

CASE REPORT

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Variant Hypersensitivity Reaction (HSR) Presented with Persistent Dry Cough after Receiving Oxaliplatin in a Pancreatic Cancer Patient

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ABSTRACT

Oxaliplatin, a third generation of platinum-based anti-neoplastic agent has been approved for colorectal cancer in both adjuvant and metastatic settings. In addition, oxaliplatin is also indicated for other gastrointestinal malignancies such as metastatic pancreatic cancer in combination with gemcitabine. Its common toxicities include infusional hypersensitivity reaction (HSR), GI symptoms with anorexia/nausea/vomiting, sensory neuropathy and bone marrow suppression.

We report a case with persistent dry cough as a variant HSR to oxaliplatin. The patient is a 75-year-old gentleman with gemcitabine refractory metastatic pancreatic cancer who received oxaliplatin and mitomycin C for palliation. He developed sudden onset dry cough without infectious etiology during the 4th infusion of oxaliplatin. Robitussin with codeine and antibiotics did not offer any relief and the cough terminated after cessation of oxaliplatin for two weeks. We believe this to be the first case in the literature with cough as a sole manifestation of HSR to oxaliplatin.

Key words: Hypersensitivity reaction; Oxaliplatin; Pancreatic cancer

INTRODUCTION

Oxaliplatin ($C_8H_{14}N_2O_4$) (Eloxatin; Sanofi-Aventis), is a third generation platinum-based chemotherapy drug after cisplatin and carboplatin.¹ It is indicated for the treatment of colorectal cancer in both adjuvant and metastatic settings.^{2,3} Oxaliplatin is also indicated in the treatment of other gastrointestinal malignancies including metastatic pancreatic cancer in combination with gemcitabine.⁴

Its common toxicities include hypersensitivity reaction (HSR), GI symptoms with anorexia/ nausea/ vomiting, sensory neuropathy and myelosuppression. HSRs to oxaliplatin have been noted more frequently in practice.⁵ The spectrum of HSR is very broad from mild symptoms such as transient facial flushing, tongue swelling, lip numbness, headache, dizziness, chest discomfort to moderate symptoms like rash/hives, fever, chills, tachycardia, dyspnea, nausea and vomiting etc. In rare cases, patient could develop bronchospasm or laryngospasm leading to respiratory distress, or even anaphylactic reactions. The reaction usually lasts shortly. Discontinuation of oxaliplatin plus administration of intravenous steroids could effectively

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stop the reaction in most cases. In this case report, we report a patient with persistent dry cough for two weeks as the sole HSR manifestation developed during the 4th infusion of oxaliplatin.

CASE REPORT

A 75 year-old gentleman who was diagnosed with metastatic pancreatic adenocarcinoma to the liver in May 2004 was put on GTX regimen (gemcitabine, docetaxol, and capecitabine) until October 2005. With evidence of progressive liver disease on restaging CT scan, treatment was subsequently changed to irinotecan 175 mg/m² for a total of 18 cycles with further evidence of progressive disease. Then he was put on a regimen consisting of oxaliplatin 85mg/m² on days 1, 15, and Mitomycin C 8mg/m² on day 1 every 28 days since Aug 2008⁶. He tolerated the first three doses of oxaliplatin and two doses of mitomycin well except for grade 3 fatigue. He did not have any severe hematological toxicity.

Due to the grade 3 fatigue, oxaliplatin was reduced from 85 mg/m² to 65 mg/m² for the 4th infusion (10/6/2008). As standard protocol, he received pre-chemo medications including 20 mg dexamethasone and 8 mg ondansetran intravenously. One hour after the start of 3-hour oxaliplatin infusion, the patient started coughing, not associated with stridor or wheezing. He had a temperature of 97.6°F, pulse of 90, blood pressure of 154/70, and a respiration rate of 20. He denied other symptoms related to hypersensitivity such as dizziness, nausea, facial flushing or numbness, abdominal discomfort or vomiting. He denied prior history of runny nose, asthma, post-nasal drip or gastroesophageal reflux. Oxaliplatin infusion was immediately stopped. Cough persisted despite treatment with 50mg diphenhydramine, 20mg famotidine, and 10mg dexamethasone intravenously. During this episode, his vital signs remained stable. Cough subsided temporarily after being observed for 3 more hours and the patient was discharged home.

However the dry cough did not completely resolve. It continued to bother him for the next two weeks. He did not develop any signs of infection such as fever, chills, headache, productive sputum, pleuritic chest pain or shortness of breath. Streptococcus screening of the throat was negative, nasal swab of influenza was also negative. Several complete blood counts did not reveal any leukocytosis, total white blood cell counts

range from 4-5.8 x 1000/uL. Robitussin with codeine did not offer any symptomatic relief. Empirical antibiotics with a course of Z-pack (azithromycin) were also tried without success. Two diagnostic CT scans of the chest including PE protocol did not show any evidence of interstitial lung disease, pulmonary embolism, infiltrates or consolidation (Figure 1).

He was closely monitored in the outpatient clinic on a weekly base. Each physical exam failed to detect any abnormality. Vital signs remained very stable. He was evaluated by pulmonologist in outpatient clinic for the dry cough. Wheezing was not found on physical exam. Although pulmonary function test (PFT) was considered, it was never performed due to two reasons: 1) the patient had a small bullous disease at the right apex on CT scan prior to the episode; 2) the dry cough resolved spontaneously after two weeks without residual symptoms. After the episode of dry cough, chemotherapy with oxaliplatin and mitomycin C was held.

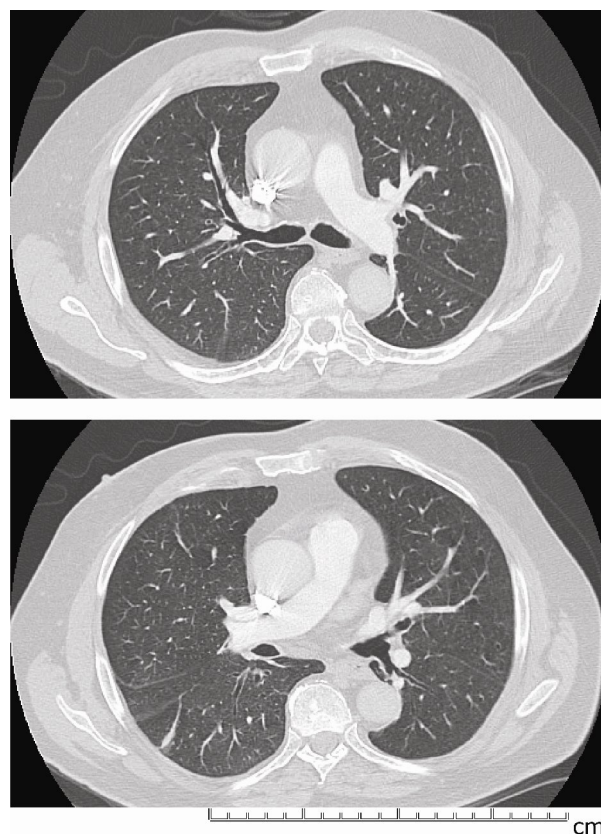


Figure 1. CT scan of the chest with PE protocol

Chemotherapy with a non-oxaliplatin based regimen (mitomycin at 5mg/m² and irinotecan at 150mg/m² on day1 every two weeks) was initiated 2 days after resolution of cough. This patient was not re-challenged for oxaliplatin-based regimen for concerns of development of a full blown HSR.

DISCUSSION

“All platinum compounds including the newer generation oxaliplatin are known to cause hypersensitivity reaction (HSR). HSR is defined as an unexpected reaction that cannot be explained by the known toxicity profile of the chemotherapeutic agent”.⁷ In 2007, we reported a case with fever as the sole manifestation of HSR.⁸ As a result of increasing clinical use, more HSRs related with oxaliplatin are being observed. A BOX warning was added for this reason. The incidence is about 12% of patients receiving oxaliplatin, however, only less than 0.55% of the patients would develop severe reactions.⁹⁻¹⁴ The clinical presentations vary from mild to moderate symptoms such as flushing, alterations in heart rate and blood pressure, bronchospasm, back pain, chest discomfort, fever, pruritis, erythema, nausea, and rash to more life-threatening anaphylactic reactions.⁹⁻¹⁴ In a study of 42 patients receiving FOLFOX (fluorouracil, folinic acid, and oxaliplatin), 39 patients were found to have immediate allergic reaction. Half of them were noted to have respiratory symptoms including bronchospasm, laryngospasm, dyspnea.¹⁵ Cough alone has never been reported as part of HSR.

The HSR in this case occurred during the 4th oxaliplatin infusion. Clearly prior exposure to platinum compounds played a role in this case. Some investigators have described these reactions as IgE-mediated (Type I).¹⁶⁻¹⁸ Stahl and colleagues supported this hypothesis with two cases successfully treated with high-dose corticosteroids for oxaliplatin-induced HSR.¹⁹ However, others believe the reaction could be T-cell mediated given the elevated TNF-alpha and IL-6 in serum^{20,21}. Binding of the platinum salts to different peptides of major histocompatibility complex (MHC) could also contribute to this reaction²². In the end, the true pathophysiology of HSR is still not well understood.

There is no effective prophylactic regimen for HSRs. Pre-medication with steroids and antihistamines can only prevent some hypersensitivity reactions to

oxaliplatin.¹⁷ This patient received proper pre-chemotherapy medications including steroids and antiemetics. When a HSR occurs, the infusion of oxaliplatin should be immediately stopped and intravenous antihistaminic drug and low-dose corticosteroids should be administered. More severe reactions may require higher dose of steroid. Although we treated the patient with some antibiotics, we believe this could be a self-limiting reaction. However, if the patient continues to receive this platinum compound, he could develop more severe HSR. Re-challenge of such a patient could be potentially risky.

In English literature, there were cases of successful desensitization of oxaliplatin with calcium and magnesium or prolonged infusion, however, the standard approach remains to be defined.^{23, 24} Our patient with a diagnosis of metastatic pancreatic cancer had already failed standard first-line gemcitabine regimen. The regimen of oxaliplatin/mitomycin C was indeed his third-line therapy which is not a curative intent option. DO NO HARM is superior to any risky attempt in such a patient. Given his excellent performance status, we offered him a non-oxaliplatin containing regimen after this variant hypersensitivity reaction rather than re-challenge him.

We present this case in order to remind physicians in practice that cough can be the sole manifestation of HSR. A CT scan to rule out pulmonary embolism, interstitial lung disease or infectious etiology is necessary in this setting. Knowledge of this rare but real toxicity of oxaliplatin is of paramount importance since the use of this drug is wide-spread in USA.

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