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Original Article

Interstitial pneumonitis after using Cetuximab in cancer patients

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Abstract: Cetuximab is a chimeric monoclonal antibody widely used for the treatment of many cancers by inhibiting epidermal growth factor receptor (EGFR). Though cetuximab-induced interstitial pneumonitis is rare, it can be fetal. Herein we will review the cases of cetuximab-induced interstitial pneumonitis, to give an insight in the main factors associated with this condition, and to describe a case observed at our Center. 10 cases including 9 cases found from Pubmed search and 1 new case diagnosed at our department were collected. The result showed that most of the patients suffered from cetuximab-induced interstitial pneumonitis were men (8/10) and they were all ≥60-year-old. Though treated with steroid, the outcome was poor, with 70% died of respiratory failure. In summary, cetuximab-induced interstitial pneumonitis is rare but fetal and clinicians should pay attention to the onset of pulmonary symptoms in patients treated with cetuximab.

Keywords: Cetuximab, interstitial pneumonitis

Introduction

Cetuximab is a chimeric (mouse/human) monoclonal antibody that competitively binds to the extracellular domain of EGFR with higher affinity than its endogenous ligands, thus blocking EGFR-driven signaling and resulting in the inhibition of cell growth and induction of apoptosis [1-3]. Cetuximab has been proven effective in patients with advanced or metastatic colorectal cancer (CRC) [4, 5] and squamous cell carcinoma of the head and neck [6, 7].

Cetuximab can induce a number of toxicities of which the cutaneous ones are the most common. Other common adverse events include gastrointestinal complaints (19-59%), headache (19%), and infusion reactions (between 15 and 20%) [8]. Cetuximab-induced interstitial pneumonitis that is fatal has been reported rarely [9, 10]. Herein we will present one case and briefly overview the current understanding of cetuximab-induced interstitial pneumonitis.

Materials and methods

Literature search

A literature survey and analysis was conducted to collect the cases of cetuximab-induced interstitial pneumonitis in the pubmed database from the earliest record in the databases to June 6, 2015. Search terms used were interstitial pneumonia OR interstitial pneumonitis OR diffuse parenchymal lung disease OR interstitial pneumonitides OR interstitial pneumonitis AND cetuximab OR IMC C225 OR IMC-C225 OR MAb C225 OR C225 OR Erbitux. Patients diagnosed with cetuximab-induced interstitial pneumonitis with detailed information.

The extracted data from each paper included: (1) characteristics of patients including age, gender, location of cancer; (2) treatment after diagnosed with cetuximab-induced interstitial pneumonitis; (3) outcome.

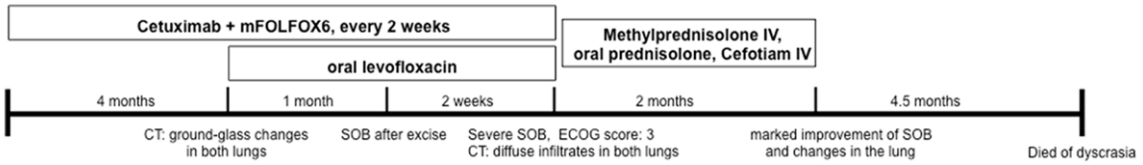

Figure 1. Disease progression history.

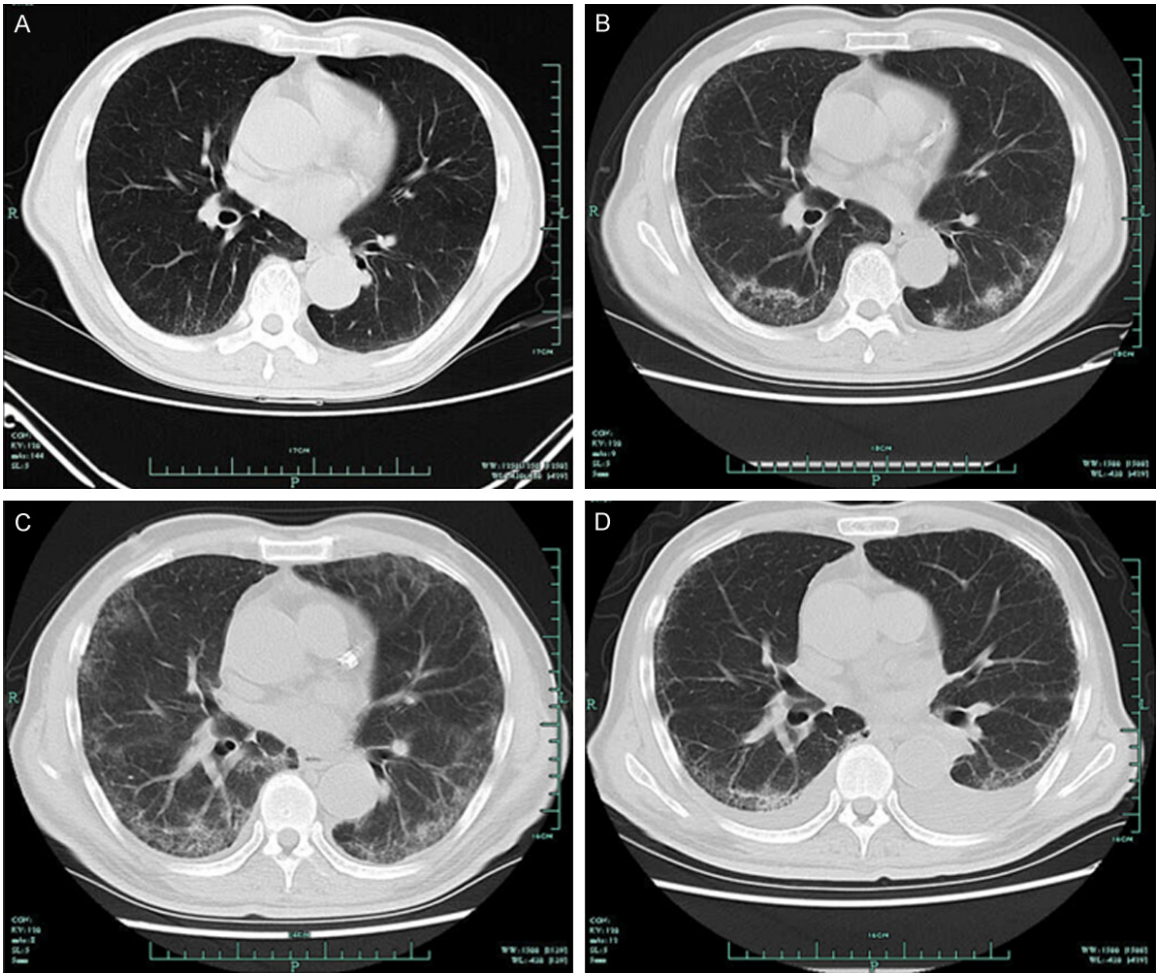

Figure 2. CT scan of the chest. (A) before cetuximab treatment, (B) after the eighth cycles' treatment of cetuximab, (C) after the eleventh cycles' treatment of cetuximab, (D) 2 months after admission of steroid pulse therapy.

Case reports

The enhancement CT scans of the abdomen was performed to evaluate lesions in the abdomen or lung. Genomic DNA was extracted from tissues for k-Ras sequencing.

Results

Case report

The patient, a 63-year-old male, was admitted to our hospital because of diminution of the stool form accompanied with paroxysmal pain in the lower abdomen lasting for one month. No other specific symptoms existed. The enhancement CT scans of the abdomen showed left colic flexure thicken accompanied by multiple peri-intestinal and retroperitoneal lymph nodes enlargement and multiple occupying lesions in the liver. The pathology result of intestinal stent endoprosthesis and biopsy under colonoscopy was adenocarcinoma of the transverse colon. KRAS and NRAS DNA sequencing found no mutations in either K-Ras or R-Ras. Therefore

Table 1. Reported cases of cetuximab-induced interstitial pneumonitis

No. of cases	Gender	Age (years)	Diagnosis
1 [11]	F	60	CRC with liver and lymph node metastases
2 [10]	M	61	CRC with lung, liver, and bone metastases
3 [14]	M	69	CRC with liver metastasis
4 [14]	M	71	CRC with lung and liver metastasis
5 [12]	M	61	Mesopharynx carcinoma
6 [12]	M	65	Tonsillar squamous cell carcinoma and oesophageal adenocarcinoma
7 [15]	M	60	Recurrent CRC
8 [13]	F	69	CRC
9 [9]	M	78	CRC with lung and liver metastasis
10	M	63	CRC with liver metastasis

M, male; F, female; CRC, colorectal cancer.

he was diagnosed with mCRC and received cetuximab (500 mg/m^2) plus mFOLFOX6 (folinic acid, fluorouracil and oxaliplatin) every 2 weeks (**Figure 1**).

The patient tolerated the treatment well, except for grade 1 acneform rash since the first cycle and worsened after the eighth dose that required intravenous cefotiam, metronidazole and topical emollient therapy. After the first cycle's treatment, his abdominal pain disappeared. The CT scans of the lung after the eighth cycles' treatment showed ground-glass changes near the pleura in both lungs that were not seen on the baseline CT (**Figure 2A** and **2B**). Since CRP (C-reaction protein) was 52.30 mg/L, pulmonary infection was first considered and oral levofloxacin was admitted. Ten cycles' treatment later, the patient reported shortness of breath on exertion with no other associated symptoms and had normal oxygen saturation levels at that time. However, after the eleventh cycle's treatment, the patient reported severe shortness of breath with ECOG score of 3 so that chemotherapy and cetuximab had to be stopped (**Figure 1**). The CT scan of the lung demonstrated diffuse infiltrates in both lungs (**Figure 2C**). Both routine blood test and oxygen saturation were normal. It was therefore considered to be cetuximab-induced pulmonary toxicity. Thus, the patient was commenced to receive low-flow oxygen, intravenous methylprednisolone 40mg once a day for five days followed by a course oral prednisolone 500 mg once a day. Intravenous cefotiam was also given to protect against any coexisting pneumonia. His symptoms improved gradually. The CT scan of the lung performed 2 months after admission of steroid pulse therapy showed marked improvement in the ground-glass changes, consistent with his symptomatic improvement (**Figure 2D**). Unfortunately, he died of dyscrasia due to the progression of colorectal cancer 11 months after the initial consultation (**Figure 1**).

Our search strategy permitted to identify 29 papers, of which 16 were excluded by title and abstract evaluation. Full-text papers were then assessed for eligibility according to given criteria. Eventually, 7 papers were included, reporting 9 cases [9-15]. And the one case described this paper were added, resulting in a total of 10 cases.

Of the 10 reported cases, 8 were male, 2 were female. Their ages ranged from 60 to 78. 8 cases were mCRC or recurrence CRC and 1 case was mesopharynx carcinoma, tonsillar squamous cell carcinoma and oesophageal adenocarcinoma, respectively (**Table 1**).

After diagnosed with cetuximab-induced interstitial pneumonitis, 8 cases were treated with steroid, 1 case started second-line treatment with mFOLFOX6 plus bevacizumab and the treatment of the rest case was unknown. Unfortunately, 9 case died with 7 died of respiratory failure, 1 died of multiple organ dysfunction syndrome and 1 died progression of the cancer. The outcome of the last case was missing (**Table 2**).

Discussion

In recent years, interstitial pneumonitis is a recognized complication of other EGFR inhibitors

Table 2. Treatment and outcome of patients

No. of cases	Treatment	Outcome
1 [11]	Supplemental oxygen, antibiotics, methylprednisolone	Died of respiratory failure, 25 days after the 6th dose of cetuximab
2 [10]	High-flow oxygen, antibiotics dexamethasone 8 mg, po, qd	Died of respiratory failure, 19 days after the 4th dose of cetuximab
3 [14]	Start second-line treatment with mFOLFOX6 plus bevacizumab	Died of respiratory failure because of the acute exacerbation of interstitial pneumonitis
4 [14]	Unreported	Died of respiratory failure because of the rapid development of interstitial pneumonitis
5 [12]	Antibiotics oral prednisone 100 mg daily	Chest x-ray was almost normal 7 days after starting steroids, discharged 10 days
6 [12]	Antibiotics and oral prednisone (40 mg), bid	Died of multiple organ dysfunction syndrome
7 [15]	Steroid pulse therapy and intensive therapy with mandatory ventilation	Died of respiratory failure
8 [13]	Steroid pulse therapy	Died of respiratory failure after 98 days from admission, possibly due to secondary infection
9 [9]	Oral prednisone 50 mg daily	Died of respiratory failure because of progressive lung metastases, 4 months later
10	Low-flow oxygen, intravenous methylprednisolone 40 mg, qd	Died of progression of cancer

such gefitinib and erlotinib [16-19]. The mechanisms of EGFR inhibitor-induced interstitial pneumonitis are poorly understood. T Higenbottam et al suggested that EGFR inhibitors may contribute an additional risk to the development of interstitial pneumonitis, albeit via a pharmacological effect through the EGFR rather than directly as a result of biotransformation or chemical injury [20].

In contrast, cetuximab-induced interstitial pneumonitis does not draw much attention. Only 10 cases of cetuximab-induced interstitial pneumonitis with detail information, including our case, have been reported in the literature. The mean age at presentation was 65.7 years (range: 60-78 years). Male patients predominated (80%). 8 cases were mCRC or recurrence CRC, 1 case was mesopharynx carcinoma and 1 case was tonsillar squamous cell carcinoma and oesophageal adenocarcinoma After diagnosed with cetuximab-induced interstitial pneumonitis, 8 cases were treated with steroid, 1 case started second-line chemotherapy with mFOLFOX6 plus bevacizumab and the treatment of the rest case was unreported. Unfortunately, 9 cases died (7 cases died of respiratory failure, 1 case died of multiple organ dysfunction syndrome and 1 case died of progression of the cancer) and 1 case was discharged (**Table 1**).

Because of the lack of patients' detailed information, not all reported patients with cetuximab-induced interstitial pneumonitis were included in our review. For instance, Taroh Satoh et al reported that cetuximab-related drug-induced lung injury occurred in 24 (1.2%) patients, but only one case was included in our review with detailed information (1). Patients reported by Neal JW et al and Neyns B et al were also excuded because of lack of patients' detailed information [21, 22]. This will exaggerate the severity of cetuximab-induced interstitial pneumonitis.

In conclusion, though rare, cetuximab-induced interstitial pneumonitis can be fatal. It is importance to increase awareness of it allowing appropriate management.

Disclosure of conflict of interest

None.

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