Biomedical Research 2019; 30 (4) *ISSN 0970-938X*
www.biomedres.info

Pulmonary adenocarcinoma misdiagnosed as interstitial pneumonia.

Yan Li[1], Jia Gao[2], Feng Zong[1], Jianqing Wu[1*]

[1]Department of Geriatric Medicine, Jiangsu Province Key Laboratory of Geriatrics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

[2]Department of Respiratory Diseases, Jiangsu Geriatric Hospital, Nanjing, China

Abstract

The idiopathic interstitial pneumonias (IIPs) represent a subset of interstitial lung diseases of unknown origin. Pulmonary fibrosis is the predominant cause of severe morbidity and mortality in IIPs and increases the risk of lung cancer. Adenocarcinoma and squamous cell carcinoma was identified to be most common in cases of lung cancer with IIP. Here we report a case of pulmonary adenocarcinoma that was almost misdiagnosed as interstitial pneumonia. Our case provides a reference for this unusual presentation and the importance of correct diagnosis and treatment.

Keywords: Pulmonary adenocarcinoma, Interstitial pneumonia, Interstitial lung diseases.

Accepted on February 13, 2019

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases with either known or unknown etiologies, including at least nine types such as idiopathic pulmonary fibrosis (IPF), cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonitis, nonspecific interstitial pneumonitis, hypersensitivity pneumonitis, acute interstitial pneumonitis, interstitial pneumonia, sarcoidosis and asbestosis [1]. ILDs have different pathogeneses and prognoses, sharing several clinical, radiological, functional, and pathological similarities, but also presenting with numerous differences [1-3]. During the course of progression of the disease, patients with ILDs will develop a cough and expectoration, present with inflammation and fibrosis of the alveolar walls and alveolar lumen to different extents, and have symptoms of progressive dyspnea and diffuse infiltration [4].

ILDs are known to be caused by bacteria, viruses and fungi, and regular exposures to inhaled irritants at work or during hobbies also cause some types if ILDs [5]. In contrast, idiopathic interstitial pneumonias (IIPs) represent a subset of interstitial lung diseases of unknown origin. Pulmonary fibrosis is the predominant cause of severe morbidity and mortality in IIPs [6]. IPF is characterized by a very poor survival, and accounts for about 25% of the cases of ILD [7,8]. Furthermore, compared with the general population, pulmonary fibrosis increases the risk of lung cancer [9,10]. Based on histological analysis, adenocarcinoma and squamous cell carcinoma was identified to be most common in cases of lung cancer with IPF. In addition, the majority of them was located in IPF-associated fibrotic peripheral lesions [11]. As the incidence of pulmonary fibrosis and lung cancer continue to rise, the correct diagnosis and treatment become increasingly important, particularly when early lung cancer lesions may easily be obscured as ILD due to the poor specificity of ILD.

Here we report a case of pulmonary adenocarcinoma that was almost misdiagnosed as interstitial pneumonia.

Case Report

A 63-year-old female patient was admitted to The First Affiliated Hospital of Nanjing Medical University in March 2015 due to chest congestion and asthma, accompanied by weakness. During the progression of the disease, the patient had experienced headache, dizziness, and precordial pain, which were relieved by resting. The patient had a history of contact with the paint, accompanied by cough and sputum mixed with blood in October 2014. During the first auscultation examination of the lungs, fine crackles were observed in the right lower lobe. The patient's vital signs showed that the axillary temperature was 36.4°C, the respiratory rate was 18-21 breaths/min, and the laboratory test results were follows: white blood cell count 15.97×10^9/l, neutrophil level 87.4%, and serum C-reactive protein level 3.28 mg/dl, D-dimer level 1.56 mg/l. Analysis of arterial blood gas (ABG) revealed a pH value of 7.43, an oxygen partial pressure of 46 mmHg and a carbon dioxide partial pressure of 33.3 mmHg. The peripheral capillary oxygen saturation level (SpO_2) was in the range of 92-95%. Chest X-ray and computed tomography (CT) revealed high-density patch-shaped areas and a change in the bilateral ground-glass opacity (Figures 1A and 1B), leading to the suspicion that the patient may have had interstitial pneumonia.

Considering the patient's condition, initial oxygen inhalation (6 l/min) was administered *via* a bilateral nasal tube. However,

following methylprednisolone pulse therapy (40 mg/q for 12 h) over 7 days, combined with an anti-infection treatment with zinacef (cefuroxime) (1.5 g twice daily) for 5 days, no improvement was observed in the patient's chest congestion, asthma or SpO_2. Instead, there was a clear exacerbation of the lungs, since the level of SpO_2 fell to the range 90-92%, or was even <90%. CT scan of the thorax revealed a diffuse nodular pattern and a patchy, high-density shadow without clear borders (Figure 2).

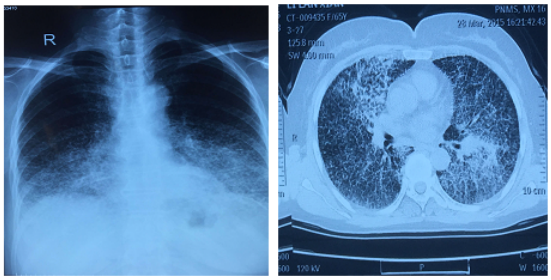

Figure 1. *(A) chest X-ray and (B) chest computed tomography examinations prior to admission. The images revealed the high-density, patch-shaped areas and bilateral ground-glass opacity changes in both lungs, with the left lung more serious.*

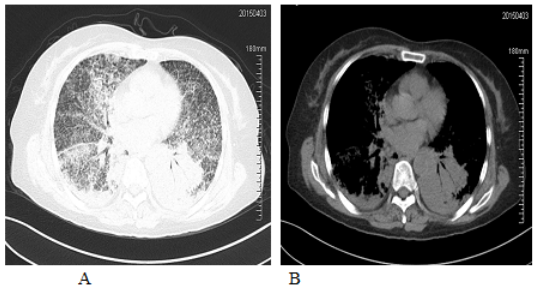

Figure 2. *Chest computed tomography performed on admission of the patient to hospital. (A) The lung window: a diffuse nodular pattern and patchy high-density shadows were indicated without clear borders. (B) The mediastinal window: The multiple small lymph nodes shadow was located at the mediastinum, with pleural thickening on both sides.*

Subsequently, the patient underwent blood tests for tumor markers, anti-nuclear antibodies, rheumatoid factor, anti-streptolysin, C-reactive protein, immunoglobulin A (IgA), IgG, IgM, complement C3 and C4 proteins, and tuberculosis antibody to exclude the possibilities of autoimmune disease and tuberculosis. The only notable findings were that the level of cytokeratin fragment 21-1 (CY21-1) was 17.1 ng/ml, and the level of neuron-specific enolase (NSE) was 33.0 ng/ml. In next 4 days, treatment with Zinacef (1.5 g twice daily) was discontinued, the anti-infection treatment strategy was changed to a combination of Azithromycin (0.5 g once daily), an antibiotic useful for the treatment of bacterial infection by inhibiting protein synthesis in the bacteria, and voriconazole (200 mg once daily), an agent for the treatment of fungal infection by inhibiting cell membrane ergosterol synthesis in the fungi, and the usage of methylprednisolone was reduced to 40 mg once daily. A CT-guided percutaneous needle aspiration biopsy of the lung was subsequently performed. The symptoms of chest congestion and asthma still showed no improvement, as the level of SpO_2 had decreased further to <90%. After 4 days, the pathological results revealed adenocarcinoma of the left lung, with the two lungs showing multiple metastases (Figure 3). At this stage, the treatment changed to IRESSA® (gefitinib 250 mg/day). After 1.5 months treatment with IRESSA®, SpO2 level reached 95% (without oxygen inhalation), ABG analysis (without oxygen inhalation) revealed a pH value of 7.42, the oxygen partial pressure was 65 mmHg, the carbon dioxide partial pressure was 40 mmHg, and CY21-1 and NSE levels declined to normal levels (<3.3 ng/ml for CY21-1 and <16.3 ng/ml for NSE). The patient exhibited marked improvements in chest congestion and asthmatic symptoms. Finally, following another 20 day course of treatment with IRESSA®, the patient was discharged. The patient continued to show improvement in her condition, and kept taking IRESSA® (250 mg/day).

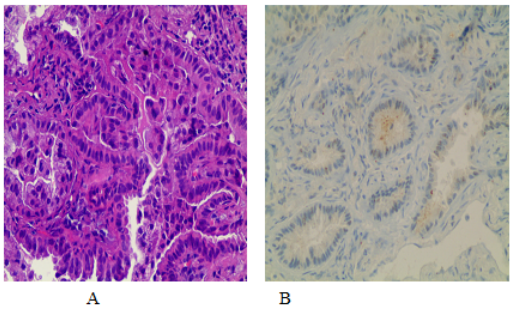

Figure 3. *Acinar adenocarcinoma. (A) This tumor forms irregular-shaped glands with malignant cells exhibiting hyperchromatic nuclei in a fibroblastic stroma. (B) Negative immunohistochemical staining for ALK.*

Discussion

ILDs are disorders of the lung parenchyma that represent a heterogeneous group of diseases characterized by different pathogeneses and prognoses [12]. IPF is a type of ILD of unknown etiology, and the incidence is estimated to be 6.8-16.3/100,000 in USA [13]. In recent years, patients with ILDs, particularly those diagnosed with IPF and lung cancer (IPF-LC), have been a challenge due to the misdiagnosis of IPF or lung cancer. It has been debated whether lung cancer may precede IPF and influence the development of fibrosis [14]. It is difficult to identify early signs and, therefore, there may be a certain delay in correct diagnosis of lung cancer. For IPF-LC, recent evidence supported the hypothesis that lung cancer occurs as a late complication of IPF, rather than as an incidental or preceding finding [15,16]. Approximately two-thirds of the patients were shown to have developed lung cancer 3 years after the diagnosis of IPF [17]. The majority of the patients with IPF were identified to be only suffering from cancer at the follow-up. Consequently, further attention needs to be paid to the diagnosis of IPF-LC.

Numerous reports have demonstrated that identical risk factors are associated with IPF and lung cancer, including age, being male, smoking, and occupational risks, e.g., exposure to and

inhalation of dust. In addition, older male smokers were identified to be more susceptible to carcinoma and IPF [10,15]. Several studies have suggested that IPF could become an independent risk factor that differs from other risk factors [18,19].

It is easy for the tumor to be overlooked when IPF is accompanied by infections, particularly associated with scarring. On the other hand, early tumor lesions are small, and they are not typically observed on imaging. In present case study, several factors indicated a diagnosis of interstitial pneumonia. In addition, the only abnormal tumor biomarkers of the patient were CY21-1 (17.1 ng/ml; normal level, <3.3 ng/ml) and NSE (33.0 ng/ml; normal level, <16.3 ng/ml), but not carcinoembryonic antigen (CEA) or carbohydrate antigen 125 (CA125). Several studies have demonstrated clinical significance associated with certain tumor biomarkers in patients with ILDs, including serum CEA and CA125 levels, which are often elevated [20]. These two markers may serve as markers for cancer in patients with ILDs. Fang et al. considered using serum NSE and CA125 levels as prognostic factors for silicosis [21]. Certain other serum tumor markers, such as CEA, NSE, CY21-1, CA125 and carbohydrate antigen 19-9 (CA19-9), not only exhibited high values in LC, but also were detected in IPF [22-24]. Therefore, these biomarkers may be useful for a diagnosis of cancer with ILD.

Finally, not only it is possible for patients with IPF-LC to be misdiagnosed with lung cancer, but this leads to important consequences with respect to the treatment of lung cancer. Chiyo et al. determined that ILD-LC group was associated with a higher incidence of pneumonia and acute exacerbation-ILD (AE-ILD) following pulmonectomy compared with the group without ILD [25]. Saito et al. reported that the 5-year survival rate of patients with ILD-LC following a pulmonectomy was lower compared to lung cancer group [26]. Therefore, the selected treatment option requires a more careful consideration, with subsequent monitoring of the course of treatment.

In conclusion, the incidence rate of cancer with ILD is rising, resulting in a challenge for the treatment and prognosis of cancer with IPF. Clinicians should pay close attention to lung cancer which may be misdiagnosed as interstitial pneumonia.

Acknowledgment

This work was supported by Jiangsu Provincial Key Discipline of Medicine (No. ZDXKA2016003).

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Ryu JH, Olson EJ, Midthun DE, Swensen SJ. Diagnostic approach to the patient with diffuse lung disease. Mayo Clin Proc 2002; 77: 1221-1227.
2. Collard HR, King TJ. Demystifying idiopathic interstitial pneumonia. Arch Intern Med 2003; 163: 17-29.
3. Bryson T, Sundaram B, Khanna D. Connective tissue disease-associated interstitial pneumonia and idiopathic interstitial pneumonia: Similarity and difference. Semin Ultrasound CT MR 2014; 35: 29-38.
4. King TE. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. Am J Respir Crit Care Med 2005; 172: 268-279.
5. Travis WD, Costabel U, Hansell DM. An official American thoracic society/european respiratory society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733-748.
6. van Moorsel CH, Hoffman TW, van Batenburg AA. Understanding idiopathic interstitial pneumonia: a gene-based review of stressed lungs. Biomed Res Int 2015; 2015: 304186.
7. Chogtu B, Malik DV, Magazine R. Idiopathic pulmonary fibrosis and myasthenia gravis: An unusual association. J Clin Diagn Res 2016; 10: 6-7.
8. Vancheri C. Common pathways in idiopathic pulmonary fibrosis and cancer. Eur Respir Rev 2013; 22: 265-272.
9. Hubbard R, Venn A, Lewis S. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med 2000; 161: 5-8.
10. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980; 35: 496-499.
11. Kim EJ, Kim SR, Jin GS. Tonsillar metastasis of small cell lung cancer in a patient with idiopathic pulmonary fibrosis: a case report. Medicine (Baltimore) 2015; 94: 565.
12. Archontogeorgis K, Steiropoulos P, Tzouvelekis A, Nena E, Bouros D. Lung cancer and interstitial lung diseases: a systematic review. Pulm Med 2012; 2012: 315918.
13. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006; 174: 810-816.
14. Daniels CE, Jett JR. Does interstitial lung disease predispose to lung cancer? Curr Opin Pulm Med 2005; 11: 431-437.
15. Tomassetti S, Gurioli C, Ryu JH, Decker PA, Ravaglia C, Tantalocco P, Buccioli M, Piciucchi S, Sverzellati N, Dubini A, Gavelli G, Chilosi M, Poletti V. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest 2015; 147: 157-164.
16. Ozawa Y, Suda T, Naito T, Enomoto N, Hashimoto D, Fujisawa T, Nakamura Y, Inui N, Nakamura H, Chida K. Cumulative incidence of and predictive factors for lung cancer in IPF. Respirology 2009; 14: 723-728.
17. Antoniou KM, Tomassetti S, Tsitoura E, Vancheri C. Idiopathic pulmonary fibrosis and lung cancer: a clinical and pathogenesis update. Curr Opin Pulm Med 2015; 21: 626-633.
18. Aubry MC, Myers JL, Douglas WW. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. Mayo Clin Proc 2002; 77: 763-770.

19. Vancheri C. Idiopathic pulmonary fibrosis and cancer: do they really look similar? BMC Med 2015; 13: 220.
20. Dai H, Liu J, Liang L, Ban C, Jiang J, Liu Y, Ye Q, Wang C. Increased lung cancer risk in patients with interstitial lung disease and elevated CEA and CA125 serum tumour markers. Respirology 2014; 19: 707-713.
21. Fang SC, Zhang HT, Wang CY, Zhang YM. Serum CA125 and NSE: biomarkers of disease severity in patients with silicosis. Clin Chim Acta 2014; 433: 123-127.
22. Brightwell R, Eng K, Lele S. Use of hematologic biomarkers during chemotherapy predicts survival in ovarian cancer patients. Eur J Gynaecol Oncol 2017; 38: 378-381.
23. Sahin F, Yildiz P. Serum CA-125: biomarker of pulmonary tuberculosis activity and evaluation of response to treatment. Clin Invest Med 2012; 35: 223-228.
24. Fang SC, Lu KH, Wang CY, Zhang HT, Zhang YM. Elevated tumor markers in patients with pulmonary alveolar proteinosis. Clin Chem Lab Med 2013; 51: 1493-1498.
25. Chiyo M, Sekine Y, Iwata T, Tatsumi K, Yasufuku K, Iyoda A, Otsuji M, Yoshida S, Shibuya K, Iizasa T, Saitoh Y, Fujisawa T. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outcomes. J Thorac Cardiovasc Surg 2003; 126: 1141-1146.
26. Saito Y, Kawai Y, Takahashi N. Survival after surgery for pathologic stage IA non-small cell lung cancer associated with idiopathic pulmonary fibrosis. Ann Thorac Surg 2011; 92: 1812-1817.

*Correspondence to

Jianqing Wu

Department of Geriatric Medicine

Jiangsu Province Key Laboratory of Geriatrics

The First Affiliated Hospital of Nanjing Medical University

China