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**Rapidly progressing primary pulmonary lymphoma masquerading as lung infectious disease: A case report and review of the literature**

Jiang JH *et al*. ALK-positive lymphoma presenting as lung infection

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**Abstract**

BACKGROUND

Primary anaplastic large cell lymphoma of the lung represents a diagnostic challenge due to diverse manifestations and non-specific radiological findings, particularly in cases that lack extra-pulmonary manifestations and lung biopsy.

CASE SUMMARY

A 40-year-old woman presented with a 6-d history of fever, dry coughing, and dyspnea. Her white blood cell count was 20100/mm3 with 90% neutrophils. PaO2 was 60 mmHg and SaO2 was 90% when breathing ambient air. Chest computed tomography (CT) identified a solid nodule, 15 mm in diameter, with a poorly defined boundary in the upper right lung, and several smaller solid nodules throughout both lungs.Pulmonary artery CT and subsequent bedside X-ray showed diffuse patchy shadows throughout both lungs. Repeated cultures of blood samples and alveolar lavage failed to identify any pathogen. Due to the mismatch between clinical and imaging features, we conducted a bone marrow biopsy, and the results showed proliferation along all three lineages but no atypical or malignant cells. The patient received empirical antibacterial, antiviral, and antifungal treatments, as well as corticosteroids.The patient’s condition deteriorated rapidly despite treatment. The patient died 6 d after hospitalization due to respiratory failure. Post-mortem lung biopsy failed to show inflammation but identified widespread infiltration of alveolar septum by anaplastic lymphoma kinase (ALK)-positive anaplastic cells.

CONCLUSION

ALK-positive anaplastic large cell lymphoma could present as a primary pulmonary disease without extra-pulmonary manifestations.

**Key Words:** Primary anaplastic large cell lymphoma; Lungs; Anaplastic lymphoma kinase; Lung infection; Differential diagnosis; Case report

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**Core Tip:** Primary anaplastic large cell lymphoma of the lung represents a diagnostic challenge due to diverse manifestations and non-specific radiological findings. We report a case of rapidly progressing anaplastic lymphoma kinase (ALK)-positive primary pulmonary anaplastic large cell lymphoma (ALCL) with bilateral multiple pulmonary consolidations, presenting initially as an acute lung infectious disease. ALK-positive ALCL could present as a primary pulmonary disease without extra-pulmonary manifestations.

**INTRODUCTION**

Anaplastic large cell lymphoma (ALCL) is a CD30 positive mature T-cell non-Hodgkin lymphoma (NHL) and in rare cases involves the lungs[1,2]. There are two variants of ALCL according to the World Health Organization classification: Anaplastic lymphoma kinase (ALK)-positive and negative ALCL[3]. The former has a characteristic t(2;5)(p23;35) chromosomal translocation, which fuses *ALK* on chromosome 2 with the nucleophosmin gene on chromosome 5, leading to ALK overexpression and constitutive tyrosine kinase activity[4,5]. ALK-positive ALCL, including ALK-positive primary pulmonary ALCL, tends to respond well to standard chemotherapy and is associated with a benign prognosis[6-8]. ALCL is one of the most curable cancers, with a cure rate of 65%-90% in children and over 70% in adults[9].

Because of its rarity, extranodal ALCL may present a diagnostic challenge, leading to delays in diagnosis and treatment and ultimately resulting in disease progression[10-12]. Herein, we report a case of rapidly progressing ALK-positive primary pulmonary ALCL with bilateral multiple pulmonary consolidations, presenting initially as an acute lung infectious disease. This case highlights the need to consider alterative diagnoses in cases of suspected lung infections that fail to respond to antibiotics treatment.

**CASE PRESENTATION**

***Chief complaints***

A 40-year-old woman presented on May 10, 2017 with a 6-d history of fever (up to 38.0 °C), non-productive cough, and exertional dyspnea.

***History of present illness***

The patient received empiric amoxycillin (1.5 g/d) at a community clinic 3 d ago, but symptoms persisted. The patient denied hemoptysis, chest pain, and weight loss.

***Personal and family history***

The patient was a nonsmoker. She had no family history of hematologic or lung malignancies.

***Physical examination***

Physical examination at admission revealed a body temperature of 39.0 °C, heart rate of 103 beats/min, blood pressure of 120/70 mmHg, and respiratory rate of 25 breaths/min. Wheezes and dry rales were not heard in bilateral lungs on auscultation. No other remarkable abnormalities were found.

***Laboratory examinations***

Laboratory test revealed hemoglobin 115 g/L, red blood cell count 3.98 × 1012/L, and increased leucocyte count (20100/mm3) with 90% neutrophils, 4% lymphocytes, and 1% eosinophils. No atypical lymphocytes were present in the peripheral blood. Laboratory investigations showed elevated C-reactive protein (230.1 mg/mL; normal reference range: < 10.0 mg/mL), procalcitonin (0.88 ng/mL; normal: < 0.10 ng/mL), and erythrocyte sedimentation rate (10 mm/h; normal: < 20 mm/h). Biochemical studies showed hypoalbuminemia (33.2 g/L; normal: 40.0-55.0 g/L), elevated alanine aminotransferase (65 U/L; normal: 7-40 U/L), aspartate transaminase (55 U/L; normal: 13-35 U/L), alkaline phosphatase (129 U/L; normal: 35-100 U/L), and lactate dehydrogenase (LDH) (549 U/L; normal: 114-240 U/L). Arterial blood gas analysis revealed PaO2 at 60 mmHg (normal: 80-100 mmHg) and SaO2 at 90% when breathing ambient air. Tumor biomarkers (*e.g.*, CEA125, CA153, and CA199) were negative. Plasma virus tests for Epstein-Barr virus, cytomegalovirus, and respiratory syncytial virus were negative.

***Imaging examinations***

Contrast-enhanced computed tomography of the chest demonstrated multiple solid nodules throughout both lungs with the largest measuring 15 mm in diameter, with poor defined boundaries in the right upper lung (Figure 1A). No mediastinal lymphadenopathy was demonstrated. A blood culture was ordered.

**FINAL DIAGNOSIS**

A preliminary diagnosis of lung infection with atypical radiologic features was made. Differential diagnosis included malignancy and atypical infections such as a fungal, viral, or atypical bacterial infection.

**TREATMENT**

Empiric cefoperazone sulbactam (1.0 g/8 h intravenously) and azithromycin (0.5 g once daily intravenously) were started. Oxygen supplementation was conducted *via* a nasal cannula.

**OUTCOME AND FOLLOW-UP**

The patient’s symptoms deteriorated rapidly and she was transferred to intensive care unit 3 d after hospital admission. Arterial blood gas analysis showed PaO2 at 48.6 mmHg and SaO2 at 84.2% when breathing oxygen at a rate of 5 L/min through a mask. Routine blood tests revealed a leucocyte count of 40800/mm3 with 96% neutrophils (39168/mm3) and again, no atypical lymphocytes. Flow cytometry showed no abnormal clones. A bone marrow smear suggested active proliferation along all three lineages, but no abnormal cells were found. A pulmonary artery computed tomography (CT) scan revealed normal pulmonary vasculature. However, diffuse patchy shadows with poorly defined boundaries were present in both lungs, with bilateral pleural effusion and an enlarged lymph node (25 mm × 21 mm) in the right hilum (Figure 1B). Fiber bronchoscopy and bronchoalveolar lavage were unremarkable. Antibiotics treatment was switched to meropenem (1.0 g/8 h) and vancomycin (1.0 g/12 h). A lung biopsy was recommended but the family members of the patient declined. Despite aggressive antimicrobial therapy, her respiratory failure continued to worsen and the patient eventually required 100% oxygen *via* the ventilator. Bedside X-ray revealed diffuse patch shadows in bilateral lungs (Figure 1C). Methylprednisolone (80 mg/8 h), ganciclovir (0.3 g/12 h intravenously), and caspofungin (70 mg for the first 24 h intravenously and 50 mg/d thereafter) were empirically initiated in order to broadly cover any atypical infection or inflammatory condition. Despite all aggressive measures, the patient’s condition deteriorated and on hospitalization day 6, she passed away due to refractory hypoxemic respiratory failure.

A post-mortem lung biopsy revealed an intact alveolar structure and no apparent inflammation. The alveolar septum was infiltrated with massive anaplastic lymphocytes and occasional neutrophils. The anaplastic lymphocytes were strongly positive for ALK and CD30, partially positive for CD7, and negative for CD20, CD3, CD5, CD4, CD8, and EBER. Most anaplastic lymphocytes were Ki-67 positive (Figure 2). Bone marrow tissue examination revealed normal karyotype and no anaplastic lymphocytes. Flow cytometry showed no abnormal clones.

**DISCUSSION**

ALK-positive primary pulmonary ALCL in the current case initially presented as an acute lung infectious disease. The patient exhibited signs mimicking a lung infection (fever, marked neutrophilia, and pulmonary consolidations). Despite a thorough work-up for infectious and non-infectious causes and aggressive antimicrobial regimen, the patient deteriorated rapidly, eventually leading to death within a week of presentation.

The case highlights the importance of promptly reassessing patients with suspected lung infectious diseases who fail to respond to antibiotics or antiviral therapy and considering alternative diagnoses including primary pulmonary ALCL.

Most clinicians are not familiar with ALK-positive primary pulmonary ALCL due to its very low incidence rate and atypical clinical features, leading to delays in diagnosis and treatment. Primary pulmonary lymphoma is defined as clonal lymphoid proliferation involving the lung parenchyma and/or bronchi without detectable extra-pulmonary lymphoma at primary diagnosis or the subsequent 3 mo[13]. Fiche *et al*[14]retrospectively analyzed the pathological features of 69 primary pulmonary NHL and there was no case of T cell lymphoma. Yao *et al*[15]only collected one case of ALK-positive primary pulmonary lymphoma in 6 years. Zhao *et al*[16]searched the PubMed for the literature on primary pulmonary ALCL and identified 16 cases (11 men, age range: 17-68 years) between 1990 and 2015. Six (6/15) of the cases were ALK-positive. In addition, 6/13 patients died from 21 d to 6 mo while our case died within 12 d of diagnosis. Although primary pulmonary ALCL may have a rapidly progressing course, a protracted course may be seen in heavily treated cases[17]. Padhi *et al*[18]have recently reviewed 39 cases of pulmonary ALCL reported over the preceding 30 decades and reported that 13/39 cases were ALK-positive.

Age, high β2 microglobulin and neutrophilia, and primary lung lesions may be closely associated with a poor prognosis of ALK-positive ALCL[19]. Other adverse prognostic events include fever, progressive respiratory failure, performance status, and high serum LDH. Leukemic phase ALCL is rare, which can occur upon initial presentation and during the course of the disease and may be associated with an aggressive course of ALCL. Several reports described three adult cases of ALK-positive ALCL with peripheral blood leukocytosis[20-22]. Two patients died and one relapsed, suggesting a poor prognosis in patients with peripheral leukocytosis in ALK-positive ALCL. Grewal *et al*[23]reported three cases of highly aggressive ALK-positive ALCL with a leukemic phase and multi-organ involvement; all three patients died within months of diagnosis. Similarly, our patient had persistent leukocytosis with neutrophils at 90%-96%, but no atypical lymphocytes in peripheral blood smears and no abnormal clones on flow cytometry. Also, bilateral lung involvement, marked respiratory distress, and significant hepatic injuries in the current cases are suggestive of high-risk malignant neoplasm[24]. In addition, lung tissues biopsy of our patient revealed a large number of infiltrating large anaplastic lymphocytes in the alveolar septum with scattered neutrophils. Without other feasible explanations, we suspected that lymphoma progression may lead to neutrophil-reactive hyperplasia but such a possibility requires more clinical observation. A report suggests a particularly poor prognosis in patients with tumor invasion into the central nervous system and the lungs[25].

Dyspnea with rapid changes in various lung imaging features may be a characteristic marker for ALK-positive primary pulmonary ALCL. Investigators have summarized the features of nodules, mass-like consolidation, alveolar or interstitial infiltrates, non-segmental infiltration with a hazy margin, a clear air bronchogram, ground-glass opacity, masses of pleural origin, pleural effusion, and peribronchial or perivascular thickening on chest CT in lung NHL patients[26-30]. However, the pace of radiological changes of ALK-positive primary pulmonary ALCL has been rarely reported. In the current case, chest CT and radiographs showed rapid radiological changes synchronous with disease progression. In recent years, 18F-2-deoxy-2-fluoro-D-glucose-positron emission tomography/CT has developed rapidly in the field of staging of lymphoma and efficacy evaluation of treatment due to its more sensitive display than conventional CT. Lee *et al*[31]showed higher standardized uptake values (SUVs) in systemic ALCL than in other types of aggressive T-cell lymphoma, as well as higher SUVs in ALK-positive ALCL patients than in ALK-negative ones. It is necessary for definite diagnosis by CT-guided percutaneous needle lung biopsies as soon as possible[32].

**CONCLUSION**

ALK-positive primary pulmonary ALCL is a rare disease with diverse clinical and radiological manifestations. Our case highlights the importance of considering alternative diagnoses including ALCL in cases suspected of lung infections but failing to respond to antimicrobial treatment.

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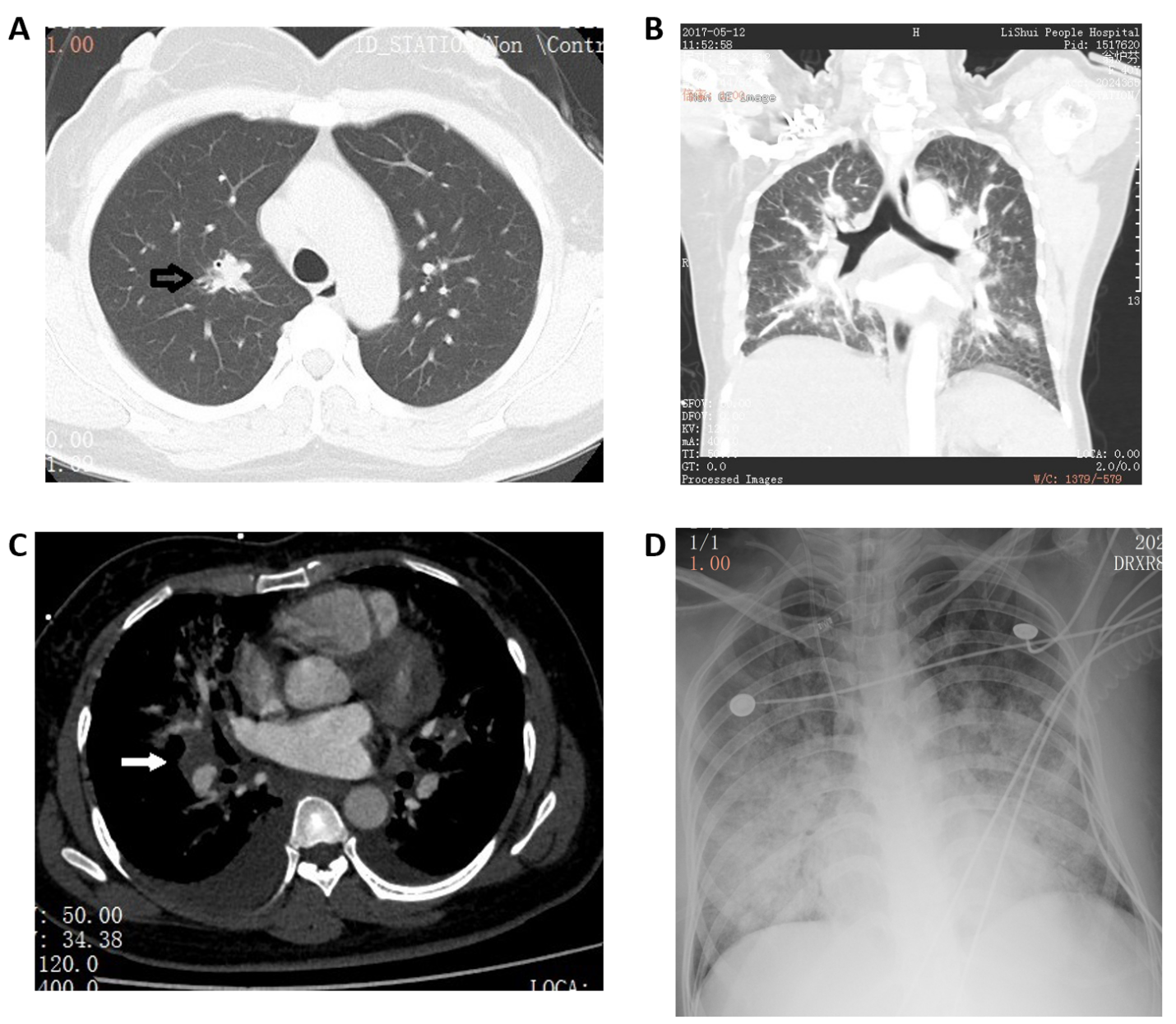
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Grade D (Fair): 0

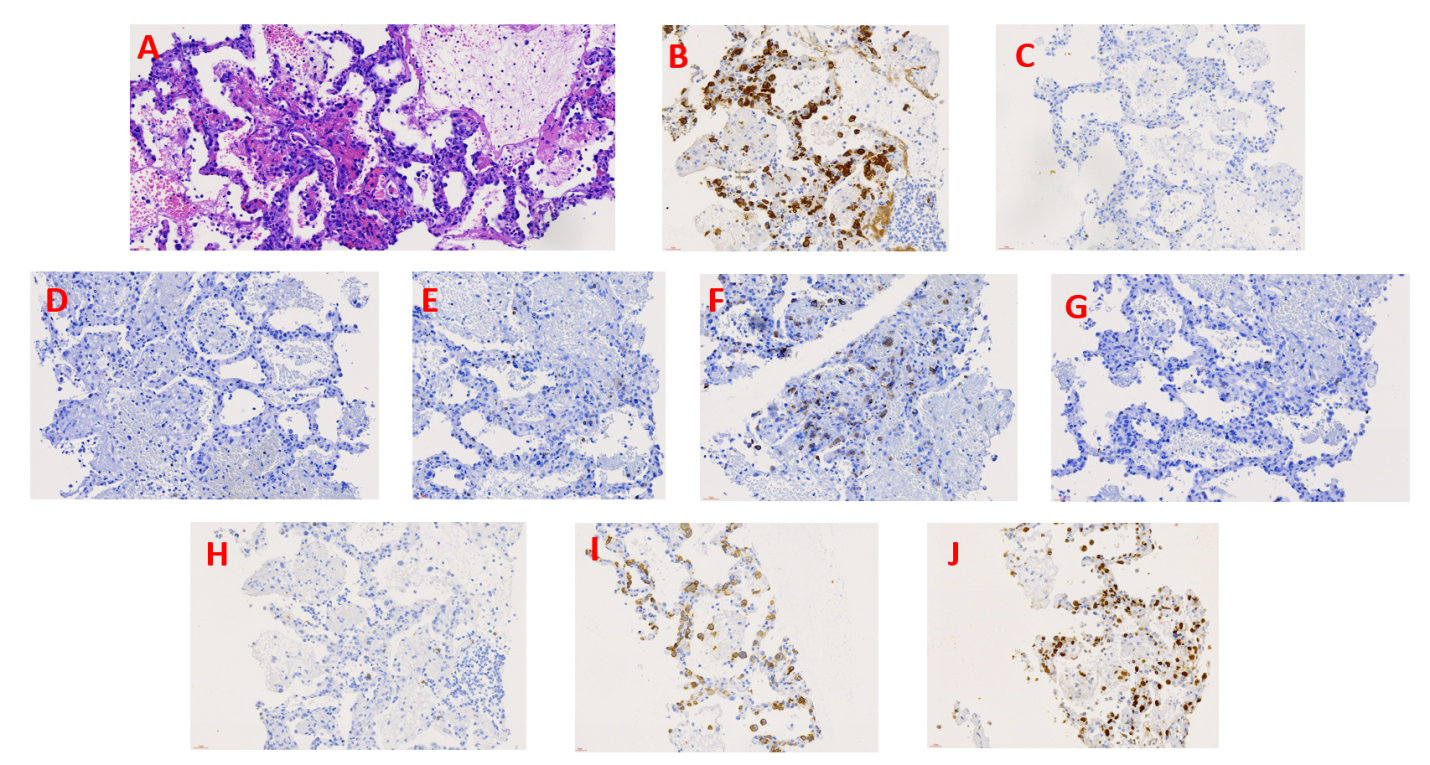
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**Figure Legends**



**Figure 1 A 40-year-old woman presented with a 6-d history of fever (up to 38.0 °C), non-productive cough, and exertional dyspnea.** A: Chest computed tomography (CT; transverse section) at admission showed a solid nodule (arrow), 15 mm in diameter, with a poorly defined boundary in the upper lobe of the right lung. Several smaller solid nodules were seen in both lungs; B: Chest CT at admission (coronal section); C: A pulmonary CT angiogram showed normal pulmonary vasculature, but diffuse patchy shadows with poorly defined boundaries were seen in both lungs, with bilateral pleural effusion and an enlarged lymph node (25 mm × 21 mm) in the right hilum; D: Chest X-ray showed diffuse patchy shadows throughout both lungs.



**Figure 2 Pathological images of lung tissue biopsy at day 5 of hospitalization.** A: Hematoxylin-eosin staining showed the alveolar structure of the lung tissue with massive infiltration by large anaplastic lymphocytes in the alveolar septum with scattered neutrophils. Magnification, 400 ×; B-J: Immunostaining revealed that the tumor cells were ALK(+) (anaplastic lymphoma kinase) (B), CD3(-) (C), CD4(-) (D), CD5(-) (E), CD7(+) (F), CD8(-) (G), CD20(-) (H), CD30 (+) (I), and Ki-67(+) (J). Magnification, 400 ×.