A RARE CASE REPORT: LUNG ADENOCARCINOMA WITH DIFFUSE LESIONS IN A YOUNG MALE PATIENT

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Abstract

The images of diffuse lung involvement are seen in various respiratory diseases, including lung adenocarcinoma (ADC). After ruling out acute infectious causes, lung biopsy is valuable for a definitive diagnosis, with transbronchial biopsy via flexible bronchoscopy being an effective and safe diagnostic approach. However, the widespread lung damage in these patients poses a challenge for transbronchial biopsy. Chemotherapy is often difficult due to the overall poor health of the patient. Targeted therapies, specifically tyrosine kinase inhibitors (TKIs), have shown efficacy in lung cancer treatment.

Keywords: Adenocarcinoma; Lung cancer; Tyrosine kinase inhibitors (TKIs).

INTRODUCTION

Lung cancer is a malignancy with increasing incidence and mortality rates. Its slow progression and nonspecific clinical symptoms contribute to low early-stage diagnosis rates, often leading to misdiagnosis or confusion with other respiratory diseases, especially in cases with atypical X-ray or computed tomography (CT) findings. ADC with diffuse lesions (named bronchioloalveolar carcinoma - BAC before) is rare in clinical practice in Vietnam, making diagnosis challenging [1, 2, 3]. In patients with epidermal growth factor receptor (EGFR) mutation and low PS [3, 4], TKIs are the first choice for treatment, in which Afatinib is a suitable indication for ADC with a G719x mutation in exon 18. With this case study, we would like to: *Present the clinical characteristics of a rapidly progressed ADC case with diffuse lesions, having G719x mutation in exon 18, and the results of treatment by Afatinib as first-line therapy.*

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CASE REPORT

Male patient, 39 years old, non-smoker, no history of tobacco use, no exposure to cancer risk factors, and no family history of cancer. Occupation: Military officer. The symptoms have been present for about 4 months, including occasional cough with minimal sputum, dull chest pain, mild progressive dyspnea, and mild fever. The patient was admitted to the Internal Department of a regional general hospital, where chest X-rays, chest CT, acid-fast bacillus (AFB) testing, and GeneXpert/MTB testing of negative sputum were conducted. Following consultation, the patient was diagnosed with miliary tuberculosis and received a 2RHZE/6RH regimen. After 3 weeks of tuberculosis treatment, the patient's symptoms were unresponsive, and respiratory distress worsened, leading to admission to the Respiratory Medicine Center, Military Hospital 103. On admission, the patient exhibited signs of respiratory failure (persistent dyspnea, cyanosis, respiratory muscle retractions; SpO_2 80%), no fever, no palpable peripheral lymph nodes, and reduced breath sounds in both lungs without rales. Imaging findings on chest X-ray and CT revealed hazy opacities interspersed with diffuse reticular patterns in both lungs, concentrated in the mid and lower zones of both lungs, with no hilar lymphadenopathy, involvement of the mediastinum, or pleural effusion (*Figure 1*).

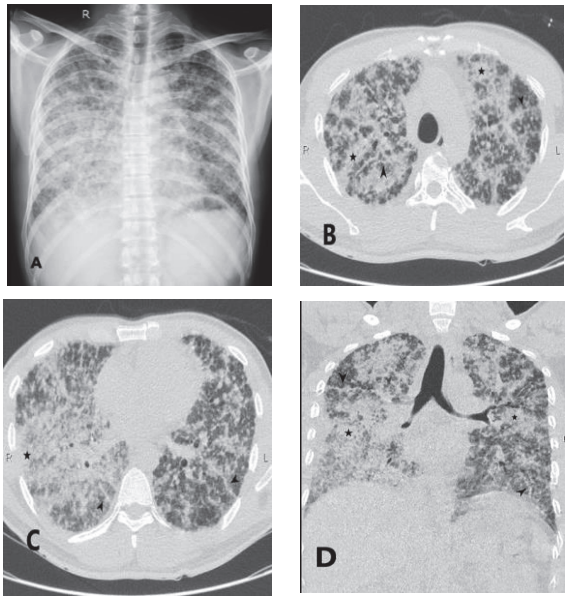
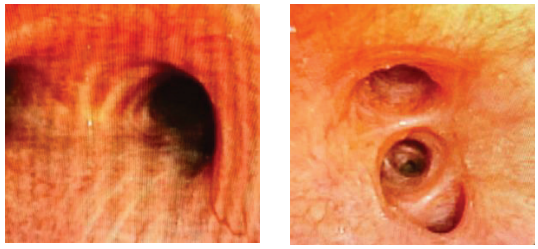


Figure 1. Initial chest X-ray (A) demonstrates bilateral diffuse reticular opacities with consolidation in the right lung predominant. Axial CT scan (B, C) and coronal reconstructed CT image (D) showed bilateral extensive septal thickening and reticular opacities (arrowhead) with consolidation (star).

Arterial blood gas (ABG) results: PaO_2 = 57 mmHg, $PaCO_2$ = 37 mmHg, pH = 7.38. The patient underwent treatment for respiratory failure (high-flow nasal cannula oxygen therapy - HFNC), symptom management, and bronchoscopy. Bronchoscopy images show normal findings with no increased mucus secretion (*Figure 2*). Selective bronchial lavage technique is applied, collecting bronchial lavage fluid for microbiological and cytological examinations, and performing transbronchial biopsy for pathological examination. Pathological examination reveals papillary ADC of the lung; EGFR mutation testing indicates a G719x mutation on exon 18 (*Figure 3*). Microbiological tests, including AFB, GeneXpert/MTB-Rif, bacterial and fungal cultures of bronchial fluid, all yield negative results. The patient undergoes additional diagnostic imaging tests (abdominal ultrasound, cranial MRI) for staging.



A **B**

Figure 2. Bronchoscopy did not detect lesions in the main bronchus (A) and segmental bronchus (B), so a transbronchial biopsy was indicated.

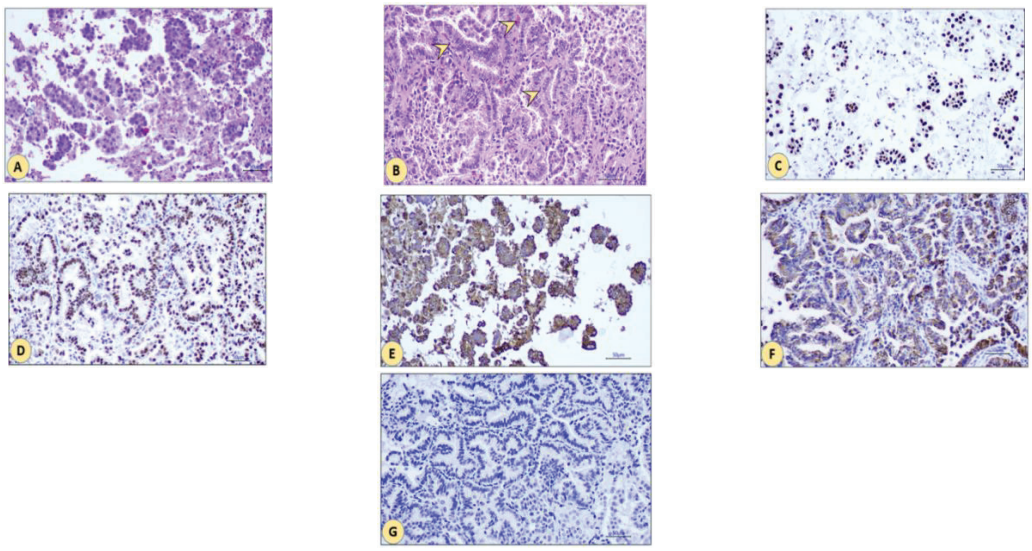


Figure 3. Initial chest X-ray (A) demonstrates bilateral diffuse reticular opacities with consolidation in the right lung predominant. Axial CT scan (B, C) and coronal reconstructed CT image (D) showed bilateral extensive septal thickening and reticular opacities (arrowhead) with consolidation (star).

The patient is diagnosed with non-mucinous ADC of the lung, stage IV ($T_{1mi}N_0M_1$), with EGFR mutation, and respiratory failure as a complication. The patient is reviewed by a multidisciplinary team and opts for treatment with second-generation TKI: Afatinib at a dose of 40 mg/day, taken 1 hour before lunch. Response assessment after 1 month indicates a partial response: Significant reduction in cough, sputum, and chest pain; weight gain (BMI 21.3 kg/m^2), no need for supplemental oxygen, and improved ABG (PaO_2 = 87 mmHg, $PaCO_2$ = 38 mmHg). Chest X-ray images show a partial reduction in lung lesions after 10 days of treatment (*Figure 4*), and CT scans demonstrate a noticeable decrease in the extent of spread compared to the patient's initial presentation (*Figure 5*). Mild adverse effects of TKIs are observed (mild skin rash). After 6 months, the patient has signs of disease progression. Afatinib should be replaced by Osimertinib as a recommendation of NCCN [7].

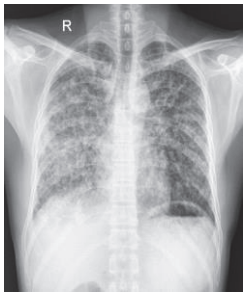


Figure 4. Chest X-ray obtained 10 days after treatment revealed a decrease in consolidation area and reticular opacities after the patient's symptoms improved.

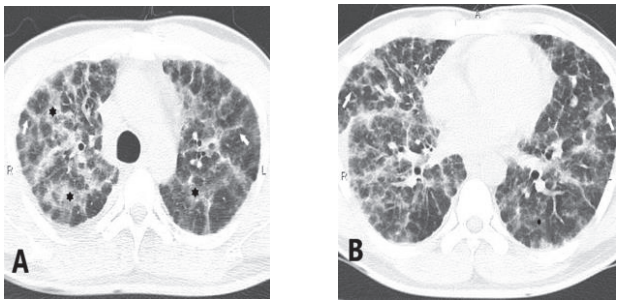


Figure 5. CT scan obtained 15 days after treatment showed a decrease in consolidation, but we still saw bilateral septal thickening, and reticular opacities (arrow) with ground glass opacities (star). (A) Axial section of apex (B) Axial section of basal.

DISCUSSION

1. Diagnosis of diffuse lung ADC

Diffuse lung ADC is a type found at a rate of 3 - 6% of all types of lung cancer. It is more commonly found in young, non-smoking females. However, this type is rare in Vietnam. Key clinical symptoms include chronic cough, progressively increased difficulty in breathing and a significant amount of coughed-up sputum. In patients with localized lesions visible on X-rays, clinical symptoms may not be apparent, and the diagnosis relies primarily on the

technique of invasive specimen collection for pathological examination. Patients with rare cases of bilateral spread of lesions present more significant diagnostic challenges, especially in late-stage patients with complicated respiratory failure, making it challenging to perform diagnostic specimen collection techniques. The choice of biopsy procedures depends on the overall condition of the patient, the characteristics of lung lesions observed on X-rays, and chest CT scans. Treatment options are limited due to the extensive spread of lung damage, and the patient's overall health index is compromised due to respiratory failure [3, 4]. Moreover, when imaging reveals lesion patterns such as nodules or a diffuse mesh spreading across both lungs, differential diagnosis is crucial to distinguish from various respiratory infections (disseminated tuberculosis, mycobacteria infection, fungi), non-infectious diffuse lung diseases (sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis), and malignant conditions (secondary lung cancer, Kaposi's sarcoma) (*Table 1*).

Table 1. Causes of diffuse pulmonary nodules.

Infections	Diffuse lung diseases	Malignancies
Miliary tuberculosis	Hypersensitivity pneumonitis	Metastasis
Atypical mycobacterial infection	Diffuse pulmonary meningotheliomatosis	Diffuse lung ADC
Lung fungal infection	Pneumoconiosis (namely silicosis)	Lymphangitic carcinomatosis
Septic emboli	Amyloidosis	Kaposi sarcoma

In the clinical case of a young patient with no risk factors for lung cancer, presenting minimal clinical symptoms, mainly gradual onset of mild breathlessness and occasional mild fever, the initial differential diagnosis considered is subacute disseminated pulmonary tuberculosis. This is a chronic infectious lung disease with widespread lesions commonly seen in Vietnam. Simultaneously, the second differential diagnosis raises the possibility of a systemic disease, a group of conditions often found in young individuals. Microbiological tests for tuberculosis, including AFB, and

GeneXpert/MTB-Rif from sputum, all yield negative results. Therefore, a lung biopsy via bronchoscopy is recommended for a conclusive diagnosis. However, due to the patient's respiratory distress, a bronchoscopy with a flexible bronchial tube is performed with the support of the ICU. As the bronchoscopy results reveal no significant mucosal lesions in the large bronchi, a transbronchial biopsy is performed at the right lower lobe, guided by chest CT scan images, focusing on areas with multiple consolidated lesions. As a result, 8 biopsy samples are safely obtained for histopathological examination. With an adequate amount of biopsy material, immunohistochemical and molecular biology techniques are employed [6]. The diagnosis confirms ADC with non-mucinous components and a G719x mutation on exon 18. The pathological findings explain the patient's clinical symptoms despite the widespread involvement of ADC in both lungs, with no prominent cough symptoms observed clinically.

2. Regarding the results of TKI treatment

The G719x mutation on exon 18 is classified as a drug-sensitive mutation, responsive to TKI treatment. Clinical studies have demonstrated that second-generation TKIs (Afatinib) yield better outcomes than the first-generation for this mutation [7, 8]. Third-generation TKIs (Osimertinib) are also an effective option in treating the G719x mutation [9]. Additionally, patients may be combined with chemotherapy and immunotherapy to enhance cancer treatment effectiveness [7, 10].

In the clinical case, despite having a confirmed diagnosis, treatment decisions for the patient are challenging due to the patient's severe overall condition, frequent respiratory failure requiring HFNC support, and low overall performance status (PS = 4). Consequently, chemotherapy is no longer recommended. Lung transplantation is a potential solution, but the patient faces a risk of mortality while awaiting a transplant. TKI treatment proves to be the most suitable option for the patient, with Afatinib as the first-line choice. However, a notable concern is the undesirable side effect of TKIs causing peripheral lung damage, which is difficult to detect due to the patient's diffuse lung involvement. Therefore, closely monitoring treatment response and the unintended effects of TKIs requires a synergistic approach between clinical and chest imaging [8].

The outcome is a positive response to both clinical and X-ray imaging treatment. Just 1 week into treatment, the patient no longer requires HFNC, and after 2 weeks, gentle physical activity is resumed.

Visible reductions in lung lesions are observed on X-ray and chest CT after 1 month of treatment. The favorable treatment response is also linked to the patient's ADC subtype with non-mucinous components, indicating a better prognosis compared to the mucinous subtype. However, the response to second-generation TKIs is limited to approximately 12.7 months [7, 8]. In the future, if the patient does not respond to Afatinib, re-biopsy for T790m mutation and immune tests will be essential to determine the next treatment approach [9, 10].

CONCLUSION

Diffuse lung involvement in primary lung cancer is rare and diagnostically challenging, particularly in BAC. The biopsy is crucial for determining the cause after excluding infectious etiologies. Testing for EGFR mutations guides treatment decisions, with second-generation TKIs like Afatinib showing effectiveness in cases with a G719x mutation.

Ethics: The authors have obtained written informed consent from the patient for the publication of this case report. The patient consented to de-identified clinical information and images being used for the purposes of this report. The authors of the manuscript retain this informed consent and can provide it to the journal upon specific request. The data supporting this research are available from the authors upon reasonable request. The Respiratory Medicine Center, Military Hospital 103, Vietnam Military Medical University granted permission for the use and publication of the research data. The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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