

## Case Report

# Anastomotic Leakage Could be Caused by Regorafenib - A Case Report

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## Abstract

A 53 years old female had an extended right hemicolectomy with anastomosis for adenocarcinoma of transverse colon with intestinal obstruction on 2008-February-19. Pathology report revealed a Dukes' C lesion with one out of 22 lymph nodes showing metastasis. Eight courses of adjuvant chemotherapy with capecitabine were given. CEA was Elevated to 11.43 ng/μl on 2011-July-19. CT scan on 2012-January-16 revealed a 1.8 cm × 1.5 cm soft tissue nodule at left anterior pararenal space showing slightly increasing in size as compared to previous CT. After failure of multiple lines of chemotherapy with Oxaliplatin, Irinotecan, Xeloda, Tegafur-uracil, Leucovorin and Biologics of Bevacizumab, Erbitux, the patient was started to receive Regorafenib from 2015-October-13. However, because of progressive enlargement of the metastatic tumor mass, surgical resection of the metastasis (metastasectomy) was suggested. The last dose of Regorafenib was taken on 2015-December-15. During laparotomy, a 4 cm × 3.5 cm × 3.5 cm in size tumor mass was located at the left upper abdomen with involvement of several loops of jejunum. Resection of metastatic sites together with a segment of small bowel and jejunojejunostomy was performed on 2015-January-5. She was found to have bile stained discharge from the drain site on 2015-January-5. An emergent laparotomy was performed on the same day. Purulent discharge was accumulated at the left upper part of the abdomen near the resected tumor site. Leakage of anastomosis was strongly suggested. Adequate drainage of intra-abdominal abscess was performed. The patient received postoperative TPN with slowly decrease of the fistula drainage and eventually healing of the anastomosis.

**Keywords:** Adenocarcinoma; Bevacizumab; Metastasectomy; Regorafenib

## Introduction

Bevacizumab is a humanized monoclonal antibody that targets the VEGF molecule. It is known to be associated with bowel perforation and bowel ischemia [1-4]. Regorafenib is an oral multikinase inhibitor targeting multiple tumour pathways [1,5,6]. Treatment with regorafenib resulted in a 50.6% reduction in the risk of progression or death over placebo in patients with metastatic colorectal cancer [7]. However, incidence of gastrointestinal perforation and thrombotic effect was not available in the clinical studies [7,8]. We have experienced a patient with leakage of bowel anastomosis following resection of metastatic sites together with a segment of small bowel and jejunojejunostomy. Emergent laparotomy with adequate

drainage of intra-abdominal abscess result in a smooth postoperative course.

## Case Presentation

A 53 years old female had an extended right hemicolectomy with anastomosis for adenocarcinoma of transverse colon with intestinal obstruction on 2008- February-19. Pathology report revealed a Dukes' C lesion with one out of 22 lymph nodes showing metastasis. Eight courses of adjuvant chemotherapy with capecitabine were given. CEA was Elevated to 11.43 ng/μl on 2011-July-19. CT scan on 2012-January-16 revealed a 1.8 cm × 1.5 cm soft tissue nodule at left anterior pararenal space showing slightly increasing in size as compared to previous CT. After failure of multiple lines of chemotherapy with Oxaliplatin, Irinotecan, Xeloda, Tegafur-uracil, Leucovorin and Biologics of Bevacizumab, Erbitux, the patient was started to receive 160 mg/day Regorafenib from 2015-October-13. CT scan on 2015-December-23 was reported as a 3 cm × 3.6 cm growing metastatic mass with central necrosis in left upper abdomen with adjacent small bowel invasion (Figure 1). Because of progressive enlargement of the metastatic tumor mass, surgical resection of the metastasis (metastasectomy) was suggested. The last dose of Regorafenib was taken on 2015-December-15. During laparotomy, a 4 cm x 3.5 cm x 3.5 cm in size tumor mass was located at the left upper abdomen with involvement of several loops of jejunum. Two metastatic tumors were also found between the omentum and abdominal wall. Resection of metastatic sites together with a segment of small bowel (Figure 2) and jejunojejunostomy was performed on

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**Figure 1:** A 4 cm x 3.5 cm necrotic omental nodule in left upper abdomen, with increasing size of the omental nodular lesion comparing to previous CT study.



**Figure 2:** Gross specimen of the resected metastatic tumor.

2015-January-5. She was found to have bile stained discharge from the drain site on 2015-January-15. An emergent laparotomy was performed on the same day. Purulent discharge was accumulated at the left upper part of the abdomen near the resected tumor site. Previous jejunojunostomy site were not able to be visualized because of severe adhesions. No apparent leakage site was able to be seen, however, leakage of anastomosis was strongly suggested. Adequate drainage of intra-abdominal abscess was performed. The patient received postoperative TPN with slowly decrease of the fistula drainage and eventually healing of the anastomosis.

## Discussion

VEGF is a key mediator of angiogenesis in normal tissues, and binds two VEGF receptors (VEGF receptor-1 and VEGF receptor-2), which are expressed on vascular endothelial cells [6]. VEGF is also thought to be a key mediator of angiogenesis in cancer [1,5]. Bevacizumab is a humanized monoclonal antibody that targets the VEGF molecule. It is hypothesized that bevacizumab works by both depriving tumors of the neovascularity they require to grow and sustain beyond a size of approximately 2 mm and by improving local delivery of chemotherapy through alterations of tumor vasculature permeability and Starling forces [1,5,9]. Although it is not effective as a standalone agent, clinical trials have demonstrated the ability of bevacizumab to enhance the effectiveness of chemotherapy for the treatment of metastatic colorectal cancer [1,2,10]. The most serious adverse events associated with bevacizumab include bowel ischemia, gastrointestinal perforation, wound healing complications, hemorrhage, and arterial thromboembolic events [1-4]. The occurrence of gastrointestinal complications relating to bowel ischemia prompted the issuance of a warning letter addressed to physicians by the manufacturer [11], and changes in the FDA product labeling to reflect these risks [12]. They postulated an increased risk for bowel complications in previously irradiated patients and suggested that radiation induced tissue damage may enhance the risk

of arterial and venous thromboses associated with bevacizumab [13]. They postulated microthrombosis as the cause of the ischemia [14]. Given the known effects of radiation therapy on microvasculature, including endothelial damage and obliterative fibrosis [15], it seems plausible that the combination of radiation therapy and bevacizumab treatment may especially predispose to the development of tissue ischemia; In the gastrointestinal tract, the effects of ischemia can be particularly dramatic and catastrophic [13,14,16]. It is generally recommended that surgery not be undertaken for at least 4 to 8 weeks following cessation of bevacizumab treatment because of its known inhibitory effects on wound healing [4,17]. Wound healing is the result of a sequence of several basic processes including inflammation, cell proliferation, matrix formation and remodeling, angiogenesis, wound contraction, and epithelialization [16].

Regorafenib (BAY 73-4506) is an oral multikinase inhibitor targeting multiple tumor pathways [1-3]. It showed inhibition of proliferation of tumor cell through biochemical activity of KIT, PDGFR, RET; Inhibition of tumor microenvironment signaling through biochemical activity of PDGFR- $\beta$ , FGFR; Inhibition of neoangiogenesis is through biochemical activity of VEGFR1-3, TIE2 [18,19]. A correct study was designed to patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy. The result showed that OS rates were consistently higher in the regorafenib arm than in the placebo arm at 6 and 12 months post-randomization. Treatment with regorafenib resulted in a 21% reduction in the risk of death over placebo. Regorafenib + BSC significantly improved Progression-Free Survival (PFS) and time to progression over placebo + BSC. Treatment with regorafenib resulted in a 50.6% reduction in the risk of progression or death over placebo [7]. Frequently seen adverse event of regorafenib include hand-foot skin reaction, fatigue, hypertension, diarrhea, and rash/desquamation. However, incidence of gastrointestinal perforation and thrombotic effect was not available in the clinical studies [7,8]. It is understandable that not many patients would have chance of major surgery following usage of regorafenib since regorafenib is a salvage therapy for the patients with colorectal cancer after multiple lines of chemotherapy. Surely the problem of bowel anastomosis would be very rare because the chance of bowel resection would be very uncommon. However, since regorafenib also have biochemical activity of VEGFR1-3, rational thought would be it might affect bowel blood supply in some extent. Stopping of regorafenib prior to major surgery such as laparotomy and bowel resection with anastomosis might be the best for the patient's interest. At the moment, we do not know how long ahead the regorafenib should be stopped before such event. This case had regorafenib stopped 20 days before laparotomy but still had an anastomotic leakage. Of course, the causes of anastomotic leakage are many. Factors affecting anastomotic healing include poor surgical technique, wrong intraoperative judgement, local complications (sepsis, bowel preparation, drains, role of omentum and peritoneum, anaesthetic drugs, protective stoma), systemic complications (nutritional status, blood loss) and surgeon-related factors [20]. However, prior usage of biologic such as regorafenib still needed to be considered. It might not be necessary like patients who are receiving bevacizumab therapy to have biologic stopped 4-6 weeks prior to surgery. However, stop regorafenib for period of time prior to surgery and major bowel resection should always be thought and carried out to avoid catastrophic complication such as an anastomotic leakage.

## Conclusion

Whether regorafenib is going to interfere with healing of bowel anastomosis is not known, pending on further study. However, awareness of the possibility by a physician, especially a surgeon, is best for the patient's benefit.

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