Acute diffuse interstitial lung disease in adults: Do not overlook lepidic adenocarcinoma of the lung

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Letter to the Editor

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1. Introduction

Primary lung adenocarcinoma is the most common type lung cancer. When it has a predominant lepidic component, it is known as lepidic predominant adenocarcinoma (LPA). We report an atypical case of LPA in patient with acute hypoxemic respiratory distress.

2. Case report

A 56-year-old nonsmoking male with no significant past medical history or occupational exposure consulted his general practitioner for cough and breathlessness. The clinical examination found isolated pulmonary crackles in the right lower lobe. The lung CT scan revealed areas of ground glass opacity with consolidation, open bronchus sign, pseudocavitation and poorly defined margins in the posterior segment of the right upper lobe and the right lower lobe (Fig. 1A). He was initially treated with amoxicillin and roxithromycin. One month later (day 0), the patient was referred to our Respiratory Intensive Care Unit (ICU) with rapidly worsening hypoxemia. The clinical examination found only bi-basal crackles. Bronchoalveolar lavage (BAL) cell count demonstrated 40% neutrophils with atypical cells, culture found 10^4 *Pseudomonas aeruginosa* and PCR for *Pneumocystis jirovecii* was slightly positive (35 copies/ml). The HIV test was negative as were serologic tests for antibodies. Transthoracic echocardiography was normal. The patient was treated with a combination of ceftazidime, ciprofloxacin and cotrimoxazole, but his condition continued to worsen. On day 7, high-flow humidified nasal oxygenation (HFFNO) was required with P/F ratio less than 100, and X-ray found rapidly extensive opacities. The patient underwent right upper lobe open lung biopsy (OLB) with mini-thoracotomy at day 9. Frozen sections revealed a nonmucinous in situ adenocarcinoma associated with LPA which was later confirmed by histopathology (Fig. 1B). A targeted therapy with erlotinib was started pending EGFR status after multidisciplinary discussion. Significant bronchorrhea (200 ml/day) stayed uncontrolled despite corticosteroids then octreotide and required iterative draining of the lungs on a daily basis. The p.G12 V mutation of exon 2 of the KRAS gene was detected. Immunolabeling was negative for PDL1 expression; EGFR and BRAF mutations were not detected; ALK and ROS 1 rearrangements were absent. The patient remained intubated after OLB. Despite the optimization of mechanical ventilation and bronchorrhea, clinical status was getting worse. Gas exchanges and hemodynamics didn't allow cytotoxic chemotherapy in second line treatment. The patient died at day 31 from terminal respiratory failure.

3. Discussion

Since 2015, what was formerly called bronchioloalveolar carcinoma was reclassified as in situ carcinoma based on the typical growth pattern of the tumor along the alveolar walls and airways in the outer regions of the lungs. When it becomes invasive, it should be referred to as lepidic predominant adenocarcinoma (LPA) [1]. It is classically a mildly aggressive form of cancer with a slower growth rate and a better prognosis. The most frequent symptoms are progressively worsening cough, sputum, shortness of breath and hemoptysis. Acute respiratory distress is a very rare presentation [2]. Our patient experienced a swift and intense progression to hypoxemic respiratory failure. Our case underlines the fact that invasive adenocarcinoma should be promptly discussed in patients suffering from acute diffuse interstitial lung disease. It is of great importance to characterize the mechanisms of hypoxemic respiratory failure to optimize both the symptomatic treatment and the aetiological treatment. When chest CT or BAL cannot identify any obvious cause, lung biopsy (OLB, transbronchial cryobiopsy, or CT-guided percutaneous lung biopsy) should be discussed in acute respiratory distress. Even if OLB has been linked with high morbi-mortality in this population (ranging from 17% to 39%) [3], decision-making was facilitated by the identification on chest CT of cheerios, a rare radiological sign typically described in LPA [4].

Pemetrexed and platinum combination chemotherapy is the first-line treatment in patients with advanced adenocarcinoma with a performance status score of 0 to 2. Older studies indicated that LPA might be less sensitive to standard chemotherapy. However, recent work from Lau et al. demonstrated that pemetrexed is effective and well tolerated in LPA [5].

In the last decade, multiple oncogenic driver alterations have been discovered, and each of them represents a potential therapeutic target. Epithelial growth factor receptor (EGFR) is one the most studied oncogenes related to lung adenocarcinoma. LPA is associated with EGFR mutations in up to 45% of cases [6]. EGFR-tyrosine kinase inhibitors (EGFR-TKIs) used in LPA improve response rates, time to progression and overall survival, and they exhibit low toxicity [7]. Despite higher frequencies of EGFR mutations, the

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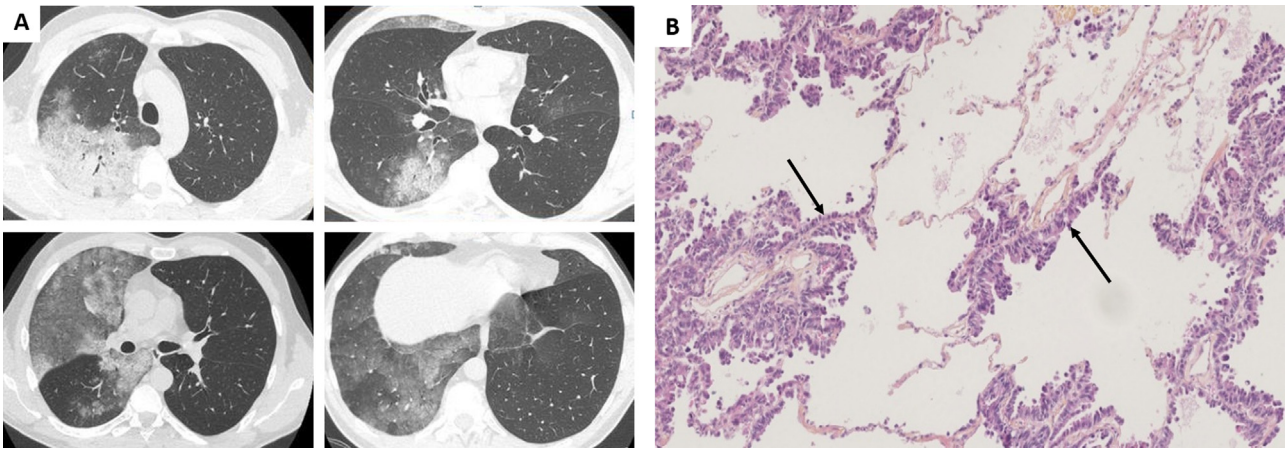

Fig. 1. A. The chest CT scan of case 1 showed bilateral ground glass attenuation with consolidation predominantly in the right lung and left lower lobe. B. Hematoxylin and eosin stain (original magnification × 10). The lepidic component is evidenced by the growth of tumor cells along the alveolar walls (arrows). The alveolar septal architecture is preserved.

prognosis of advanced LPA with diffuse infiltrate was not dramatically improved with the use of EGFR-TKIs, and median survival remains approximately 1 year. The efficacy of EGFR-TKIs seems to differ between the histologic subtype. In mucinous subtypes, the incidence of EGFR mutation is rare and KRAS mutation is frequent ranging from 67 to 86% [8,9]. The most frequent KRAS mutation is G12D (67%) followed by G12 V (24%), G12 C (5%) and G12A (5%) [10]. G12 V KRAS mutation is especially observed in non-smokers [11]. Genetic alterations of EGFR and KRAS typically are mutually exclusive but a few cases have been reported with concomitant EGFR and KRAS mutations [10]. Currently, G12 V KRAS mutant patients treated with platinum-based chemotherapy tend to have a higher response rate and longer progression-free survival [11]. The use of lung transplant for the diffuse form of the disease has been justified in certain cases because LPA is a potentially lung-limited malignancy with a low rate of extrathoracic metastases. Thus far, fewer than 100 lung transplants have been reported for advanced LPA. Overall survival was similar to that of the general transplant population with approximately half the patients surviving to 5 years. However, the reported rate of recurrence is high, up to 59% of patients [12].

4. Conclusion

Clinicians should carefully search for evidence of lung malignancies in patients hospitalized for acute hypoxemic diffuse interstitial lung disease without obvious infectious aetiology. The presence of cheerios should justify lung biopsy despite the known risks. Early identification of LPA allows the early implementation of specific innovative treatments including pemetrexed or EGFR-TKIs, increasing the chances of a favorable outcome. Prompt diagnosis may also be beneficial for end-of-life therapeutic discussions.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

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