaloid material, which was suggestive of anastomotic leakage (Figure 1).

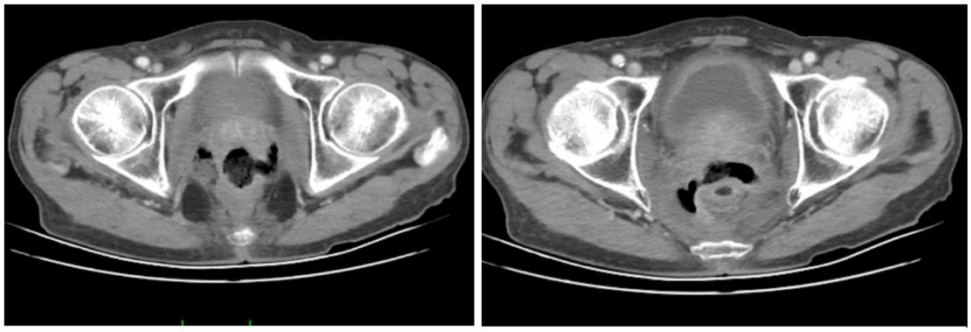

Figure 1. CT imaging showing anastomotic dehiscence

Subsequent colonoscopy confirmed a 3-4 cm opening in the perirectal area at the anastomotic site, located 3 cm proximal to the anal verge. The proximal colonic anastomosis in the ascending colon was intact (Figure 2).

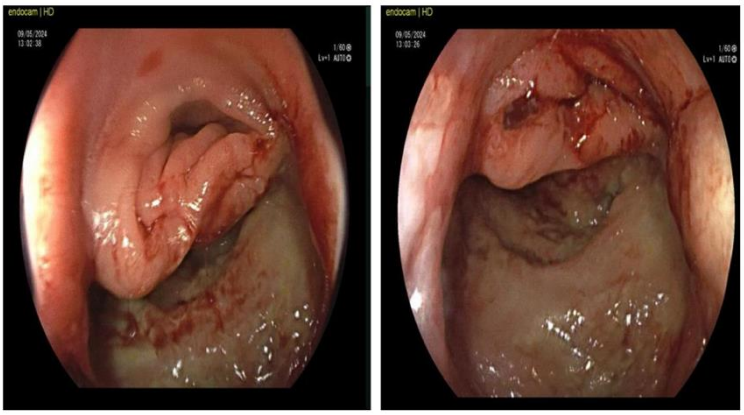

Figure 2. Colonoscopic view of the defect with granulation tissue

The patient was taken to surgery, where intra-abdominal contamination, a presacral abscess, and intestinal contents at the anastomotic site were observed. The anastomotic line was found to be partially dehiscent in a crescent-shaped pattern. After extensive peritoneal lavage, a diverting colostomy was created from the left colonic segment, and the operation was completed. The patient had an uneventful postoperative recovery,

tolerated oral intake, and was discharged. His follow-up is ongoing.

3. Discussion

Bevacizumab is a humanized monoclonal antibody targeting VEGF, which inhibits tumor neovascularization and enhances chemotherapy efficacy by modifying tumor vasculature permeability and Starling forces. Although not effective as a single agent, clinical studies have demonstrated that bevacizumab enhances the effectiveness of chemotherapy in metastatic CRC (9, 10).

Serious adverse events associated with bevacizumab include intestinal ischemia, gastrointestinal perforation, impaired wound healing, bleeding, and arterial thromboembolic events (11, 12). The exact pathophysiological mechanism leading to intestinal perforation is not well understood. One hypothesis is that tumor-related necrosis caused by bevacizumab predisposes patients to perforation (13). Another theory suggests that bevacizumab-induced thrombosis impairs microvascularization, disrupting tissue perfusion and leading to ischemia and perforation (14).

Bevacizumab has also been associated with delayed anastomotic leakage due to impaired wound healing (13). Patients who have undergone previous pelvic radiotherapy and multiple surgeries are at particularly high risk for anastomotic leakage (8). Current guidelines recommend a minimum interval of six weeks between bevacizumab therapy and surgery (9, 15). However, in this case, anastomotic failure occurred despite an extended interval after receiving 5-FU and panitumumab prior to bevacizumab, suggesting an increased risk of delayed anastomotic leakage.

While antiangiogenic agents prolong survival in metastatic CRC, their negative impact on postoperative healing should not be overlooked. This case is particularly unique due to the exceptionally delayed onset (26 months postoperatively) of anastomotic leakage, a complication rarely described in current literature. In most reported cases, anastomotic dehiscence associated with bevacizumab occurs within weeks to months postoperatively, often in the early treatment phase.

Our case stands out in that the patient had completed adjuvant therapy, underwent late ileostomy closure, and had a clinically silent course for over two years before presenting with leakage. This suggests that delayed vascular compromise or microenvironmental changes due to anti-VEGF therapy may have contributed to progressive anastomotic weakening long after initial healing.

Before initiating bevacizumab therapy, anastomotic integrity should be assessed via endoscopic and imaging techniques. Additionally, surgical interventions should be scheduled at least 6-8 weeks after bevacizumab therapy, with close postoperative monitoring.

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