Case Report

Oxaliplatin-Induced Lung Injury with Allergic Reaction

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DOI: 10.1007/s11670-011-0232-y

ABSTRACT

A 79-year-old man was diagnosed as stage IV colon cancer and treated with a modified FOLFOX6 (mFOLFOX6) regimen. On the 12th cycle, we observed erythema and dyspnea. Radiographs showed ground grass opacities. Blood tests showed elevated levels of eosinophils and immunoglobulin E. We diagnosed this finding as response to drug allergy and administered high-dose methylprednisolone. The treatment was successful and he was discharged. The drug lymphocyte stimulating test against oxaliplatin was positive, indicating a type I and IV allergic reaction due to oxaliplatin. Regimens including oxaliplatin must be carefully monitored and frequent blood tests and chest radiographs are needed.

Key words: Oxaliplatin; mFOLFOX6; Drug-induced pneumonia; Drug lymphocyte stimulating test; Immunoglobulin E

INTRODUCTION

Modified FOLFOX6 (mFOLFOX6) is a key regimen for advanced-stage colorectal cancer, and the regimen includes oxaliplatin, levofolinate calcium, and 5-fluorouracil[1]. Lung injury or hypersensitivity reactions to oxaliplatin have been rarely reported. The incidence of hypersensitivity reactions increases with multiple courses of the drugs and they generally occur after 4 to 6 cycles. The cumulative median dose of oxaliplatin received in that previous study was 650 mg/m^2 (range of 100–2400 mg/m^2)[1]. However, Meyer et al. suggested that hypersensitivity reactions related to oxaliplatin have been frequently under-diagnosed, with mild symptoms being missed, and they estimated the incidence to be approximately 12%[2].

Lung injuries related to oxaliplatin may include cytotoxic and immunological reactions. Cytotoxic reactions are the direct injury to components of lung cells. These reactions are in general caused by chemotherapeutic agents or their metabolites and are usually dose-dependent. Immunological reactions caused by the drug can be assumed to occur in 2 ways[3]. One is known to be anaphylactic reactions (type I hypersensitivity), which usually occur within minutes of administration in patients with prior exposure, including facial edema, bronchospasm, hypotension, tachycardia, pruritus, and erythema. These symptoms result from degranulation of mast cells and basophils following immunoglobulin E (IgE) binding to those cells. The second way is late phase allergic reactions (type IV hypersensitivity), which are not related to antibody reactions. The main activated cells are T lymphocytes, i.e., Th1, Th2, Treg, and Th17, and the balance of these subsets is assumed to be important. Delayed symptoms include fever, chills, abdominal pain, nausea, diarrhea, and hypotension.

Oxaliplatin-induced lung injury with an allergic reaction might be related to our case.

CASE REPORT

A 79-year-old man has been diagnosed in November 2008 as stage IV sigmoid colon cancer with metastatic lung cancer. In December 2008, he was started on a mFOLFOX6 regimen. Up to the 11th cycle of this regimen, the findings on his radiological images were stable, and tumor marker levels decreased, but he developed erythema on the first day of the sixth cycle of chemotherapy with this regimen.

On the first day of the 12th cycle of chemotherapy, he had erythema on his limbs and trunk. On the second day, he additionally manifested dyspnea and fever. Promptly, blood tests and radiological tests were conducted along with administration of oxygen at 3 L/min.

Chest radiography and computed tomography (CT) revealed bilateral ground grass opacities. The images were compatible with that of cryptogenic organizing pneumonia (COP) pattern (Figure 1). Blood tests just after the reaction demonstrated a marked elevation of eosinophils to 792/μl, KL-6 to 956 U/ml, and IgE to 1800 IU/L. Arterial blood gas analysis while he was breathing oxygen of 6 L/min showed a pH of 7.456, $PaCO_2$ of 35.8 mmHg, PaO_2 of 69.8 mmHg, HCO_3 of 24.7 mEq/L, base excess (BE) of 1.2 mEq/L, $AaDO_2$

Received 2011–05–11; **Accepted** 2011–07–12
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of 114.89 mmHg. The sputum culture showed no infectious species but few fractions of eosinophils were seen. We diagnosed the patient as an mFOLFOX6-related drug-induced lung injury and started treatment with 1000 mg methylprednisolone (mPSL) for 3 consecutive days, which was then tapered down to 30 mg in a month. Abnormal lung shadows vanished and he was discharged without experiencing any respiratory failure. The later result of the drug lymphocyte stimulating test (DLST) against oxaliplatin gave a value of 534% as compared with control serum. The test results for other chemotherapeutic agents were negative.

After discharge, extension of colorectal cancer was observed. He received the FOLFIRI regimen, which includes 5-fluorouracil, irinotecan hydrochloride, and levofolinate calcium, from August 2008 without experiencing any allergic events.

DISCUSSION

For metastatic colorectal cancer, oxaliplatin combined with mFOLFOX6 is used worldwide as the first-line regimen[1].

The occurrence rate of lung injuries induced by oxaliplatin combined with FOLFOX is about 0.2% (11/5008 cases) in Japan, which was surveyed by the manufacturer, Yakult Corp., in 2007. Some patients died due to lung injury caused by the chemotherapy. In addition, an allergic reaction was seen in about 1% of the patients treated. The incidence of lung injuries is not so high; however, they could be lethal.

In our case, we were not able to obtain bronchoalveolar lavage fluid (BALF) due to severe respiratory failure. BALF is an important specimen in the diagnosis of respiratory diseases. In cases with severe acute respiratory failure, like ours, BALF is not always easy to obtain. In some cases of oxaliplatin-induced lung injury, BALF included lymphocytes and some eosinophils[4]. A previous report pointed out that BALF of patients with COP patterned drug-induced lung injury contains lymphocytes, neutrophils, macrophages, mast cells, and eosinophils[5]. Our case showed a COP pattern and eosinophils were seen in the sputum. In general, lymphocytes are involved in drug-induced lung injuries and assumed to play a pivotal role during the injury. The involvement of eosinophils may be a marker for allergic reactions in the lung when oxaliplatin is administered. BALF is also important in order to exclude infections. In our case, sputum cultures were available to exclude infections and recovery by mPSL also supported the hypothesis that infections were not the cause of respiratory failure. When BALF cannot be obtained, a good sample of sputum might be used to make a differential diagnosis.

The mechanisms of adverse events by oxaliplatin are not known precisely. Drug-induced lung injury is thought to occur via 2 pathways. The first pathway is a direct toxic effect on the cells and the second is an immunological effect of the drug. The mechanism of chemotherapeutic agents like oxaliplatin is thought to be the former one. One theory is that oxaliplatin may deplete glutathione, which is a protector against oxidative damage in the lung[5, 6]. However, further studies are needed to confirm the mechanisms of oxaliplatin-induced lung injury.

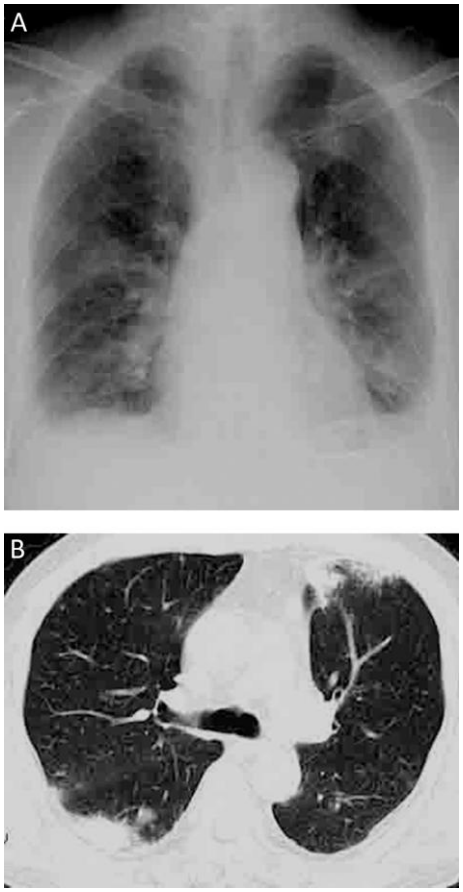

Figure 1. Image finding. Chest radiography (A) and CT (B) revealed bilateral ground grass opacities after administration of oxaliplatin. The images were compatible with that COP pattern.

Making a differential diagnosis in patients with chest infiltrates who are undergoing chemotherapy is always difficult. We diagnosed this case by referring to previously published reports[7]. Differential diagnoses of abnormal chest shadows during treatment for malignancies are infections, heart failure, lung bleeding, lymphangitis, and drug toxicity, including allergy. First, we administered an antibiotic drug for 3 days before we started treatment with mPSL. During that time, we tested sputum, urine, and blood cultures for any kind of infection. In addition, we also evaluated the results of the blood samples, which may indicate toxicity or allergy. The cultures were negative for any pathogen. Elevated levels of serum IgE and eosinophils and the positive result of DLST against oxaliplatin were confirmed in our case. Toxicity and allergy caused by oxaliplatin were highly suspected as cause of the lung shadows.

There is controversy regarding the usefulness of DLST. From other studies, a positive DLST does not always mean that the drug is the cause of the allergy[8]. It is very likely that the agent is the cause if tests showed that it is cytotoxic. Chemotherapeutic agents are often administered as

Table1. Previous cases with oxaliplatin-induced lung injury

No	Reported year	Age/Sex	Smoking	Allergy	Pre-exsisting ILD	CT pattern	No. of cycles	Total dose of L-OHP (mg/m^2)	High dose mPSL	DLST	Out come
1	2001[16]	60 M	never	none	none	AIP	7	700	-	negative	remission
2	2002[9]	60 F	never	none	none	CEP	8	680	-	Not done	remission
3	2005[17]	68 F	NA	NA	none	IPF	6	510	-	not done	died
4	2006[18]	67 M	NA	NA	none	COP	11	1100	+	not done	remission
5	2006[19]	64 M	NA	NA	none	COP	2	200	+	not done	remission
6	2006[19]	75 M	NA	NA	none	AIP	1	100	+	not done	remission
7	2006[20]	74 M	NA	NA	none	AIP	6	510	+	not done	died
8	2007[21]	66 M	NA	NA	none	AIP	12	1020	-	not done	died
9	2007[22]	30 F	NA	NA	none	COP	6	510	-	not done	remission
10	2008[23]	71 M	NA	NA	ILD	AIP	6	510	-	not done	died
11	2008[23]	77 F	never	none	none	COP	12	1020	-	not done	remission
12	2008[23]	69 M	NA	NA	none	COP	6	510	-	not done	remission
13	2008[24]	73 F	NA	NA	none	AIP	4	340	+	not done	died
14	2008[24]	71 M	NA	NA	none	COP	4	340	+	not done	died
15	2008[25]	70 M	50 p/y	NA	none	COP	11	1100	+	not done	remission
16	2008[25]	62 M	15 p/y	NA	none	COP	12	1200	+	not done	remission
17	2008[25]	43 F	never	NA	none	COP	5	500	+	not done	remission
18	2009[26]	62 M	NA	NA	none	COP	7	595	+	not done	remission
19	2009[26]	77 M	NA	NA	none	COP	7	595	+	not done	remission
20	2009[27]	82 M	never	none	none	COP	10	850	+	not done	remission
21	2010[28]	47 M	NA	NA	none	COP	4	NA	-	not done	remission

M: male; F: female; NA: not available; never: never smoker; p/y: pack per year; ILD: interstitial lung disease; AIP: acute interstitial pneumonia; CEP: chronic eosinophilic pneumonia; IPF: idiopathic pulmonary fibrosis; COP: cryptogenic organizing pneumonia; L-OHP: oxaliplatin; mPSL: methylprednisolone; DLST: drug lymphocyte stimulating test.

combinations. The mFOLFOX6 regimen includes 3 types of cytotoxic drugs. As far as we know, there are limited studies or case reports about the experience of administering a single agent[9]. For that reason, the other 2 drugs in the regimen may modify the reaction of oxaliplatin in the body. After recovery from the lung injury, our patient received the FOLFIRI regimen, which is similar to the mFOLFOX6 regimen, except for the change of oxaliplatin to irinotecan hydrochloride. This regimen was safely administered, which indicated that oxaliplatin was most likely the cause.

From previously published English written reports, we were able to review 21 cases of oxaliplatin-related lung injuries (Table 1). The characteristics of patients with oxaliplatin-related lung injuries are: mean age was 65.1 years, 71.4% were men, and mean administered dose of oxaliplatin was 644.5 mg/m^2, the chest CT revealed a COP pattern in 61.9%, and 28.5% died of the lung injury. The characteristics of our case were similar. Of the 13 cases that showed COP patterns, none was a DLST performed, and 12 received high-dose mPSL as treatment, and the treatment was unsuccessful in 6 cases. With regard to our case, it should be noted that the result of DLST was positive against oxaliplatin, and the patient successfully recovered following high-dose mPSL therapy.

Risk factors for drug-induced lung injury are thought to be a history of smoking, pre-existing interstitial lung disease, male gender, high age, and renal dysfunction[10,11]. Our patient had grade 1 erythema on the first day of the eighth cycle of the regimen, but he tolerated the side effect well. Skin manifestation or any type I allergic symptoms may be a predictor for severe toxic drug effects. The findings of our case may suggest that patients with symptoms of a type I allergy should be tested for the existence of a type IV allergy by using DLST or other methods. With regard to risk factors and predictors for lethal lung injuries, further studies are needed to investigate this association.

During chemotherapy with the mFOLFOX6 regimen, obtaining regular chest radiographs is not always necessary. On the basis of the findings of our case and other reported cases, an objective examination of the lung, e.g., lung function tests and radiographs should be recommended in all cases receiving chemotherapy that exceeds 7 cycles or a total dose of 650 mg/m^2 of oxaliplatin. Early signs may be seen in some of the patients, e.g., erythema or other unusual toxic events caused by oxaliplatin. There is evidence about the usefulness of skin tests for the prevention of allergic events due to oxaliplatin[12]. DLST may also be a helpful tool to make an earlier diagnosis. Making the appropriate decision for the administration of high-dose corticosteroids may be a key to survival. Recently, cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR), or bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is added to the oxaliplatin-based regimen for metastatic colorectal cancer[13,14]. These new chemo- therapeutic agents may cause drug-related allergies or lung injuries, or may increase the incidence of adverse events of an oxaliplatin-based regimen.

Chest radiographs and blood tests should be utilized more frequently for detecting lethal lung damage, including allergies. Skin allergies are usually easy to detect by the patient and may be a sign for lethal events. Early treatment by high-dose corticosteroids may rescue the patient from

lethal lung damage. Chemotherapeutic agents like paclitaxel also cause lung injuries and allergic events[15]. Since IgE and eosinophils seemed to be related to the lung injury and allergy observed in our case, pretreatment with steroids and anti-histamine receptors may have a preventable effect, as has been shown for paclitaxel. However, further studies are needed. Those studies should focus on the treatment after the event as well as on the prevention of drug-induced lethal lung injuries and related allergies.

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