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Lepidic Type Lung Adenocarcinoma Masquerading as Chronic Infectious Pneumonia: A Case Report

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ABSTRACT

Background: Lepidic-type adenocarcinoma (previously known as bronchioloalveolar carcinoma) represents a unique subtype of lung adenocarcinoma that is characterized by the growth of atypical epithelial cells along pre-existing alveolar structures without evidence of stromal, vascular, or pleural invasion. Its radiographic presentation often overlaps with chronic infections like tuberculosis or fungal disease, which can lead to delays in diagnosis, particularly in endemic areas.

Case Presentation: We report the case of a 58-year-old, nonsmoking woman from Swabi, Pakistan, who presented to our institution with progressive shortness of breath, productive cough, chest pain, and constitutional symptoms over two months. She had a history of herpes zoster infection and received empiric antituberculous treatment. Chest radiography demonstrated bilateral patchy opacities and cystic lesions. Multiple sputum studies, GeneXpert, and fungal culture studies were negative for infectious etiologies. Computed tomography demonstrated bilateral multiple consolidations with cavitary nodules and minimal pleural effusion. Bronchoscopic evaluation with transbronchial lung biopsy revealed findings consistent with lung adenocarcinoma, lepidic pattern.

Conclusion: When considering individuals with non-resolving pneumonia, especially in patients undergoing infection treatments, the diagnosis of lepidic adenocarcinoma should be given consideration. Early histopathologic diagnosis is important for accurate diagnosis and management, ideally through bronchoscopy and/or lung biopsy.

Keywords: Lepidic Adenocarcinoma; Bronchioloalveolar Carcinoma; Nonresolving Pneumonia; Pakistan

Introduction

Lung cancer remains the leading cause of cancer-related mortality in the world, accounting for nearly 1.8 million deaths each year, with adenocarcinoma being the most common histologic subtype.[1] Between adenocarcinomas, the lepidic pattern (previously referred to as bronchioloalveolar carcinoma, BAC) represents a unique growth pattern in which neoplastic cells proliferate along the pre-existing alveolar septa without stromal, vascular, or pleural invasion.[2] According to the 2015 WHO classification, lepidic adenocarcinoma is now categorized as part of a spectrum that ranges from adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) to invasive adenocarcinoma, predominantly lepidic type.[3]

This subtype is often a diagnostic challenge due to its indolent course and non-specific clinical features. Patients usually present with cough, dyspnea, low-grade fever, or weight loss—signs that often have significant overlap with chronic infections (such as tuberculosis [TB], fungal pneumonia, or organizing pneumonia).[4] In countries endemic for TB (like Pakistan), this overlap frequently leads to empiric anti-TB therapy prior to pursuing further diagnostics, resulting in routine delays in diagnosis.[5]

Radiologically, lepidic adenocarcinoma may exhibit various patterns, including focal or diffuse ground-glass opacities, patchy consolidations, nodules, or cystic changes, and may be indistinguishable from non-resolving pneumonia.[6,7] Nonresponsiveness to conventional antimicrobial or antituberculous therapy should raise suspicion of a neoplasm. High-resolution computed tomography (HRCT) may aid in diagnosis by revealing characteristic findings, including multifocal ground-glass opacities without air bronchograms; however, the standard for diagnosis remains histological evidence from pathology.[8]

Histologically, the tumor displays lepidic (surface-spreading) growth of atypical type II pneumocytes or Clara cells, while maintaining the alveolar architecture that underlies the tumor. Immunohistochemistry typically reveals positivity for thyroid transcription factor-1 (TTF-1) and Napsin-A, indicating a pulmonary origin.[9]

We present a case of lepidic-type adenocarcinoma, with biopsy evidence, in a middle-aged, nonsmoking female from Pakistan, who was initially treated as pulmonary tuberculosis due to her clinical and radiological presentation. The aim of this report is to emphasize the importance of maintaining a broad differential diagnosis in non-resolving pulmonary infiltrates and the role of biopsy in determining the diagnosis in high-prevalence areas.

Case Presentation

A 58-year-old female patient came to the pulmonary clinic in Swabi, Pakistan, with dyspnea that had worsened over the past two months. Her dyspnea was associated with a productive cough and left-sided pleuritic chest pain. The cough was moderate in severity, producing a whitish sputum, and had not improved with a course of empirical antibiotics. She also reported having a high-grade intermittent fever for ten days, approximately 10 kg of unintentional weight loss, and a decreased appetite. She was a lifelong nonsmoker and denied any history of exposure to biomass fuels, asbestos, or occupational dust.

Her past medical history was significant for herpes zoster three months earlier, and for empiric antituberculous therapy for two months, which she had just discontinued due to a lack of clinical improvement. She denied hemoptysis and any known exposure to tuberculosis.

On general examination, the patient appeared thin and was mildly dyspneic at rest. She had a pulse of 105 beats per minute, a respiratory rate of 24 breaths per minute, blood pressure of 110/70 mmHg, a temperature of 99°F, and oxygen saturation of 92% on room air. Lung examination demonstrated normal vesicular breath sounds with diffuse bilateral fine crackles. There were no signs of lymphadenopathy, digital clubbing, or peripheral edema noted on examination. Cardiology and abdominal findings were unremarkable.

Routine hematological and biochemical studies (complete blood count, liver function tests, and renal profile) were within normal limits. The chest X-ray showed bilateral patchy heterogeneous opacities in all lung zones, more pronounced in the lower lobes, with scattered cystic changes and blunting of the left costophrenic angle. Given that tuberculosis is endemic, tests for acid-fast bacilli (AFB) in the sputum using GeneXpert and XDR GeneXpert were performed, and all results were negative. Both the AFB culture and a fungal smear were negative. Sputum cytology did show atypical cells.

Diagnostic thoracentesis of the left pleural effusion showed exudative fluid with a lymphocytic predominance. Cytology of the pleural fluid was negative for malignant cells. HRCT of the chest revealed bilateral multiple patchy consolidations and multiple cavitary nodules in all lobes, with bilateral minimal pleural effusions, more pronounced in the lower lobes (Figure 1).

A flexible bronchoscopy was then performed for further evaluation and did not reveal any endobronchial or mucosal lesion. Bronchial washings were sent for microbiological and cytological testing, which were negative for AFB, GeneXpert, XDR GeneXpert, and fungi. A transbronchial lung biopsy (TBLB) was performed. The histopathological examination exhibited features of airway spaces with disruption of alveolar architecture, cellular interstitial inflammation, and a sudden transition to a neoplastic lesion with a bronchioloalveolar (lepidic) growth pattern. Tumor cells displayed round to oval pleomorphic nuclei, atypical mitotic figures, and moderate foamy cytoplasm, all of which were morphol-

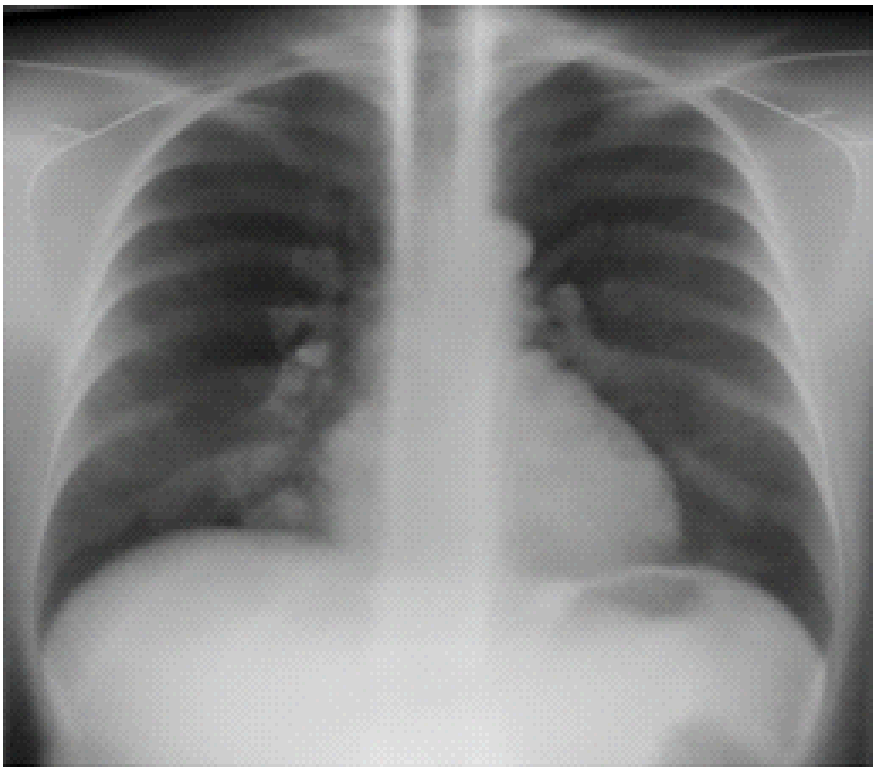

Figure 1. Chest radiograph showing bilateral patchy heterogeneous opacities involving all lung zones, predominantly in the lower lobes, with a few scattered cystic lesions and blunting of the left costophrenic angle

ogically consistent with lung adenocarcinoma, lepidic type (formerly bronchioloalveolar carcinoma) (Figure 2).
Based on this information, a definitive diagnosis of lung adenocarcinoma, lepidic predominant, was made. The patient was then referred to the multidisciplinary oncology team for staging and management. It was recommended that PET-CT and molecular profiling for mutations in EGFR, ALK, and ROS1 might be useful in guiding treatment for targeted therapy. The plan was to start targeted treatment if the patient had a mutation positive for treatment or to initiate palliative chemotherapy if the mutation was negative. Supportive management was also initiated, including oxygen supplementation, bronchodilators, nutritional rehabilitation, and psychosocial counseling.

Discussion

Lepidic adenocarcinoma of the lung is a distinct histological subtype characterized by neoplastic cells proliferating along unaltered alveolar septa without destructive growth patterns. Lepidic growth pattern is less aggressive than other invasive adenocarcinoma subtypes, especially when detected early. In the current IASLC/ATS/ERS and WHO classification, what we used to describe as bronchioloalveolar carcinoma (BAC) has been reconstituted into adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma with lepidic-predominant growth based on the degree of advancement of invasive growth.[10]
In an area of high endemicity for tuberculosis (TB), such as Pakistan or in other regions of South Asia, lepidic adenocarcinoma, or neoplastic pneumonia, is not uncommon. It is often misdiagnosed as an infectious, typically non-resolving pneumonia or pulmonary TB. These patients are often commenced early on empirically directed anti-tuberculosis therapy even before a recognized tissue diagnosis, which can significantly delay the correct diagnosis. This highlights the need for the clinician to maintain a high index of suspicion for neoplastic etiologies, especially if the individual does not respond to standard anti-infective treatment.
Radiologically, lepidic adenocarcinoma presents in various ways. It can present as a solitary nodule, possibly mimicking a tuberculoma, as multifocal or diffuse consolidations similar to pneumonia or interstitial lung disease, or as cystic or cavitary lesions, as seen in our patient. The range of imaging findings adds diagnostic difficulty, particularly with widespread involvement of multiple lobes or minimal bilateral pleural effusion. In this case, the combination of bilateral patchy opacities, cavitary nodules, and negative microbiological studies

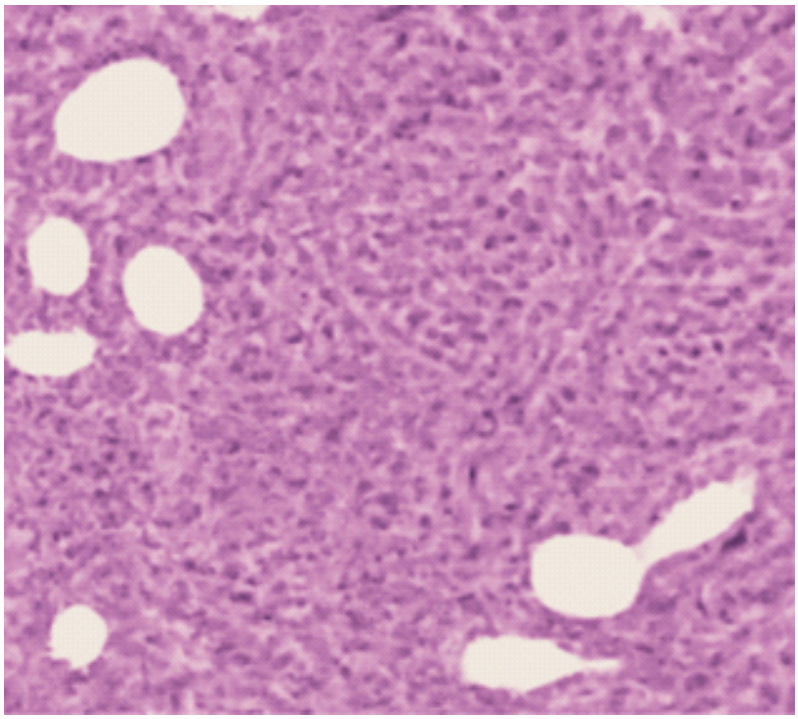

Figure 2. Histopathological section of lung tissue (H&E stain, ×400) demonstrating lepidic pattern adenocarcinoma with alveolar architecture distortion, interstitial inflammation, and neoplastic cells having pleomorphic nuclei, atypical mitoses, and moderate foamy cytoplasm

suggested a non-infectious etiology, which required biopsy and histopathological examination.

The definitive diagnosis of lepidic adenocarcinoma relies on histopathology. The usual microscopic findings include the proliferation of atypical type II pneumocytes (or Clara cells) lining alveolar structures, with no invasiveness and preservation of alveolar architecture. In some instances, overlapping inflammation or fibrosis may be present. Immunohistochemical stains usually demonstrate positive staining for thyroid transcription factor-1 (TTF-1) and Napsin-A, demonstrating the pulmonary origin of the tumor.

From a prognostic standpoint, lepidic-predominant adenocarcinoma is usually associated with favorable outcomes. For example, five-year disease-free survival rates in small resected lesions (particularly those with atypical adenomatous hyperplasia and minimally invasive lesions) are approaching 100%.[11] The outcomes of lepidic adenocarcinoma are even better than those with more aggressive growth patterns when looking at invasive lepidic adenocarcinoma. One surgical-based cohort study reported a five-year survival rate of approximately 70% for lepidic-predominant invasive adenocarcinoma compared with significantly lower survival in solid or micropapillary predominant subtypes.[12]

At the same time, intratumoral heterogeneity can alter prognostic outcomes. For example, in a recent report of prognostic significance, having high-risk patterns such as solid or micropapillary components, even as minor components within a lepidic-predominant tumor can impact prognosis.

The tumor resulted in worse disease-free survival.[13] These findings support a differentiated prognostic outcome based not only on the predominant pattern but also on the number of components with increasingly aggressive histologies. Remarkably, even non-predominant lepidic components appear to be of prognostic benefit i.e., in a large cohort of stage I invasive non-mucinous adenocarcinoma, non-predominant lepidic pattern was independently associated with better recurrence-free and overall survival.[2]

Additionally, other pathological factors, such as lymphovascular invasion, may be crucial prognostic markers. The presence of all lepidic growth in tumors is typically associated with a low rate of lymphatic vessel invasion, which in turn may lead to better clinical outcomes. Likewise, in the case of mixed subtype lepidic-predominant adenocarcinomas, such as acinar- or papillary-predominant tumors, the prognosis is better with lepidic growth being at least 20%, as recurrence rates are lower.[3]

Treatment of lepidic adenocarcinoma might vary based on the stage of the disease and/or the molecular characteristics of the specimen. Surgery remains the

preferred treatment for localized disease, as it may be curative. In cases of advanced or unresectable disease, molecular testing may be performed to guide the selection of targeted therapy treatments associated with favorable outcomes (tests or treatments including EGFR, ALK, and ROS1). If no actionable mutations are found through tumor testing, oncologists may opt for systemic chemotherapy or immunotherapy, depending on the patient's performance status.

The temporal delay in accurate diagnosis in our patient is justifiable, as there was a significant overlap in clinical manifestations and radiographic features with the infectious disease. However, the decision to perform bronchoscopy and transbronchial biopsy was crucial, as it led to the definitive histopathological diagnosis and, consequently, to the oncological referral and personalized therapy. Since lepidic adenocarcinoma often has a more indolent course and a better prognosis than other invasive subtypes, early recognition is particularly important.

Lepidic-predominant lung adenocarcinoma is a relatively fast-growing tumor that may easily pose as an infection in regions where tuberculosis is endemic. The doctors should include it in the differential diagnosis of nonresolving or atypical pneumonias. Histopathological examination, which includes measuring tumor growth patterns and molecular profiling, conveys vital information regarding prognosis and treatment. The presence of minor solid or micropapillary components in the tumor—which represents a type of intratumoral heterogeneity—should be thoroughly documented, as it impacts the clinical course and overall outcome.

Conclusion

Lepidic adenocarcinoma of the lung, though rare, is still an important entity that very often gets mistaken for infectious pneumonia or tuberculosis, especially in areas of high tuberculosis incidence, like Pakistan. The shared clinical and radiological characteristics make it take longer before the right diagnosis is made and the patient receives the correct treatment. It is very important to keep suspecting lung cancer in patients who do not respond to treatment and have negative cultures.

Histopathological diagnosis is still the main method of detecting cancer, although immunohistochemistry can help in identifying the origin of the tumor as coming from the lung. A quick and precise diagnosis through tissue sampling allows for the combination of staging and molecular profiling, which are crucial for targeted therapy. In the case of lepidic adenocarcinoma, although the prognosis is relatively favorable compared to other subtypes of invasive adenocarcinoma, early detection and proper management can significantly improve the patient's outcome.

In conclusion, vaporous lung shadows that do not clear with the use of normal antibiotics or antituberculous drugs should prompt doctors to consider lepidic adenocarcinoma. For accurate diagnosis and planning of the best treatment, the teamwork of pulmonologists, radiologists, and pathologists is crucial.

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