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Case Report

Diffuse alveolar hemorrhage after erlotinib combined with concurrent chemoradiotherapy in a patient with esophageal carcinoma

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Abstract: Diffuse alveolar hemorrhage (DAH) is a life-threatening clinical pathologic syndrome caused by a variety of diseases. We report a case of DAH related to combination therapy of chemoradiotherapy and erlotinib. As to know, DAH following chemoradiotherapy was only reported among hematopoietic stem cell transplant recipients with hematologic malignancies till now. DAH associated with chemoradiotherapy for oesophageal carcinoma has not been reported. This is the first DAH report on erlotinib-combined chemoradiotherapy for esophageal cancer. The authors believe epidermal growth factor receptor tyrosine kinase inhibitor erlotinib increased the lung injury. Molecular targeted drugs are gradually applied to be combined with chemoradiation, whether this combination will cause the increase of serious adverse reactions need further study. This case can provide certain reference for erlotinib in the treatment. Meanwhile, after long term hormone therapy for DAH, the patient was diagnosed with pneumocystis carinii pneumonia. It reminds us to attach importance to the immunosuppressive diseases after long-term hormone treatment.

Keywords: Diffuse alveolar hemorrhage, chemoradiotherapy, erlotinib, esophageal carcinoma

Introduction

Diffuse alveolar hemorrhage (DAH) is a rare yet serious clinical syndrome caused by a variety of diseases. It is characterized by the accumulation of intraalveolar RBCs originating from the alveolar capillaries. The main clinical manifestations include hemoptysis, anemia, diffuse radiographic pulmonary infiltrates and hypoxemic respiratory failure. Difficult to diagnose early due to untypical clinical symptoms and rapid onset of acute respiratory failure, DAH is a life-threatening condition, with high mortality rates [1].

DAH may result from multiple different causes, such as Wegener granulomatosis, Goodpasture syndrome, idiopathic pulmonary hemosiderosis (IPH), collagen vascular diseases, microscopic polyangiitis (MPA) and cytotoxic drugs [2]. Some other pathogenesis remains unclear. Chemoradiation also can cause DAH. DAH following radiotherapy was only reported among hematopoietic stem cell transplant recipients with hematologic malignancies, its risk factors include: old age, basic thrombocytopenia, total body irradiation, high-dose chemotherapy before transplantation and severe acute graft versus host disease [3]. Chemotherapy drugs including cyclophosphamide and carmustine have been reported to cause DAH [4]. Definitive concurrent chemoradiation is a preferred primary treatment for unresectable esophageal cancer. To improve progression-free survival (PFS) and overall survival (OS), molecular targeted drugs, such as cetuximab, erlotinib, gefitinib, have been applied to the patients with esophageal cancer [5]. Paxlitaxel and radiotherapy combined with or without erlotinib is a novel protocol in a open-label, randomized, controlled phase III clinical trial we are carrying out (NCT01752205). In this trial, one patient suffered from DAH in the treatment process. As we know, DAH following chemoradiation occurs

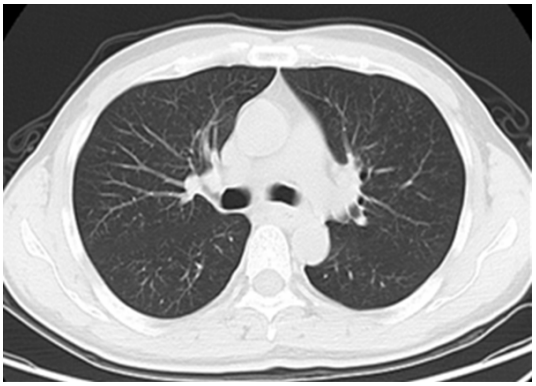

Figure 1. Chest CT scan revealed no lung lesions before treatment.

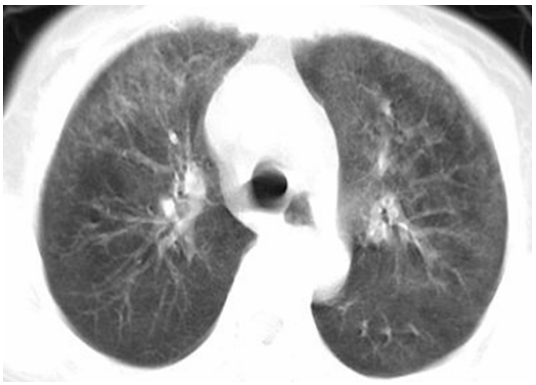

Figure 2. Chest CT scan showed diffuse ground-glass imaging on April 25, 2013.

more frequently post-transplant. DAH associated with chemoradiotherapy for oesophageal carcinoma has not been reported. This is the first DAH report on erlotinib-combined chemoradiotherapy for esophageal cancer till now.

Case present

A 40-year-old man was admitted to our hospital for progressive dysphagia lasting for two months on March 13, 2013. On admission, he underwent full clinical evaluation. His ECOG performance status was grade 0. He had no history of tobacco smoking and drinking. Esophageal X-ray findings were typical for cancer of the middle esophagus. Endoscopically, the esophageal ulcer-like uplift tumor was confirmed at 26-34 cm, and iodine staining was positive at 20 cm. The tumor was fragile and bled readily on touch. Ultrasonic gastroscopy indicated the stage was $T_{4a}N_0M_x$, and biopsy pathology results were poorly differentiated squamouscarcinoma (26-34 cm), severe atypical hyperplasia squamous epithelium (20 cm). There were no signs of distant metastases from the primary disease. Chest CT scan revealed no lung lesions and mediastinal lymph node metastasis (**Figure 1**). Hemogram, coagulation function, cardiac function and pulmonary function tests were normal. The patient was diagnosed with esophageal squamous cell carcinoma ($T_{4a}N_0M_0$, stage IVA TNM-UICC). Unsuitable for surgical resection after a multidisciplinary consultation, the patient signed a written informed consent to participate in the clinical trial (NCT01752205). He was randomized to the experimental group, the treatment plan was to take 150 mg erlotinib daily, paxlitaxel weekly with intensity modulated conformal radiation therapy (IMRT). Gross tumor volume (GTV) was determined based on thoracic CT and the endoscopy results, clinical target volume (CTV) included GTV, supravicular and mediastinal lymph node region. Planning target volume (PTV) was generated as CTV plus 5 mm of margin. 95% PTV planned dose 60Gy/2Gy/30f, 2Gy/f, 5f/w. From March 18 to April 15, 2013, he had received radiation of 42Gy/2Gy/21f and was simultaneously given erlotinib for 29 days, paxlitaxel weekly for 4 times.

However, he developed fever from April 16 to 18 with maximum body temperature reaching 38.5 degrees C, with no cough and no dyspnea. Vital signs were as follows: heart rate, 100 beats/min with a regular rhythm; breathing, 20 times/min; SpO_2, 95% (on room air) and blood pressure was 138/83 mmHg. Physical examination revealed harsh breath sounds in two lungs. A complete blood count revealed a white blood cell count of 6.23×10^9/L with 64% neutrophils, 23% lymphocytes, 10% monocytes, and 3% eosinophils. The hemoglobin level was 10.3 g/dL and the platelet count was 216×10^9/L. Blood coagulation function, C-reactive protein (CRP), Procalcitonin (PCT) were normal. All cultures and viral markers, including CMV IgM, EBV VCAM, HSV, HIV, Parvovirus B19, Coxakie virus B1-B6, Influenza A and B and parainfluenza 1-3, were negative except for the presence of a titer of 1:60 for CMV IgG. There was no evidence of renal or hepatic dysfunction or auto-immune diseases. Any heart failure and platelet dysfunction were not suspect from the laboratory findings. A chest radiograph revealed the increase of lung marking, and a diagnosis

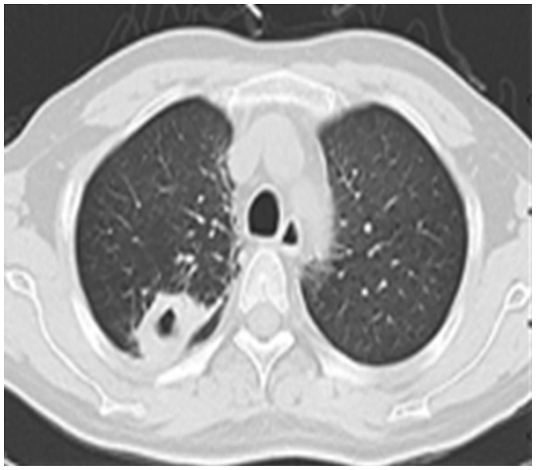

Figure 3. Chest CT scan showed a big lung shadow on the lower right lung on June 18.

of community-acquired pneumonia was made. Piperacillin sodium and tazobactam sodium for injection (containing piperacillin sodium 2000 mg and tazobactam sodium 250 mg every 8 hours) was initiated on April 20 for possible bacterial infection. But he had further worse fever, even no cough but slight dyspnea. The high-resolution computed tomography (HRCT) scan on April 25, 2013 showed diffuse ground-glass imaging (**Figure 2**). Radiation-induced pneumonia, no infectious sign, was diagnosed. Dexamethasone injection (5 mg/d, intravenous) was given for possible radiation pneumonitis. The temperature became normal and dyspnea became worse. On April 28, the arterial blood gas analysis in room air showed pH 7.302, PCO_2 35 mmHg, PO_2 55 mmHg and oxygen saturation 86%. Hemoglobin fell from 9.3 g/dL to 8.3 g/dL within 2 day. Diagnostic bronchoscopy for bronchoalveolar lavage (BAL) was performed on April 29. The bronchoscope examination results: the airway unobstructed, in the middle of both lungs and lower lobe nozzle with physiological saline, recovery liquid are hemorrhagic. The cytologic examination results: more red blood cells and ciliated columnar epithelium, visible tissue cells, occasional neutrophils. Iron stain results: a large number of macrophages containing iron red element, then a diagnosis of DAH without any identifiable pathogens including P. jaroveci, fungi or viruses by bronchoalveolar lavage fluid (BALF). The patient received methylprednisolone 500 mg every 12 hours intravenously. At the same time noninvasive ventilator help to breathe (inspiratory

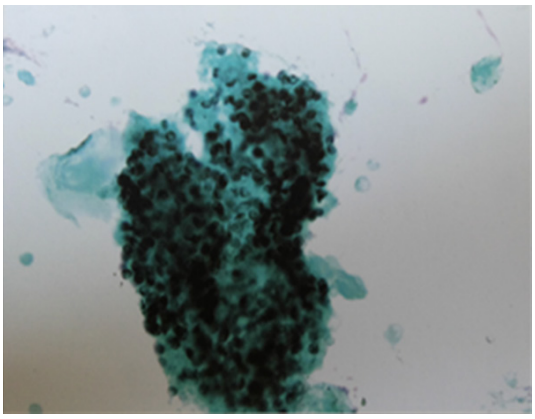

Figure 4. Pneumocystis carinii was found in BALF on June 20 (Grocott Methenamine Silver Stain).

phase positive pressure 12 cmH_2O, expiratory phase positive pressure 6 cmH_2O). Three days later, he had no difficulty in breathing after large dose hormone shock therapy. Hormone decrement step by step, after 2 months hormone withdrawal gradually. BAL and BALF found nothing abnormal on May 15. No fever until June 15, the patient's body temperature rose to 38.3 degrees. Follow-up CT-scan on June 18 showed a complete resolution of diffuse ground-glass imaging, but a big lung shadow on the lower right lung. The mass was 2.5 cm in diameter (**Figure 3**). BAL was performed again on June 20, showed no DAH, but pneumocystis carinii was found in BALF (**Figure 4**). The sensitive antibiotics sulfamethoxazole were given simultaneously for 2 weeks to heal the pneumocystis carinii pneumonia (PCP). On July 15, chest CT found nothing abnormal (**Figure 5**). One month later, Gastroscopy showed a complete response, CT-scan and BAL found nothing abnormal. So far, he was periodically examined, as a result, no tumor recurrence and metastasis.

Discussion

DAH is a life-threatening complication, most of the cases have experienced a long misunderstanding, and even delay the rescue time. Reports of DAH gradually increased over the years, which have drawn great attention of scholars. To our knowledge, this is the first reported case of chemoradiotherapy and erlotinib associated with DAH in an immuno competent patient without other risk factors. We would highlight three points from this case.

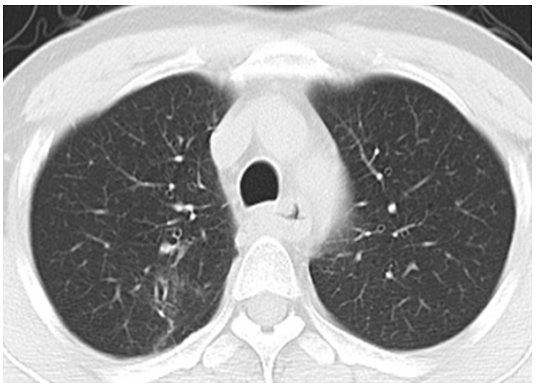

Figure 5. Chest CT found nothing abnormal on July 15.

Firstly, it is very important to confirm an early diagnosis in clinically suspected patients with DAH, because it can be lethal due to anemia and respiratory failure [6]. However, many symptoms are not typical. The core symptom is haemoptysis, which may occur suddenly, also may take several days or several weeks to progress continuously. In addition, as much as 33% of patients had no haemoptysis, and these patients should be paid higher attention [7]. In this case, the patient had no haemoptysis and our understanding of DAH was insufficient, which lead to delay in early diagnosis and treatment. Other symptoms include: fever, chest pain, cough and asthma. When the hemoglobin of patients declines, the physician should be alert to the possibility of DAH. In addition to the medical history, physical examination, regular laboratory tests, serological test are helpful for diagnosis of DAH. Chest X-ray is nonspecific, chest CT can confirm the chest X-ray results, and can be more accurate to determine the severity degree of the disease. Patients with ongoing or received radiotherapy, are easily misdiagnosed as radiation pneumonia or infectious pneumonia, which chest X-ray or CT examination is very difficult to identify. Fiber bronchoscope can establish the clinical diagnosis of DAH and eliminate infection, BAL is the gold standard of diagnosis. However, a careful approach is needed because bronchoscopy itself can cause massive pulmonary bleeding.

This case has been misdiagnosed as radiation pneumonia, but progressive decline in hemoglobin suggest the possibility of DAH, further BAL found multistage hemorrhage, more than 20% of BALF cells were pulmonary alveolar macrophages containing hemosiderin, so the diagnosis of DAH is clear. The results of Cartesian pneumocystis, virology, BALF bacteria fungi cultivation were all negative, ruling out the possibility of the infectious pneumonia. A month and a half after hormone therapy, the patient had fever again. Pneumocystis carinii was found in BALF, made the secondary infection diagnosis PCP clear.

Secondly, molecular targeted therapy has become the hotspot and focus of comprehensive treatment of cancer, which is proposed against the molecular biological targets such as tumor cell growth, apoptosis, cell cycle, invasion and angiogenesis. Its side effects are less and different from traditional radiation and chemotherapy. More application of targeted drugs, more side effects are gradually be recognized, such as skin toxicity of EGFR-TKI, high blood pressure of vascular endothelial cell growth factor (VEGF) antagonist, especially some rare adverse reactions [8].

Bortezomib (Velcade) was the first proteasome inhibitors for multiple myeloma (MM), a DAH case has been reported [9]. Japanese scholars reported anti-VEGF antibody bevacizumab caused DAH [10]. Enbrel is a targeted drug for tumor necrosis factor-α, Khaja M reported a case of DAH caused by Enbrel in the treatment of rheumatoid arthritis [11].

At present, the targeted drugs in combination with radiation and chemotherapy can improve treatment outcome has been verified in many solid tumors. However, whether the comprehensive treatment results in the increase of adverse reactions or not should also be taken seriously. Esophageal chemoradiation can cause radiation pneumonitis is not uncommon, but no DAH is reported. The reported incidence of lung injury by erlotinib is 0.8%-1%, mostly are interstitial pneumonia [12]. No DAH has been reported, especially when chemoradiotherapy combined with erlotinib. The possible reasons for this DAH case:

1. Erlotinib is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). The epidermal growth factor is highly expressed on human alveolar epithelial type II cells, participating in the repair of alveolar walls [13]. Erlotinib may hinder the repair of alveolar so as to cause or worsen the lung injury caused by chemotherapy, radiation or other reasons [14].

The hyperplasia and reconstruction of alveolar epithelial type II cells also play an important role in the occurrence of pulmonary fibrosis, erlotinib may increase pulmonary fibrosis [15].

2. Radiation and chemotherapy can cause cellular damage mediated by immune cells [16]. A variety of cytokines including chemokines, tumor necrosis factor can be detected in bronchoalveolar lavage fluid after radiation and chemotherapy, and a variety of inflammatory cells gathered. The early histologic performance is alveolar inflammation, the late performance is pulmonary fibrosis. Fiber cell hyperplasia or activation is related to immune injury, with the participation of a variety of cytokines, suggests that the immune mechanism plays an important role in the fibrosis [17]. Studies have shown that EGFR inhibits alveolar macrophage chemotaxis, so as to modulate inflammation and immune response, and EGFR inhibitors can make inflammation and immune response out of control, thus increasing cell damage [18]. The exact mechanism of these interactions remains unclear, and further investigation is necessary.

Thirdly, Glucocorticoids are the main treatment of DAH. The shock therapy of glucocorticoids as initial therapy is methylprednisolone 1 g daily for 3 days, decreased to 1-2 mg/kg/day by fourth day, and switched to oral prednisone over next few days, maintenance treatment for two months [19]. As prospective controlled studies are lacking, so optimal management therapy of DAH has not been established. The use of oral prednisone therapy in past was associated with high mortality. This prompted the introduction of high-dose intravenous pulse corticosteroids, but due to lack of data, there are no guidelines for the optimal dose and duration of therapy. When the treatment effect is not ideal, the immune inhibitors can be considered, such as cyclophosphamide treatment [20]. Clotting factor VIIa is reported to obtain good effect on DAH [21].

However, after the long term hormone therapy, patients prone to immunosuppressive diseases such as pneumocystis pneumonia, fungal infection and so on. Supportive measure must be established early in the management. Timely stop using hormone and immune enhancer may help to prevent the happening of the immunosuppressive diseases.

EGFR-targeted drugs are gradually applied to be combined with chemoradiation, whether this combination will cause the increase of serious adverse reactions need further study. This case can provide certain reference for targeted drugs in the treatment.

Disclosure of conflict of interest

None.

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