

LETTER

Radiation Recall Phenomenon Secondary to Bevacizumab in a Patient with Pancreatic Cancer

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Dear Sir:

Radiation recall is an acute inflammatory reaction in an area that has been previously irradiated that is incited by a pharmacologic agent [1]. Reactions associated with gemcitabine include dermatitis, optic neuritis, brainstem radionecrosis, colitis, and lymphangitis [2, 3, 4]. In the treatment of pancreatic cancer, gemcitabine has been implicated in radiation recall manifested as myositis in two case reports [5, 6]. Gemcitabine linked radiation recall has also resulted in gastritis and duodenitis in a patient who presented with an upper GI bleed [7]. Bevacizumab is a monoclonal antibody that binds vascular endothelial growth factor (VEGF), thus inhibiting angiogenesis. There are no case reports of bevacizumab related radiation recall. In this report, we present a case of radiation recall of a patient with locally advanced pancreatic cancer on gemcitabine and bevacizumab combination therapy.

CASE REPORT

The patient is a 67-year-old female with a past medical history significant for rheumatoid arthritis on infliximab who initially presented to her primary care physician with weight loss and abdominal pain in the summer 2005. The abdominal pain persisted and subsequently the patient underwent a CT scan in October 2005 of the chest, abdomen, and pelvis revealing

prominent mesenteric vessels, mesenteric lymphadenopathy, and poor visualization of the distal body and tail of the pancreas. She subsequently had an MRI of the abdomen revealing a large mass in the body of the pancreas extending to the head, measuring 5 cm at its widest dimension, lobulated, and poorly defined. There was compromise of the superior mesenteric artery and superior mesenteric vein, and no clear fat plane surrounding the vessels. In addition, splenic vein involvement was noted with dilation more distally. There was no evidence for metastatic disease at the time. One week later, an endoscopic ultrasound was performed with fine needle aspiration with findings suggestive of a T4 neoplasm (involving the portal vein, splenic artery and vein and superior mesenteric artery) with a hypoechoic mass measuring 5.1 cm in the pancreatic body-head with several peripancreatic lymph nodes. The fine needle aspiration was positive for malignant cells consistent with adenocarcinoma. The patient was enrolled in a clinical trial in which she received concurrent radiotherapy, capecitabine, and bevacizumab followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic adenocarcinoma. Capecitabine was administered at a dose of 825 mg/m² given twice daily Monday through Friday in conjunction with radiotherapy. Bevacizumab was infused every 2 weeks at a dosage of 5 mg/kg for a total of 6 weeks. Baseline laboratories at the beginning of

chemotherapy showed a hemoglobin of 11.5 g/dL and a platelet count of $180 \times 10^3/\mu\text{L}$. A follow-up CT scan showed slight interval decrease in the size of the pancreatic mass with persistent vascular encasement and venous occlusion. Subsequently the patient was started on gemcitabine at $1,000 \text{ mg/m}^2$ i.v. weekly for 3 weeks on and one week off with continuation of the bevacizumab at the previous dose and frequency. During this phase of the chemotherapy, the patient became thrombocytopenic, with nadir at $56 \times 10^3/\mu\text{L}$ eventually coming off protocol. She was then changed to gemcitabine $1,500 \text{ mg/m}^2$ every 2 weeks with concomitant bevacizumab. Subsequently, the patient's platelet count dropped to $87 \times 10^3/\mu\text{L}$ requiring a dose reduction to $1,000 \text{ mg/m}^2$ every 2 weeks. After a short interruption of treatment for a hospitalization, she restarted this regimen and developed a gastrointestinal bleed. The patient's labs at this time were significant for a hemoglobin of 8.8 g/dL and a platelet count of $52 \times 10^3/\mu\text{L}$. The patient's hemoglobin returned to baseline after transfusion of packed red blood cells. The gastrointestinal bleeding was found to be secondary to some gastric lesions and ulcers (Figure 1). The gastric lesions were consistent with radiation-induced injury and treated with endoscopic ablation. In addition, the patient had vaginal bleeding while on this regimen with a transvaginal ultrasound significant only

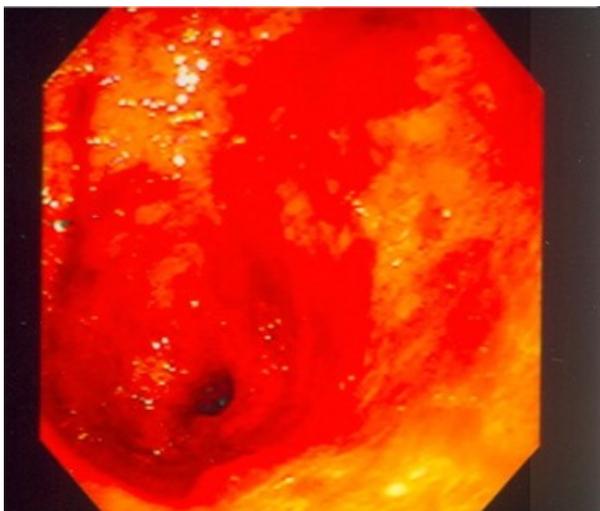


Figure 1. Endoscopic findings consistent with radiation recall syndrome.

for some uterine atrophy. At this point, bevacizumab was discontinued and the patient was continued on gemcitabine monotherapy with no recurrence of bleeding.

DISCUSSION

Gemcitabine-related radiation recall manifesting as antritis and duodenitis leading to gastrointestinal bleeding has been previously described [7]. Similarly, in our case, the patient received concomitant radiation and capecitabine and subsequently developed bleeding while on gemcitabine.

Radiation recall has been described in the context of gemcitabine chemotherapy. Of the cases reported [2, 3, 4, 5, 7, 8, 9, 10, 11, 12], there were four patients that were noted to continue gemcitabine after the radiation recall reaction. One of these patients continued without any further reactions [4]. Another patient was restarted on half the original dose of gemcitabine without incident [12]. In one study, two patients with lymphoma were continued on gemcitabine after having developed pericardial effusions as a recall reaction, neither developed any further reactions; however they did die within 3 months of the event [10].

However, our case differs in two crucial aspects. After the episodes of bleeding, the patient was continued on gemcitabine without any further episodes of bleeding. Can patients be re-challenged on an anti-neoplastic agent that was the culprit of the radiation recall reaction? Also, at the time of GI bleeding, our patient was receiving bevacizumab in addition to gemcitabine. Could the recall reaction have been secondary to bevacizumab?

Bevacizumab is an IgG1 recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that blocks binding of human VEGF to its receptors. Bevacizumab has been approved for first-line and second-line treatment of advanced colorectal cancer in combination with other agents as well as for the treatment of non-squamous lung cancer and metastatic breast cancer. Severe pulmonary toxicity has not been usually reported in patients receiving bevacizumab. Nevertheless, hemoptysis was

encountered frequently in a randomized phase II study in patients with non-small-cell lung cancer. Although hemoptysis can be a symptom of lung cancer, the incidence was significantly higher among patients receiving bevacizumab (20% versus 6%). Four patients receiving bevacizumab suffered severe hemoptysis. In patients treated with bevacizumab, serious bleeding was also reported in the form of hematemesis [13]. Such bleeding episodes have not been reported in patients with colorectal, renal, breast or prostate cancer [14]. In all cases tumors were centrally located and in the proximity of major blood vessels. Furthermore, squamous histology may possibly present a risk factor for major bleeding and have been excluded from the ongoing trial [13].

We believe that the radiation recall was possibly related to bevacizumab supported by the findings that patient had gastric lesions consistent with radiation-induced injury concomitantly with vaginal bleeding. Secondly, the patient continued on gemcitabine monotherapy with no recurrence of bleeding after bevacizumab was discontinued.

A PubMed search was performed to identify cases of radiation recall induced by gemcitabine and bevacizumab combination. No such clear case was found. However, bleeding associated with the doublet was found in the phase II study by Kindler *et al.* [15]. In this study, most bleeding episodes were usually mild and included epistaxis in 23% of the patients and gum bleeding in 4% of the patients. A lethal gastrointestinal bleed occurred in a 79-year-old man (Table 1). Endoscopic retrograde cholangiopancreatography demonstrated an actively bleeding vessel and extensive ulceration resulting from malignant invasion from the duodenal bulb and ampullary region [15].

The exact pathogenesis for radiation recall phenomenon remains unclear. Some investigators have suggested that it may be the result of vascular damage, epithelial stem cell sensitivity, or drug hypersensitivity [2, 16]. One proposed mechanism suggests a

lowering of the inflammatory threshold in irradiated tissue, which leads to a non-immune inflammatory reaction upon exposure to certain drugs.

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