Radiation Recall Gastritis Secondary to Erlotinib in a Patient with Pancreatic Cancer

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Abstract. *Background: Radiation recall refers to chemotherapy-triggered inflammation in healthy areas previously exposed to irradiation. Chemotherapeutics known to be associated with radiation recall phenomenon include anthracyclines, taxanes and antimetabolites, such as gemcitabine and capecitabine. Case reports detailing radiation recall dermatitis and pneumonitis associated with erlotinib have been previously described in the literature, however, there are no reported cases describing radiation gastritis associated with erlotinib. We report a patient with pancreatic cancer who developed gastrointestinal bleeding secondary to radiation recall gastritis related to erlotinib exposure. Case Report: A 57-year-old Hispanic male with pancreatic cancer initially received 7 cycles of FOLFIRINOX followed by capecitabine with radiation therapy for 28 fractions for a total of 5,040 cGy. Re-staging with computed tomography demonstrated stable disease. The patient was then treated with erlotinib and capecitabine for approximately two months before restaging demonstrated progressive disease. Shortly after discontinuing erlotinib and capecitabine, the patient reported maroon colored stools. Laboratory studies demonstrated a precipitous drop in hemoglobin and hematocrit from pre-treatment baseline, ultimately requiring transfusion with packed red blood cells. Subsequent esophagogastroduodenoscopy demonstrated findings consistent with radiation gastritis, with oozing in the gastric body and antrum, which was treated therapeutically with argon plasma coagulation. The patient's gastrointestinal bleed was difficult to control. Over the course of a two-month period – the patient required multiple admissions, repeat therapeutic esophagogastroduodenoscopies and transfusions. Discussion: Radiation recall from erlotinib is rare but can potentially arise in any site that has been previously irradiated. There may be an association between the pathogenesis of radiation recall and erlotinib's up-regulation of the angiogenic growth factor thymidine phosphorylase. Treating physicians are reminded of the potential toxicity from erlotinib either given concomitantly or followed by radiation. We suggest discontinuing erlotinib if radiation gastritis is observed. We encourage physicians with similar experiences with erlotinib to report their findings. Further studies are warranted to investigate the pathogenesis of this unique phenomenon and its association with erlotinib.*

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Erlotinib is a tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) approved for use in the United States in combination with the anti-metabolite drug gemcitabine for the treatment of locally advanced, unresectable or metastatic pancreatic cancer. Erlotinib, when combined with gemcitabine, demonstrated a modest increased in survival in patients with advanced pancreatic cancer compared to gemcitabine alone as demonstrated by a Phase III study conducted by the National Cancer Institute of Canada (NCIC) (1). Several studies have investigated the efficacy of concomitant use of erlotinib with capecitabine in pancreatic cancer (2, 3). Common side-effects of erlotinib include fatigue, rash, nausea, anorexia and diarrhea (4).

Radiation recall is a poorly understood phenomenon associated with chemotherapy-triggered inflammation in areas previously subjected to radiation therapy. The true incidence is difficult to quantify given that this phenomenon is mostly described in case reports, though several limited observational studies have reported incidences of 8.8% (5) and 11.5% (6). The majority of cases of radiation recall phenomenon that have been described have been associated with skin reactions, though involvement of other organs has also been noted. The pathophysiology surrounding radiation recall is largely unknown, though several hypotheses have been proposed, including stem cell depletion, increased stem cell sensitivity and hypersensitivity reaction (7). Numerous case reports describing radiation recall have identified a

number of chemotherapeutic agents associated with radiation recall, however, those most commonly associated with radiation recall include anthracyclines (*i.e.* doxorubicin), taxanes (*i.e.* docetaxel and paclitaxel) and anti-metabolites (*i.e.* gemcitabine and capecitabine) (7).

A PubMed search demonstrates four previous cases of radiation recall after treatment with erlotinib; three pertaining to radiation pneumonitis and one case describing radiation dermatitis (8-11). However, no case reports reporting radiation gastritis after erlotinib are available. In this case report, we present a case of case of radiation recall gastritis following erlotinib treatment complicated by a prolonged course of gastrointestinal bleeding.

Case Report

This is a 53-year old Hispanic man with past medical history significant for atrial fibrillation, type II diabetes, hypertension, hyperlipidemia and chronic back pain who initially presented in July 2012 in the setting of recent lumbar fusion with obstructive jaundice and severe post-prandial right upper quadrant pain that radiated to the midback. Diagnosis was initially delayed as several physicians were not willing to work-up his pain. In August 2012, the patient began developing dark colored urine and light colored stool along with jaundiced skin and scleral icterus. A magnetic resonance imaging (MRI) study demonstrated a pancreatic head mass. He underwent an endoscopic retrograde cholangiopancreatography (ERCP), sphincterotomy and bile duct stent placement in October 2012 with brushings of the common bile duct stricture revealing atypical cells with abundant ductal clusters of epithelium with high nuclear to cytoplasmic ratio and irregular content. A fine needle aspiration of the pancreatic mass revealed atypical glands consistent with adenocarcinoma in a necrotic background. Computed tomography (CT) revealed a 3.9 cm mass in the pancreatic neck with stenosis of the superior mesenteric vein and occlusion of the extrahepatic portal vein compatible with tumoral involvement. No liver metastases were noted at this time. The patient was staged as T4/MX/NX. CA19-9 in October 2012 was 1871 units/ml.

In November 2012, the patient started neoadjuvant FOLFIRINOX (oxaliplatin (85 mg/m^2), irinotecan (150 mg/m^2), leucovorin (400 mg/m^2) and 5-fluorouracil (400 mg/m^2) given as a bolus followed by 2,400 mg/m^2 given as a 46-h continuous infusion, every 2 weeks). Restaging CT imaging following 4 cycles of FOLFIRINOX showed stable disease. An additional three cycles of FOLFIRINOX were administered, the last of which was given in March 2013. Of note, patient's cycle #5 doses of 5-fluorouracil and irinotecan were decreased due to mucositis and thrombocytopenia. Patient's cycle #6 was delayed one week for recovering thrombocytopenia and the patient had his 5-flourouracil held as part of his cycle #6 regimen. Following 7 cycles of FOLFIRINOX, CA19-9 had decreased from baseline to 204 units/ml but re-staging CT revealed a residual pancreatic head mass with obliteration of the portal vein, confluence surrounding the pancreatic head vessels with encasement of the hepatic artery and portal vein consistent with stable disease. Given the level of tumor involvement, the patient was deemed not a surgical candidate and referred for chemoradiation. He was started on oral capecitabine at 1,650 mg twice a day Monday-Friday while receiving concurrent radiation therapy for 28 fractions for a total of 5,040 cGy starting in March 2013 and ending in May 2013.

A post-radiation re-staging CT scan demonstrated stable disease but CA19-9 had risen to 1,237 units/ml. Decision was made to resume capecitabine at 1,500 mg per os (*p.o.*) twice daily (BID) days 1-14 q3weeks. Due to a rising CA19-9 from baseline (1,248 units/ml), erlotinib 100 mg *p.o.* daily was started in June 2013. Both capecitabine and erlotinib were continued through July 2013.

Re-staging CT in July 2013 demonstrated progressive disease as demonstrated by larger low attenuation area within the pancreatic uncinate and increased attenuation in the peripancreatic fat and CA19-9 was 2,680 units/ml. Given the patient's progressive disease, erlotinib and capecitabine were discontinued, with last doses administered in July 2013. At routine follow-up several days after discontinuing erlotinib and cepecitabine, the patient endorsed fatigue and maroon colored stools. Laboratory studies demonstrated a precipitous drop in hemoglobin and hemocrit (Figure 1).

The patient was transfused two units packed red blood cells (pRBCs), given hemoccult cards to complete as an outpatient with tentative plans for outpatient esophagogastroduodenoscopy (EGD) and colonoscopy. The patient was shortly thereafter admitted for persistent symptomatic gastrointestinal bleeding, during which time he received 1 unit pRBCs. EGD demonstrated normal esophagus, multiple areas of friability and oozing in the gastric body and antrum, consistent with radiation gastritis. A colonoscopy demonstrated hemorrhoids in the rectum but no blood in the colon. The patient was soon discharged but several days later required 2 units pRBCs as an outpatient for symptomatic anemia. The patient was seen in clinic for follow-up with complaints of bright red blood per rectum with grossly bloody stools. He was readmitted for gastrointestinal bleeding and stabilized on intravenous proton pump inhibitors. A nuclear medicine gastrointestinal bleeding scan demonstrated no active bleeding. A repeat EGD performed demonstrated normal esophagus, multiple areas of friability and oozing in the gastric body and antrum, which was treated therapeutically with argon plasma coagulation. The patient was considered hemodynamically stable with good hemostasis and discharged. He was subsequently re-admitted

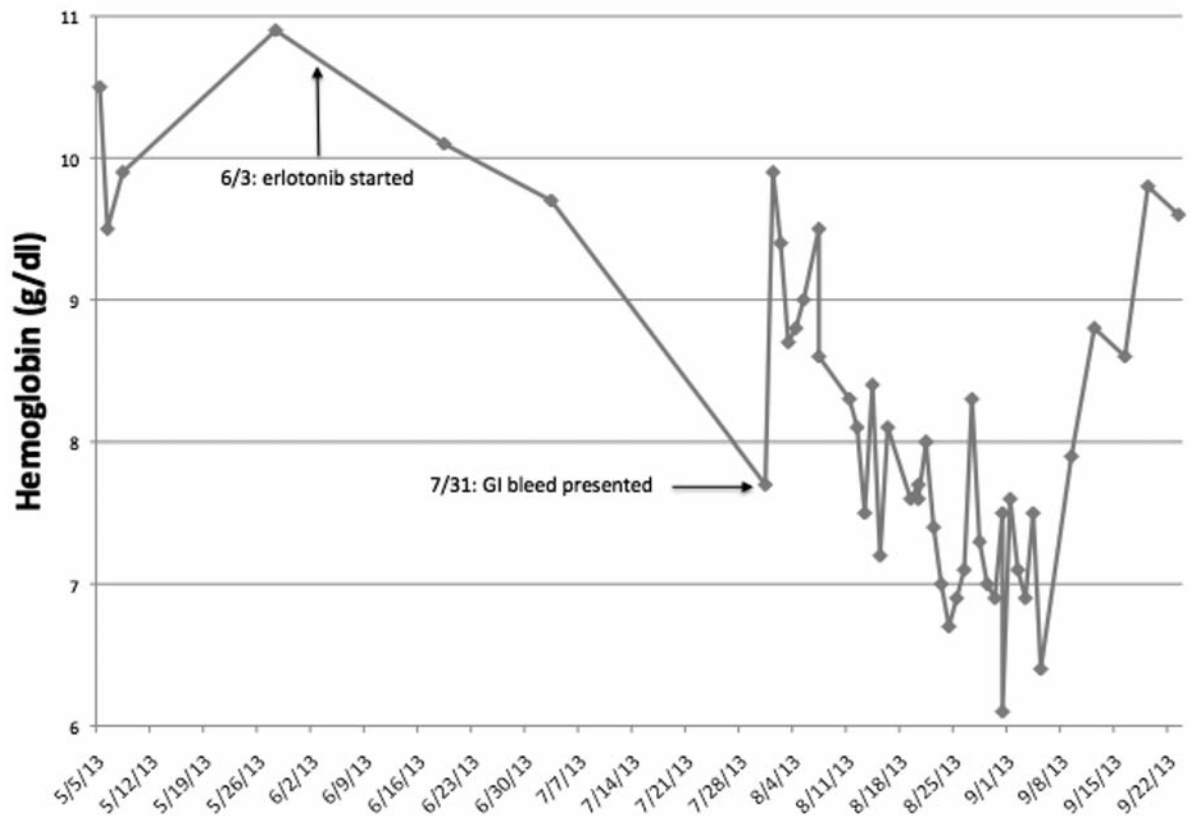

Figure 1. *Patient's hemoglobin at baseline prior to erlotinib and through multiple episodes of GI bleeding.*

several days later after presenting with three episodes of bright red blood per rectum and maroon colored stools. Repeat colonoscopy demonstrated no active bleeding but showed black stool in the right colon suggestive of a proximal source of bleeding. Diverticulosis was noted in the sigmoid and transverse colons with no rectal varices noted. A repeat nuclear medicine gastrointestinal bleeding scan demonstrated increasing radiotracer activity in the medial left upper quadrant consistent with small bowel bleed. Delayed imaging of the abdomen at 24 h demonstrated tracer in the ascending, transverse and splenic flexure of colon most likely representing transfer from the small bowel to the large bowel. Video capsule endoscopy visualized blood only in the stomach. A trial of aminocaproic acid was entertained – first *via i.v.* drip and then *via* oral tablet – but without success. Repeat EGD (Figure 2a-b) visualized erythema of the antrum and pylorus consistent with prior radiation gastritis and argon plasma coagulation was again applied at this time. Duodenitis was also noted in the duodenal bulb at this time. Bleeding was slow but difficult to maintain and the patient was deemed stable for discharge in September 2013. Oral dexamethasone was later added for promotion of healing. Several weeks later, a repeat therapeutic EGD was performed with argon plasma coagulation applied to the patient's gastric antrum and pylorus, with endoscopy demonstrating unchanged duodenitis and no evidence of jejunal lesions. No clinically significant bleeding episodes were noted after this time.

With regards to the patient's pancreatic cancer, he was initially planned to start gemcitabine and nab-paclitaxel after progressive disease was noted in July 2013. However, due to the patient's persistent GI bleeding, he was unable to start gemcitabine until September 2013 at which point his CA-19-9 had risen to 23,613 units/ml. The treating team elected not to administer nab-paclitaxel due to the patient's gastrointestinal bleed.

Discussion

Radiation recall refers to chemotherapy triggered inflammation in healthy areas previously exposed to irradiation. The incidence of radiation recall is largely unknown as most instances are noted in case reports. The drugs commonly associated with radiation recall include anthracyclines, taxanes and antimetabolites (*i.e.* gemcitabine

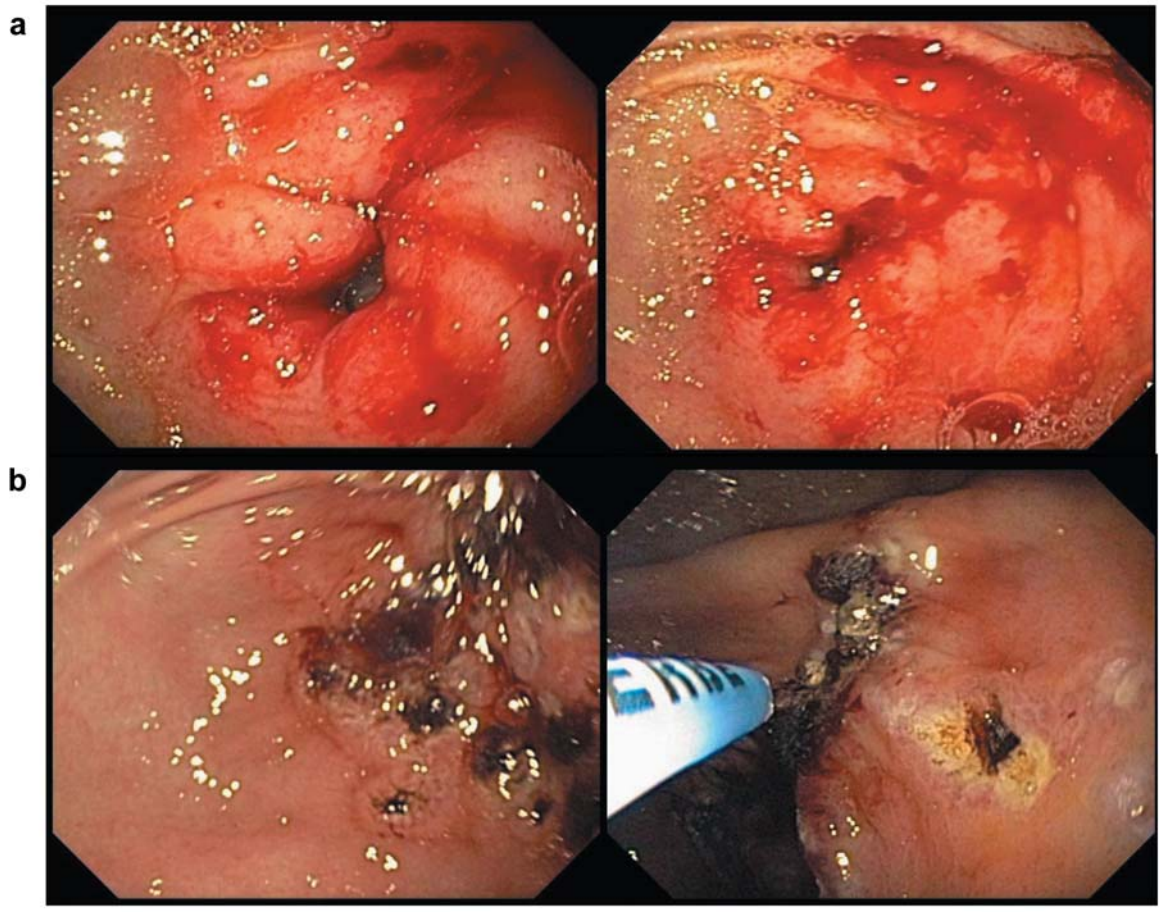

Figure 2. *Esophagogastroduodenoscopy (EGD) findings from August 2013 demonstrating gastrointestinal bleeding secondary to radiation gastritis pre- (a) and post-argon plasma coagulation (b).*

Table I. *Summary of cases associated with erlotinib induced radiation recall phenomenon.*

Publication	Malignancy under treatment	Radiation regimen	Interval between radiation and erlotinib	Interval between erlotinib and event	Adverse event
Onal *et al*., 2012	NSCLC	30 Gy, 10 fractions	28 weeks	2 weeks	Pneumonitis
Togashi *et al*., 2010	NSCLC	60 Gy, unknown # of fractions	28 weeks	2 weeks	Pneumonitis
Arakawa *et al*., 2011	NSCLC	63 Gy, 35 fractions	28 weeks	2 weeks, 5 days	Pneumonitis
Dauendorffer *et al*., 2009	Pancreatic cancer	45 Gy, unknown # of fractions (for previous breast cancer)	~8 years	24h	Dermatitis
Graziani *et al*., 2014	Pancreatic cancer	5,040 Gy, 28 fractions	6 weeks, 5 days	8 weeks, 2 days	Gastritis

and capecitabine). Erlotinib is commonly associated with causing fatigue, rash, nausea, anorexia and diarrhea. However, there have been four previous cases of radiation recall phenomenon attributed to erlotinib described in the literature (Table I).

Our case report is important in that it presents that first report of radiation recall gastritis associated with erlotinib. Several factors distinguish the case of our patient with the previously described instances of erlotinib associated radiation recall. Of note, our patient received much higher doses of radiation in treatment of his cancer, which may have put him at further risk for radiation recall. Additionally, our patient had a shorter interval between starting radiation and starting erlotinib compared to the previous cases reported. Also, our patient had the longest interval between starting erlotinib and presenting with radiation recall.

It is important to note that our patient also received capecitabine – another instigator of radiation recall – while receiving radiation treatment and shortly thereafter. One study suggests that capecitabine up-regulates the angiogenic growth factor thymidine phosphorylase (TP) also known as platelet-derived endothelial cell growth factor. It is thought that up-regulated TP may induce angiogenesis in the previously irradiated area and increase local capecitabine activation. Similarly, another study evaluating antitumor activity of erlotinib in tumor xenograft models suggests that erlotinib may up-regulate TP. Given this relationship between erlotinib and TP, it may be that erlotinib's up-regulation of TP plays a pivotal role in the development of radiation gastritis similar to that seen with capecitabine. Given the patient's presentation and time course, we cannot exclude a relationship between erlotinib and the patient's radiation gastritis. It is possible that the radiation recall described was secondary to a combination of capecitabine and erlotinib or due to the capecitabine alone.

Ultimately, the gastrointestinal bleed caused by the patient's radiation recall gastritis produced much morbidity and delayed treatment of his pancreatic cancer to the point that his CA19-9 levels demonstrated progressive disease. Since erlotinib is approved for both lung and pancreatic cancer, physicians prescribing erlotinib for either indication need to be aware of this potentially devastating toxicity.

Summary

Radiation recall from erlotinib is rare but can potentially arise in any site that has been previously irradiated. Treating physicians are reminded of the potential toxicity from erlotinib either given concomitantly or followed by radiation. We suggest discontinuing erlotinib if radiation gastritis is observed. We encourage physicians with similar experiences to report their findings. Further studies are warranted to investigate the pathogenesis of this unique phenomenon and its association with erlotinib.

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