Journal of
Pulmonology and
Intensive Care

Case Report

DOI: 10.51271/JOPIC-0050

Adenocarcinoma of the lung mimicking interstitial lung disease

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Cite this article: Duygulu S, Yılmaz Demirci N, Çelik A, Türktaş H. Adenocarcinoma of the lung mimicking interstitial lung disease. *J Pulmonol Intens Care*. 2025;3(1):18-20.

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Received: 08/01/2025 ◆ **Accepted**: 04/02/2025 ◆ **Published**: 21/02/2025

ABSTRACT

Although benign reactive conditions can be misinterpreted as malignancies, a number of malignant lesions can in turn be mistaken for interstitial lung disease. A nonsmoking male aged 66 years who presented with multifocal dispersed, parenchymal and subpleural nodules, most of them cavitated or pseudocavitated, and that radiologically mimicked non-malignant conditions, such as pulmonary Langerhans cell histiocytosis or peribronchiolar organising pneumonia with bronchiectasis on computed tomography scan, was hospitalised. Microbiological and immunological tests were negative. Since sufficient tissue could not be obtained via bronchoscopy, the patient was scheduled for video-assisted thoracic surgery. The final diagnosis revealed invasive adenocarcinoma with a predominant lepidic pattern.

Keywords: Lung cancer, adenocarcinoma, lepidic pattern, interstitial lung diseases, mimick

INTRODUCTION

Some diseases masquerade as tuberculosis or fungal infections. More rarely, lung cancer can mimick interstitial lung diseases. Herein, we report a lepidic predominant adenocarcinoma presenting with clinical and radiological features suggestive of interstitial lung disease.

CASE

A nonsmoking male aged 66 years presented with a 3-month history of progressive dyspnoea on mild exertion. He had initially been diagnosed with bronchiectasis 4 years ago, and underwent right lower lobectomy; there was no malignancy. He denied any history of fever, haemoptysis and/or other extrapulmonary symptoms. He was hypertensive and had a history of diabetes mellitus. He had no known exposure to tuberculosis, and no history of a positive tuberculin skin test. In addition, his family medical history was unremarkable. His vital signs were within the normal range: arterial blood pressure was 120/80 mm Hg, heart rate was 80 beats per minute and transcutaneous arterial oxygen saturation was 98%, while breathing room air. General physical examination was unremarkable, and initial laboratory evaluations were all normal. The chest radiograph taken on admission revealed ill-defined parenchymal opacities in the peripheral areas of both lungs (**Figure 1**). A thorax computed tomography (CT) scan revealed bilateral, parenchymal and subpleural nodules of different shapes and sizes, surrounded by ground-glass areas (halo sign). The nodules presented with random apical-to-basilar distribution, and most showed cavitation or pseudocavitation. There were also some cystic lesions of variable wall thickness. Opacities were noted along the bronchi, and were observed in both the peripheral and central zones. No features of mass or mediastinal lymph nodes enlargement were found (**Figure 2**).

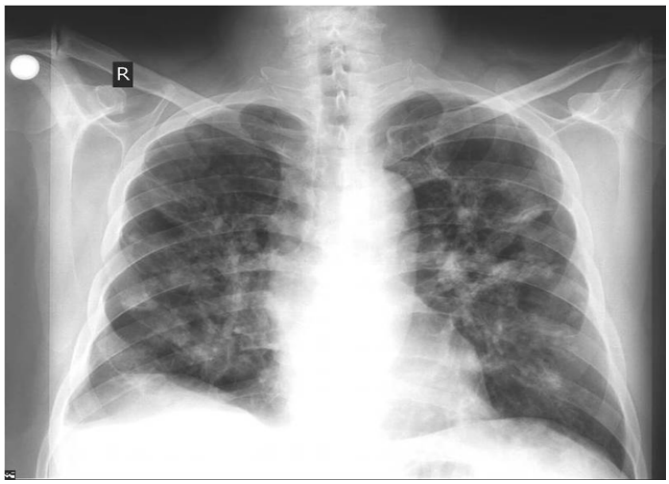

Figure 1. The chest X-ray on admission demonstrated ill-defined parenchymal opacities in the peripheral areas of both lungs

There are numerous differential diagnoses of multiple patchy and mostly cavitary nodules in the lung. The most likely diagnoses included peribronchiolar organising pneumonia, pulmonary langerhans cell histiocytosis (PLCH), granulomatosis with polyangiitis, connective tissue disease with pulmonary involvement, bronchocentric granulomatosis, tuberculosis infection with atypical

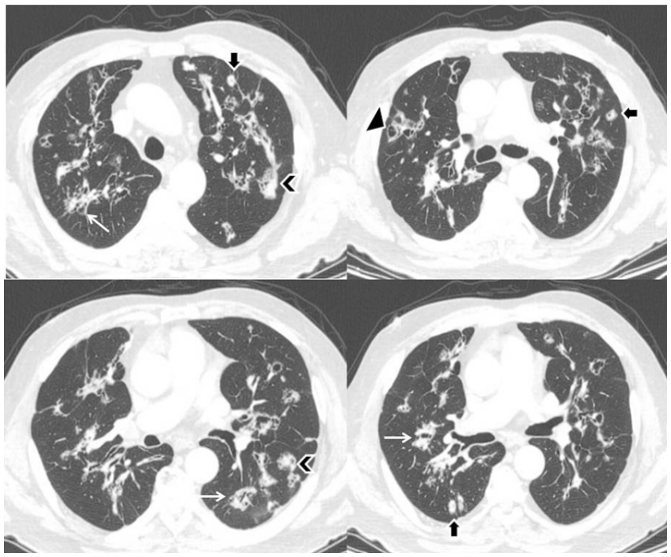

Figure 2. Thin-section computed tomography scans through different sections demonstrate radiolucencies (thin arrows) mimicking pseudocavitations, thin wall cavities (arrowheads), nodules (square brackets) surrounded by a halo of ground-glass attenuation (halo sign) and nodules with central lucency – the 'Cheerio sign' (thick arrows)

mycobacteria, pulmonary sarcoidosis, metastatic malignancies and primary carcinoma of the lung. Fiberoptic bronchoscopy was performed; no malignant cells were found in the bronchial lavage, and no specific diagnosis could be made. Transbronchial lung biopsy of the left upper lobe was also performed and was non-diagnostic. A full autoimmune screen, including antinuclear, antineutrophil cytoplasmic and double-stranded antibodies, was carried out and was negative. The patient was scheduled for video-assisted thoracic surgery with lung biopsy, and the final diagnosis revealed invasive adenocarcinoma with a predominant lepidic pattern, and positivity for thyroid transcription factor-1 (TTF-1) expression. As the next step, fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan imaging revealed multiple solid parenchymal and subpleural nodules, some of which were cavitated with slightly increased FDG uptake (SUVmax:3.1) (**Figure 3**). No other pathological FDG uptake was detected, and the bilateral pulmonary involvement meant that the patient was staged as T4N0M1a. The epidermal growth factor receptor (EGFR) gene and echinoderm microtubule-associated protein-like 4 (EML4) anaplastic lymphoma kinase (ALK) fusion gene were negative for mutations. The patient was instructed to follow up with an oncologist for chemotherapy.

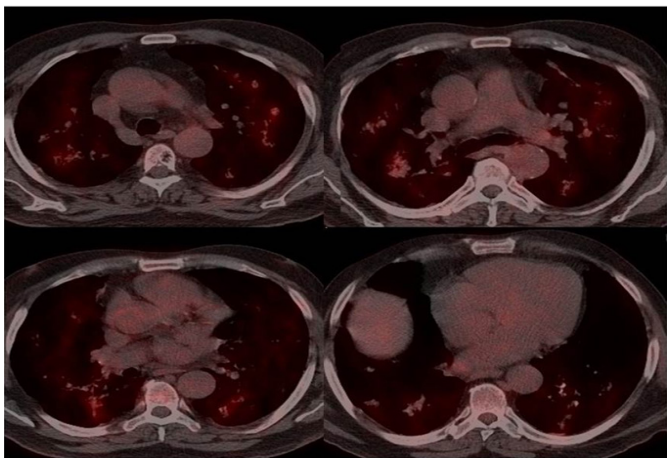

Figure 3. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scan showing moderate uptake of FDG in the bilateral interstitial infiltrations

DISCUSSION

Adenocarcinoma has a tendency to manifest in a multifocal fashion. Over the years, many authors have documented several unique characteristics of multifocal adenocarcinomas. For example, some studies have reported a predominance in females, while others have shown a male predominance. Similarly, some studies have reported a predominance in non-smokers, while others have shown a smoker predominance.[1] Our patient was a non-smoking male.

Most patients with multifocal adenocarcinomas are asymptomatic and are incidentally diagnosed. Symptomatic patients can present with cough (28–30%), haemoptysis (6–13%), weight loss (2–6%), chest pain (6–7%) and dyspnoea (2–4%).[1] Our patient had progressive dyspnea.

The previously used classification of *bronchoalveolar carcinoma* (BAC) included a heterogenous spectrum of subtypes, but the revised classification of 2011 better reflects the pathological, radiological and clinical correlation of lung adenocarcinoma; therefore, it is more practical and useful. BAC is now categorised into the following termas: adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, predominantly invasive adenocarcinoma with some nonmucinous lepidic components and invasive mucinous adenocarcinoma. Interestingly, this group of tumours tends to be multifocal.[2]

Radiographical findings that suggest multifocal adenocarcinomas have several remarkable characteristics. These are often difficult to distinguish from non-malignant conditions and include; (a) patent intratumoural bronchioles (air bronchiologram); (b) bubble-like lucencies or pseudocavitations; (c) cavitation; (d) serpentine radiolucencies; (e) internal alveologram; and (f) multiple, thin-walled cystic lesions. Bronchioloalveolar carcinoma may have a widespread multinodular pattern, but the cavitary form is very uncommon.[3] A cavitary nodule, with a central lucency observed on CT, is reminiscent of the breakfast cereal 'Cheerios', and was first defined as 'the Cheerio sign'.[4] A Cheerio in the lung arises from proliferation of either neoplastic cells, such as adenocarcinoma, other primary lung cancers, metastases or non-malignant cells, such as PLCH, mycobacterial or fungal infections, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and rheumatoid nodules.[5] All of these diseases were differential diagnoses and we sequentially excluded all of them.

Adenocarcinoma in situ, minimally invasive adenocarcinoma, invasive lepidic predominant adenocarcinoma and invasive mucinous adenocarcinoma may give rise to the Cheerio sign. The lepidic growth pattern of the tumour cells, whether solely, predominantly or partially present in these lesions, classically maintains alveolar architecture and bronchial patency, thereby creating Cheerio signs on CT at times[2,5]; some of our patient's nodules showed the Cheerio sign (**Figure 2**). Tailor et al.[6] demonstrated that pseudocavitation on CT is more common in lung adenocarcinoma than in other types of

non-small-cell lung carcinoma, with low sensitivity, but high specificity (>90%). They also showed that pseudocavitation on CT is associated with lepidic growth at histopathology. Multiple pseudocavitations were observed on our patient's CT scan (**Figure 2**).

PET scans are less sensitive, independent of tumour size, and secondary to the slow rate of proliferation of these lesions compared with other lung cancers, and are often negative.[7,8] In our case, all lesions showed slightly increased FDG uptake.

Multifocal adenocarcinomas may exhibit a lower tendency for nodal or extra-thoracic metastasis than other types of lung cancer. Although 65% of multifocal adenocarcinomas are confined to a single lobe, 12% are bilateral.[1] According to the tumour, node, metastasis (TNM) classification of lung cancer, multifocal adenocarcinoma involving more than one lobe is classified as T4, and multifocal adenocarcinoma involving the same lobe is classified as T3. The upcoming eighth edition of American joint commission on cancer (AJCC) staging for lung cancer recognises multifocal adenocarcinoma as a unique disease entity and adopts the size of the largest nodule for staging. A letter 'm' in parentheses will denote the multifocal nature of the disease.[9] The bilateral pulmonary involvement meant that our patient was staged as T4N0M1a.

The curative therapy for multifocal adenocarcinoma is surgical resection, and inappropriate patients should be directed to systemic treatment. Both cytotoxic chemotherapy and targeted therapy have a role in treating patients with advanced disease. Tissue should be tested for molecular markers (EGFR mutation and ALK rearrangement). Targeted therapy should be first-line only for patients with an EGFR mutation or the ALK fusion oncogene.[1] Liu et al.[10] analysed 78 patients with multifocal adenocarcinomas presenting as ground glass opacity for EGFR mutations in exons 18–21, and identified at least one EGFR mutation in at least one specimen in nearly 50% of patients. The authors concluded that the majority of the multifocal adenocarcinomas they investigated appeared to have arisen as independent events.

CONCLUSION

Unfortunately, molecular markers were negative in our patient, so he was scheduled to receive cytotoxic chemotherapy.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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