Duodenal Perforation Secondary to Erlotinib Therapy in a Patient With Non-Small Cell Lung Cancer

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ABSTRACT

Lung cancer is a lethal disease with high mortality, and treatment modality varies with type of tumor and stage of the disease. Targeted molecular therapies have been developed for patients with advanced non-small cell lung cancer. The presence of epidermal growth factor receptor (EGFR) mutation qualifies the patient for EGFR-TKI (tyrosine kinase inhibitor) therapy such as erlotinib, which is not without risk. We report an interesting case of duodenal perforation secondary to erlotinib therapy. This is the second reported case of bowel perforation after erlotinib therapy in a patient with advanced non-small cell lung cancer.

INTRODUCTION

According to most recent statistics, there are 526,510 individuals in the United States living with a history of lung cancer. It is estimated that an additional 224,390 cases will be diagnosed in 2016, with the median age at diagnosis of 70 years,[1] although it has been reported that the number of lung cancer deaths has declined due to a decrease in smoking frequency.[2] The choice of chemotherapy, surgery, radiotherapy, or a combination of therapies depends on the type of lung cancer, staging, and performance status of the patient, as well as patient choices. These therapies all can have substantial side effects and complications.[3]

Research in the field of non-small cell lung cancer (NSCLC) has revealed that it is a combination of a heterogenous group of pathologies. Adjuvant chemotherapy is one of the most important treatment strategies for NSCLC. Research has shown cisplatin-based regimens have demonstrated survival benefits for stage II and stage IIIA disease.[4-10] Targeted molecular therapies have been developed for patients with advanced NSCLC. The presence of epidermal growth factor receptor (EGFR) mutation qualifies the patient for EGFR-TKI (tyrosine kinase inhibitor) therapy such as erlotinib, gefitinib, and afatinib.[11] Testing for EGFR mutation typically occurs only in patients with adenocarcinoma; however, EGFR-TK1 therapy is appropriate for later line treatment of progressive metastatic disease in any histology type. Erlotinib is associated with some serious complications including fatal pulmonary toxicities, liver failure, and hepatorenal syndrome. One rare complication is gastrointestinal perforation. We report a case of duodenal perforation, which is the second reported case of bowel perforation after erlotinib therapy in a patient with advanced NSCLC.[12]

CASE REPORT

A 53-year-old woman with a primary medical history of metastatic squamous cell lung cancer with an anaplastic component of undifferentiated carcinoma with mediastinal lymphadenopathy, who was receiving erlotinib, presented to the oncology clinic with abdominal pain. She had been seen in the oncology clinic 1 day before admission for shortness of breath. She did not have any chest pain and was saturating well on room air. Computed tomography (CT) of the chest showed no evidence of pulmonary embolism. When she presented again to the oncology clinic, she complained of abdominal pain that had started the night before, 8/10 in severity, was right-sided and radiating to the back. She reported nausea but no vomiting, and absolute constipation since morning. She has been compliant with erlotinib therapy for her lung cancer and denied any hematemesis or melena. She was admitted to the

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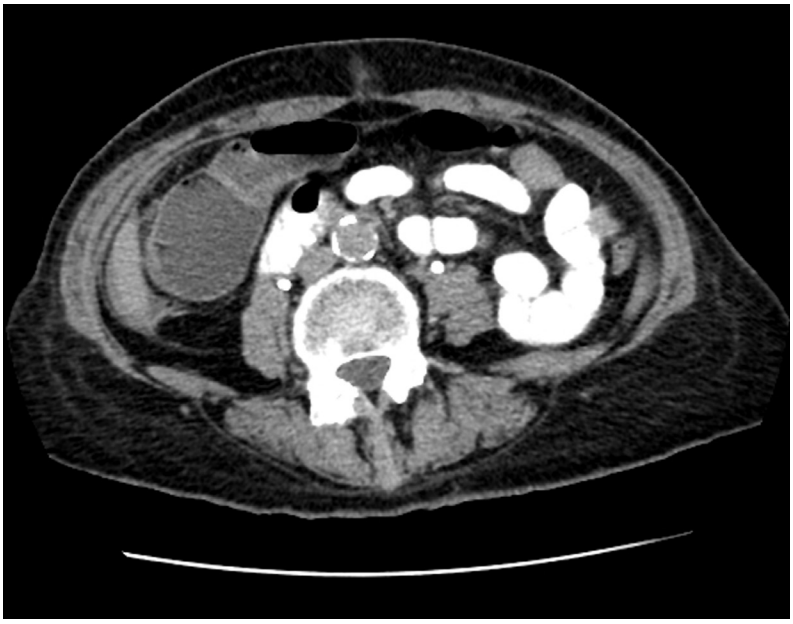
hospitalist service for further workup and management.

The patient's oncology history was significant for metastatic squamous cell lung cancer with anaplastic component of undifferentiated carcinoma diagnosed in July 2012. The cancer was stage IV, (cT3, CN2, cM1), with a right lung mass 6.6 cm x 7.3 cm, with mediastinal lymphadenopathy, 4.8 cm right temporal mass with edema, and right frontal region lesion. Her oncology management included palliative whole brain radiation therapy in August 2012. She received carboplatin AUC 6, paclitaxel (dose 300 mg intravenous [IV] in 500 ml normal saline), and bevacizumab (dose of 1100 mg IV in 100 ml normal saline, added after the third cycle). This regimen was repeated every 3 weeks for 6 cycles, completed in mid-November 2012. Pemetrexed (dose 900 mg IV in 100 ml normal saline) was started in early December 2012 as maintenance therapy. Pemetrexed was stopped mid-March 2013, as her chest CT showed significant progression of disease. Per her oncologist, the patient has squamous cell cancer but also has a component of anaplastic large cells that are undifferentiated. Since squamous cells typically do not respond to pemetrexed, it was stopped. She also received pemetrexed as maintenance therapy every 3 weeks times 5 cycles from December 2012 to February 2013. She was started on erlotinib (dose 150 mg once daily) as subsequent monotherapy in March 2013 for progressive disease based on a chest CT. She had used erlotinib as monotherapy for only 47 days before the current presentation. Erlotinib was stopped in early May 2013 with the hospitalization for acute abdominal pain. After cessation of erlotinib, carboplatin and paclitaxel were started 2 months later in July 2013.

Figure. Computed Tomography of the Abdomen and Pelvis Revealing Evidence of Duodenal Bulb Perforation With Extra Luminal Air Near the Anterior Surface of Liver



On physical examination, the patient was hemodynamically stable with dry mucous membranes. Abdominal examination revealed guarding throughout, with tenderness on the right side of the belly, more prominent in the right flank area and right lower quadrant. She demonstrated guarding and mild rigidity and had hypoactive bowel sounds. CT of the abdomen and pelvis revealed evidence of duodenal bulb perforation with extra luminal air near the anterior surface of liver (Figure). She had a normal appendix, was given nothing by mouth and was hydrated with normal saline. She subsequently underwent laparotomy with repair of the duodenal perforation with omental patch. There was no evidence of bowel metastasis found during laparotomy and on histology of the surgical specimen. The patient had an excellent recovery, and erlotinib was stopped. She was followed by her oncologist and primary care physician with no further complications.

DISCUSSION

Carcinoma of the lung is the 7th leading cancer in women and the 8th leading cancer in men in the United States.[1] Erlotinib is the second-line therapy for refractory and advanced NSCLC. The favorable response factors for erlotinib therapy are female gender, nonsmoker, Asian race, and adenocarcinoma.[13,14] The most frequently reported side effect of erlotinib is skin rash (49%-85%). Other reported complications of erlotinib include diarrhea, anemia, muscle weakness, and, rarely, gastrointestinal perforation. The exact mechanism of erlotinib causing bowel perforation is not clear. Our patient had a history of steroid use (though the duration is not clear) and a vascular endothelial growth factor receptor (VEGFR) inhibitor (bevacizumab), which can potentially cause bowel ischemia leading to peptic ulcer disease. She did not have any record of endoscopy-proven peptic ulcer disease, but she was using proton pump inhibitors for gastrointestinal prophylaxis. There was no documented history of colonoscopy, bowel perforation, bowel surgery, diverticulosis, or any evidence of alternative etiology that may have led to the bowel perforation. Our patient had poor re-epithelization in the presence of erlotinib.

Cheon et al[12] reported the case of a 66-year-old woman who developed an enterocutaneous fistula secondary to erlotinib therapy for metastatic NSCLC. Theirs was the first reported case of

bowel perforation secondary to erlotinib therapy in a patient with NSCLC. Their patient did not have bowel wall metastasis and had received erlotinib for 9 months before the bowel perforation.[12] We are reporting a case of a 53-year-old woman who developed duodenal perforation after erlotinib therapy for advanced metastatic NSCLC. Our case is the 2nd reported case of bowel perforation secondary to erlotinib, similar in many respects to Cheon et al's case: female, similar age group, and NSCLC. Our patient developed duodenal perforation after 47 days of erlotinib, while Cheon et al[12] reported bowel perforation after 9 months of therapy. Our patient also did not have bowel metastasis at time of duodenal perforation.

In June 2012, a CT of the abdomen in our patient did not show any bowel wall metastasis, and the operative specimen of the bowel also did not show any bowel wall metastasis or evidence of cancer. The prescribing information for erlotinib states that patients at a high risk for gastrointestinal perforation and complications are those who have concomitant use of angiogenic therapy (VEGFR inhibitor, eg, bevacizumab), nonsteroidal antinflammatory medications, steroids, and taxane-based chemotherapy. Our patient was receiving only erlotinib as subsequent (not concomitant) monotherapy for 47 days before the duodenal perforation. Patients with a history of diverticular disease or peptic ulcer disease are also at increased risk of gastrointestinal complications secondary to erlotinib.[13,14] Our patient had some of these risk factors, such as previous taxane-based chemotherapy, steroid use, and therapy with bevacizumab. Cheon et al's patient also had some of these risk factors.[12]

CONCLUSION

Gastrointestinal perforation is a rare but potentially lethal complication of erlotinib therapy, especially in patients with risk factors like taxane-based therapy, steroid use, concomitant or previous therapy with bevacizumab, or other gastrointestinal comorbidities such as diverticular disease and peptic ulcer disease. This rare complication of erlotinib should be considered in patients who present with abdominal pain to prevent mortality.

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