Lung Cancer with Diffuse Ground-glass Shadow in Two Lungs and Respiratory Failure

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Introduction

Pulmonary ground-glass shadow is a common clinical imaging manifestation shared by many pulmonary diseases such as interstitial pneumonia, pulmonary fungal infection, parasitic infection, viral pneumonia, and heart failure. Some of the lung cancers, especially lung adenocarcinoma, can also present ground-glass-like nodules. The early diagnosis and differential diagnosis of the ground-glass shadow are very important for lung cancer. Even though there are a lot of studies in this field in recent years, diffuse and uniform ground-glass opacity is rarely reported in lung adenocarcinoma. In this study, a case of lung adenocarcinoma complicated with respiratory failure is reported to show diffuse uniform ground-glass shadow in the chest computed tomography (CT). In addition, we discuss this case in the context of related literation hoping clinical and imaging doctors could be aware of this in clinical practice.

Case Report

A 56-year-old female patient was admitted to Hangzhou Normal University Affiliated Hospital on November 12, 2014. She had fever for 1 week with the highest temperature reaching 39°C, coughed white sputum with no blood or yellowish stuff, and complained chest tightness and dyspnea when severe coughing. She felt nausea and even vomit in the course but no coffee-like objects were vomited. She was treated with intravenous cefuroxime and levofloxacin in outpatient service for 3 days without expected improvement. She had been diagnosed as type 2 diabetes in the past and had been given metformin and acarbose treatment. Clozapine and trihexyphenidyl and other drugs were daily administrated orally to treat schizophrenia diagnosed previously. She has no smoking and drinking history, no omophagia fish, and shrimp history. No obvious abnormalities were found in the regular physical examination and chest X-ray scan [Figure 1a] performed a half year before. Physical examination showed body temperature of 38.2°C, pulse rate of 89/min, respiratory rate of 22 breaths/min, blood pressure of 125/70 mmHg (1 mmHg = 0.133 kPa), and pulse oxygen saturation of 85% (concentration of oxygen inhalation: 21%). Her consciousness was clear,with poor spirit and mild cyanosis. No enlarged superficial lymph nodes were found and widely moist rales could be heard in two lungs. Her heart rate was 89 beats/min with no pathological murmur. The abdomen is soft, no lower limbs dropsy. On auxiliary examination, chest CT scan [Figure 1b–1e, November 12, 2014] found diffused uniform ground-glass shadow in two lungs with no enlarged mediastinal lymph nodes. On admission, preliminary diagnosis revealed: (1) diffuse lung disease of unknown origin, respiratory failure, (2) type 2 diabetes, and (3) schizophrenia. After admission, the patient presented high fever and pulmonary diffuse exudate with respiratory failure. Considering previous history of type 2 diabetes, we suspected pulmonary infection with unknown pathogen. Oxygen therapy and

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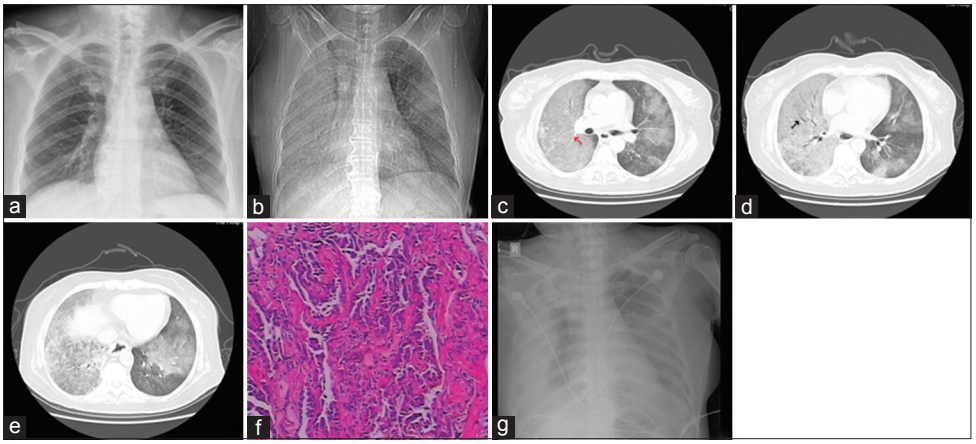

Figure 1: Imaging and pathology of the patient. (a) Chest X-ray image of half a year ago; (b-e) chest computed tomography images when the patient admitted to hospital; (f) Pathology: Adenocarcinoma (Hematoxylin-eosin staining, original magnification ×100); (g) Chest X-rays shows "S"-shaped curve, when the patients often lie in right lateral; Red arrow: Diffuse ground-glass shadow; Black arrow: Air bronchogram.

hypoglycemic therapy were given. In addition, 4.5 g of piperacillin-tazobactam by intravenous drip bid and 0.4 g of moxifloxacin once a day (QD) combined with anti-infection and cough expectorant were given to relieve symptoms and simultaneously improve the relevant inspection.

Laboratory examination: Routine blood test + high-sensitive C-reactive protein (hs-CRP), leukocyte 19.67 × 10^9/L, percentage of neutrophils 91.0%, 6.1% of lymphocyte percentage and 0 of eosinophil cell percentage, red-cell count 4.65 × 10^{12}/L and 130 g/L of hemoglobin, platelet count of 216 × 10^9/L, hs-CRP 30.99 mg/L. Arterial blood gas analysis: pH 7.31, partial pressure of carbon dioxide in artery 27.10 mmHg, arterial partial pressure of oxygen 57.90 mmHg, arterial oxygen saturation 87.10%. B-type natriuretic peptide: 65.30 pg/ml. Allergen determination: total immunoglobulin E 11.50 IU/ml, no specific allergen was detected. Procalcitonin <0.5 ng/ml. Antinuclear antibodies, double-stranded-DNA, anti-Sjogren syndrome A antibody, anti-Sjogren syndrome B antibody and other autoantibodies were all negative. Perinuclear antineutrophil cytoplasmic antibody, cytoplasmic antineutrophil cytoplasmic antibodies and myeloperoxidase antibody was negative. Tumor screening: α-fetoprotein - 3.61 ng/ml, carcinoembryonic antigen (CEA) - 2.5 ng/ml, carbohydrate antigen (CA) 199-25 kU/L, CA 125-14 U/ml, all were in the normal range. Interferon gamma release test for tuberculosis infection: negative. 1,3-beta-glucan test: 300.2 pg/ml (reference value <100.5 pg/ml); galactomannan test: negative. Nucleic acid detection of influenza A virus (throat swab): negative; human immunodeficiency virus antibody: negative, urine cytomegalovirus DNA detection: negative. Acid fast bacilli is negative in 3 smear tests. Sputum cytology found no tumor cells. Electrocardiograph: sinus rhythm.

Cough, shortness of breath gradually worsened after 3 days treatment with piperacillin-tazobactam combined with moxifloxacin. Body temperature had been fluctuating between 37°C and 38°C since the admission. The patient was administered with 0.2 g voriconazole by intravenous drip q12h and 40 mg methylprednisolone by intravenous QD to inhibit fungal infections and inflammation for 4 days. Intermittent noninvasive ventilation was given as needed. On the 5th day of admission, electronic bronchoscopy was performed and showed that the trachea and bronchial lumen was smooth and the mucosa was congested. A huge amount of white foam sputum was found in the tracheal cavity to be constantly emitted after suction; no stenosis and neoformation, no cheese-like necrosis tissue was observed. Oxygen saturation increased from 70% to 80% to above 93% after foamy sputum was suctioned. Transbronchial lung biopsy (TBLB) was performed in the right lower lung and TBLB pathology reported adenocarcinoma [Figure 1f]. Epidermal growth factor (*EGFR*) gene and anaplastic lymphoma kinase-echinoderm microtubule-associated protein-like (*ALK-EML4*) fusion gene were further analyzed, and no mutation was found. The patient was given antitumor Chinese traditional medicine, anti-infection treatment, and nutritional support together with noninvasive ventilation and other treatment to relieve symptom. The patient died of respiratory failure on the 20th day after admission.

Discussion

Diffuse pulmonary effusion in the two lungs in imaging examination is very common. In clinical practice, the chest CT scan showed ground-glass-like change due to diffuse exudation in two lungs often suggests special pathogen infection (such as hematogenous pulmonary tuberculosis, pulmonary fungal infection, and viral pneumonia), exogenous allergic pulmonary inflammation, interstitial pneumonia, acute pulmonary edema, etc. For this kind of imaging pattern, infectious and noninfectious diseases are two aspects routinely considered in diagnosis and differential diagnosis.

The hematogenous pulmonary tuberculosis is characterized by toxic symptoms of tuberculosis infection such as fever, night sweats, cough, and expectoration. In the chest

X-ray, small nodular shadows with special pattern in size, distribution, and uniformity of the density are found in the two lungs in the acute stage. The diameter of the nodules is usually in the range of 1–3 mm, and the density and the distribution are even. While in subacute and chronic hematogenous pulmonary tuberculosis, nodules are mainly located in the middle and upper lung, with the diameter varies in a wider range of 3–7 mm. The density and distribution of these nodules are uneven, and some are with the patches and cord-like exudation. The pulmonary shadow occurs 1–3 weeks behind the clinical symptoms, and most of the lesions are fused into two pulmonary diffuse shadows. Viral pneumonia is inflammation caused by viral invasion of lung parenchyma and interstitial. The chest CT mainly manifests features of the interstitial pneumonia such as increased lung texture, the ground-glass-like shadow, and small patch or the like. Severe viral pneumonias, such as highly pathogenic avian influenza virus infection, severe acute respiratory syndrome virus infection, often progress rapidly into dangerous condition. Cytomegalovirus pneumonia, frequently happen to immunocompromised patients, shows imaging of cloud and mist effusion in two lungs. Examination of the virus DNA or RNA in the blood, body fluids and secretions of the viral pneumonia patients, and serum virus-specific antibodies can help diagnosis. Pneumocystis carinii pneumonia is prone to immune function defect patients. Diffuse ground-glass opacity is the most distinguished imaging features. With the progress of this disease, the shadow expands rapidly from hilus, then developed alveolar consolidation. Finding of hydatid in specific staining such as Giemsa staining, methylene amine blue staining, and Gomori Daya hexamine silver staining in sputum smear, bronchoalveolar lavage fluid smear, or TBLB specimen can be used as the basis of diagnosis. Detection of serum antibody and complement binding test can also provide evidence for diagnosis. Acute allergic pulmonary inflammation is a lung disease caused by immune response induced by exposure to organic dust antigen in susceptible individuals. CT scan shows ground-glass shadow, diffusedly located in both lungs or mainly in lower lung. Micronodules can be seen sometimes, with blurred edge and less than 3 mm in diameter. Symptoms can be relieved after antigen removal. Acute interstitial pneumonia is acute onset, manifested as glass-like change with fuzzy hair, or a wide range of distribution of the linear, reticular, small nodules, or even the consolidated shadow.

The chest X-ray performed half a year ago before the patient was admitted to hospital was reviewed and it showed clear lung fields with no obvious abnormalities. At the time of admission, the chest CT showed diffuse exudation, uniform ground-glass shadow, which is more obvious in the right lung, visible air bronchogram sign in the right lower lobe of the lung. Considering the patient is with acute onset, fever and chills, and elevated leukocyte counts and hs-CRP inflammatory index while tumor marker test were within normal range, we first suspected infectious diseases on admission based on type 2 diabetes histories. Through examination, the pulmonary tuberculosis, pulmonary spore bacteria pneumonia, cytomegalovirus pneumonia, human infection with highly pathogenic avian influenza, and other diseases such as severe viral pneumonia were excluded. Congest heart failure and acute pulmonary edema are also excluded. Therefore, pathologic analysis is very important to disease diagnosis and treatment.

The types of lung cancer from different anatomic sites also differ. The central type of lung cancer is mainly squamous cell carcinoma and small cell carcinoma while peripheral lung cancer is mostly adenocarcinoma. It was reported that the pathological types of lung cancer with diffuse exudation in chest CT were adenocarcinoma,[1] which mainly occurred in Clara cells, type II alveolar epithelial cells, and mucous cells. In diffuse lung adenocarcinoma, cancer cells usually grow invasively along alveolar and alveolar ducts, spread along the lymphatic vessels, or metastasis to bilateral lungs by the way of lymph and blood.[2,3] As a result, diffuse pulmonary adenocarcinoma in the X-ray manifests pulmonary diffuse nodular or patchy shadow. In the chest CT[4] examination, it shows multiple or diffuse nodules or patchy exudation shadow. Nodules are miliary, occasionally acinar with size of 3–5 mm in diameter, fuzzy edge could be found in some lesions. The nodules in the lungs are distributed randomly, asymmetrically, and unevenly with various densities. Patchy shadow commonly shows multiplely and diffusedly. These lesions often merge with each other, involving a segment or the entire lung.

The patient was diagnosed as lung adenocarcinoma by TBLB examination. For the pathological diagnosis of diffuse pulmonary disease, percutaneous lung puncture and TBLB is a common clinical biopsy method. Compared with percutaneous lung puncture, TBLB has the advantages of simplicity, fast, and safeness. In clinical work, safe, effective method of biopsy should be selected according to the severity of the patient's condition, imaging performance, general situation, and other factors. The positive rate of TBLB in diffuse lung adenocarcinoma was about 58.3%.[5] The pathological diagnosis of diffuse lung adenocarcinoma patients was more advanced, no surgical opportunity.[6] Genes analysis of *EGFR*, *ALK-EML4* fusion gene, *K-RAS*,[7] etc., should be routinely performed. The patient with corresponding mutation might benefit more from EGFR tyrosine kinase inhibitor, new angiogenesis inhibitors, and other targeted drug treatment.

The remarkable diffuse, uniform grinding glass-like shadow is different from the nodular or patchy shadow of majority diffuse lung adenocarcinoma, but rarely reported. Moreover, with fever, increased inflammation index, normal CEA, and other tumor marker test together with diabetes history, it is prone to be misdiagnosed as fungal infection, cytomegalovirus pneumonia, interstitial pneumonia, allergic pneumonia, congest heart failure, and other diseases. An interesting phenomenon was the right lung formed an "S"-shaped curve in the chest X-ray scan because the patient prefers to lie on the right side in her illness [Figure 1g].

Visible large white frothy sputum observed in bronchoscopy suggested that the diffuse ground-glass shadow was relevant to the infiltration of cancer cells and hypersecretion infiltrates. Because of the hypersecretion traits of cancer cells, a large number of secretions gathered in the lung, causing diffuse infiltration, exudation. With the change of body position, "S"-shaped curve appeared in the chest X-ray due to the gravity effect of liquid.

In summary, the diffuse, uniform ground-glass shadow as the main imaging features of lung cancer in chest CT is very rare. Clinicians should be aware of this possibility. In clinical practice, we should follow the correct diagnostic method and strengthen differential diagnosis from pulmonary tuberculosis, fungal infection, viral pneumonia, interstitial pneumonia, heart failure and so on. The formation of diffuse ground-glass shadow was related with infiltration hypersecretion of cancer cell.

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Conflicts of interest

There are no conflicts of interest.

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