Large cell carcinoma of the lung presenting as diffuse pulmonary infiltrates with haemoptysis

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Abstract
Due to rapid advances in our understanding of the molecular pathogenesis of non-small cell lung cancer (NSCLC), the 2015 World Health Organization (WHO) classification has defined large cell carcinoma (LCC) as a subtype that is lacking glandular or squamous cells, and any neuroendocrine differentiation. Accordingly, LCC is one of the rarest subtypes of NSCLC. LCC usually presents as a large peripheral tumour with prominent necrosis and its specific characteristics are not well known. Here, we report a case of LCC identified during differential diagnosis of diffuse alveolar haemorrhage in a patient with haemoptysis.

Introduction
Lung cancer is the most common cancer worldwide and is responsible for the most cancer-related deaths in both men and women. Classification of lung carcinomas by histopathological subtyping is important for predicting prognosis and determining optimal treatment for patients.

Large cell carcinoma (LCC) of the lung is defined as an undifferentiated non-small cell carcinoma that lacks the cytological, architectural, and immunohistochemical features of other lung cancer subtypes such as adenocarcinoma, squamous, small cell, and neuroendocrine carcinoma. The incidence rate was reported at an estimated 10% in the past; however, after being redefined by the 2015 World Health Organization (WHO) classification, it is now possible to diagnose more accurately and LCC accounts for approximately 3% of all lung cancers [1,2]. The specific characteristics of the tumour are not well reported; it tends to occur in the periphery and grows rapidly. Overall survival is significantly worse in patients diagnosed with LCC compared to the other pathological subtypes [3,4]. Here, we report a case of massive alveolar haemorrhage associated with LCC, which failed to be diagnosed using repeated transbronchial lung biopsy (TBLB).

Case Report
A 45-year-old man was admitted to this hospital because of persistent haemoptysis and dyspnoea with associated pulmonary infiltrates. The patient had reportedly been well until, approximately one month before the admission, he displayed symptoms of fatigue, febrile sense, a dry cough with right upper chest pain, sputum, weight loss, and a skin rash but no fever. The patient had smoked one pack of cigarettes daily for 20 years and had started using e-cigarettes approximately six months earlier. He reported no use of any medication, no new environmental exposures, and no recent travel. He was then admitted to another hospital. A chest radiograph showed diffuse hazy opacity in the right lung, especially the right upper lobe (RUL). Computed tomography (CT) of the chest revealed extensive ground-glass attenuation with a “crazy-paving” pattern.
appearance in the right lung and in the small mediastinal lymph nodes. The patient was diagnosed with atypical pneumonia and treated empirically with antibiotics, but symptoms persisted, and chest radiographs showed progressing disease.

The patient was then transferred to this hospital for further evaluation. He continued to cough up approximately 50 mL of fresh blood per day. Laboratory tests revealed a white cell count of 156,000 cells/mm³, haemoglobin of 8.7 g/dL, C-reactive protein of 2.62 mg/dL, and lactate dehydrogenase of 1071 IU/L. Follow-up chest CT scans showed interval increased extent of extensive ground-glass attenuation with RUL consolidation (Fig. 1). As a patient with diffuse pulmonary infiltration and subacute haemoptysis, tests for differential diagnosis of diffuse alveolar haemorrhage were performed.

Flexible bronchoscopy was performed under general anaesthesia. Bronchoscopy showed a large amount of bright red blood along the right side of the bronchus and no endobronchial lesions could be seen. Bronchoalveolar lavage (BAL) and blind TBLB were performed in both the apical segment of the RUL and the lateral segment of the right middle lobe. BAL fluid was persistently bloody and reportedly contained 44% neutrophils, 25% lymphocytes, 30% macrophages, and 1% eosinophils; microbiological testing and cytological examination were all negative. Autoimmune disease screening tests were all negative, as were tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCAs), rheumatoid factor, anti-cyclic citrullinated peptide, and anti-glomerular basement membrane antibodies. Alpha-fetoprotein and carcinoembryonic antigen were also normal. A lung biopsy indicated alveolar haemorrhage but no other remarkable findings. There was no evidence of vasculitis, vaping-associated lung injury, or malignancy and, therefore, a repeated biopsy was planned for more precise diagnosis. Radial endobronchial ultrasonography (EBUS)-guided transbronchial biopsy using a guide sheath was performed to achieve a more accurate biopsy of the RUL consolidation. After confirming the lesion by ultrasound, a biopsy was performed and a total of nine pieces of lung tissue were obtained. However, the tissue biopsy specimens resulted in no significant findings to aid a differential diagnosis. Ziehl–Neelsen, Grocott methenamine-silver, and periodic acid-Schiff staining

Figure 1. (A–C) Chest radiograph and computed tomography (CT) scan obtained one month before admission at another hospital show extensive opacity in the right lung with focal right upper lung consolidation. (D) Chest radiograph conducted after being transferred to this hospital, extensive infiltration of both sides of the lung is further increased, and the right upper lobe (RUL) consolidation has increased. (E, F) An axial image of a chest CT scan with lung windows shows extensive ground-glass attenuation with a “crazy-paving” appearance in the right whole lung and the left lower lung. Increased extent of consolidation with haematoma is observed in the apical segment of the RUL.
failed to reveal any acid-fast bacilli or fungal organisms. There were no abnormal substances or cell deposits and immunoglobulin G (IgG)-related diseases were also excluded. Empirical treatment with anthelmintic, anti-fungal drug, and systemic steroids were administered sequentially. However, the patient continued to have haemoptysis. The chest X-ray showed a further spread of the pulmonary infiltrates. Percutaneous biopsy was considered, but it was difficult to clarify the target lesion due to haematoma and the risk of complications was high due to bullae and air cysts in the right upper lung.

On the 27th hospital day, the patient underwent a right upper lobectomy for both diagnostic and therapeutic purposes. Gross evaluation of the right upper lobectomy specimen revealed a solid spherical tumour with poorly demarcated margins, measuring 7.5 cm in the greatest dimension. On section, the tumour showed a bulging, lobulated, and variegated cut surface with central necrosis and haemorrhage (Fig. 2A). Under the microscope, the tumour displayed large, polygonal, and anaplastic cells growing in sheets or solid nests. Poorly differentiated carcinomas with a null immunophenotype lacking clear pneumocyte, squamous, or neuroendocrine markers can be classified as LCC of the lung (Fig. 2B–F).

After the confirmative diagnosis, the patient was transferred to oncology. Additional examinations for staging were performed and palliative chemotherapy was planned. The final diagnosis is stage IV (T4N2M1b) LCC of the lung with adrenal metastasis.

Discussion

This 45-year-old previously healthy man presented with a one-month history of haemoptysis accompanied by progressive and diffuse ground-glass opacities and peripheral consolidation of the right upper lung. Due to the diffuse lung infiltration at a young age, the first impression was that alveolar inflammation and haemorrhage had been caused by an autoimmune disease or by organizing pneumonia; however, he was finally diagnosed with lung cancer.

Although the consolidative lesion of RUL increased, it was considered as haematoma of the surrounding air cyst due to bleeding. Fast-growing tumour was underestimated by the surrounding haematoma. There was no evidence of malignancy in repeated biopsy and cytology, which further delayed the diagnosis. We believe that the haematoma surrounding the tumour has interfered with adequate sample collection.

Figure 2. Specimens of the right upper lobectomy. (A) The gross specimen revealed a 7.0 × 7.5 cm solid spherical tumour with a poorly demarcated margin. On section, tumour had a bulging, lobulated, and variegated cut surface with central necrosis and haemorrhage. (B) A microscopic view of the tumour shows large, polygonal, and anaplastic cells growing in sheets or solid nests (haematoxylin and eosin (H&E), 100x). (C) A high-power microscopic view reveals large pleomorphic cells with a moderate to abundant amount of cytoplasm, vesicular nuclei, and prominent nucleoli. Brisk mitotic figures are also noted (black arrow) (H&E, 400x). (D–F) Tumour cells show negative immunoreactivity for thyroid transcription factor-1 (TTF-1), p40, and synaptophysin (Immunohistochemistry, 200x).
LCC is one of the histological types of non-small cell lung carcinomas (NSCLC). LCC lack morphological or immunohistochemical evidence of a clear lineage, with negative or uninformative staining for squamous cell carcinoma and adenocarcinoma [5]. The diagnosis of LCC requires thoroughly sampled resected tumour and cannot be made on biopsy or cytology specimens alone [1,6,7].

LCC typically presents as a large peripheral mass of solid attenuation with irregular margins. The tumour often grows rapidly and metastasizes early with an accompanying focal necrosis. But little research has been done on the characteristics and prognosis of LCC, and it is widely assumed that it is similar to other NSCLC subtypes [8]. LCC has a rapid mean volume doubling time of around 67–134 days. In some cases of LCC where the volume doubling time is exceptionally rapid, clinical presentation may mimic acute lung pathologies such as pneumonia and other interstitial lung disease [9]. In this case, it grew from 1 to 7 cm in about 40 days. The accompanying large amount of bleeding led to late diagnosis and excessive surgical intervention.

Up to 20% of lung cancer patients experience haemoptysis at some point in their clinical course but massive haemoptysis affects only 3% of this population. Squamous cell carcinoma is responsible for more than half of the cases of massive haemoptysis caused by cancer. Considering the low incidence of LCC, it also accounts for a relatively large proportion of these cases [10].

In this case, diffuse alveolar haemorrhage was diagnosed due to the diffuse infiltration of the lung observed in chest radiography and CT scans. The differential diagnosis of subacute peripheral consolidation includes organizing pneumonia, chronic eosinophilic pneumonia, sarcoidosis, and cancer including lymphoma or adenocarcinoma. Nevertheless, diffuse ground-glass opacities would be unusual in patients with these conditions. Repeated tissue biopsy, cytological examination, and blood tests were performed for differential diagnosis, but none revealed any evidence of malignancy. The rapidly growing mass in the RUL was also difficult to prioritize a cancerous lesion. The cause of the bland pulmonary haemorrhage pattern was not clear and could only be diagnosed as LCC after surgical resection. Retrospectively, the bleeding observed in the CT scan was mostly caused by aspiration rather than diffuse inflammation, and this led to a confused medical judgement. Another reason reaching a diagnosis was difficult was the fact that the patient was young and there were no specific findings in any tissue biopsies or cell block cytology. In the presence of a large amount of tissue haematoma, the diagnostic yield of a lung biopsy may be reduced, and it is therefore considered to be a just decision to perform an early surgical examination.

In conclusion, extensive lung involvement does not always account for extensive systemic disease. In this case, bleeding that was aspirated was mistaken for diffuse alveolar haemorrhage, producing difficulties in achieving an accurate diagnosis. LCC of the lung is a very rare cause of massive haemoptysis but progresses very rapidly and has the worst prognosis. Therefore, a detailed and thorough assessment of tissues is essential to achieve the correct diagnosis.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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