

COEXISTENT PULMONARY ADENOCARCINOMA WITH LEPIDIC GROWTH PATTERN AND GRANULOMATOUS INFLAMMATION SUGGESTIVE OF TUBERCULOSIS IN AN ELDERLY MALE: A DIAGNOSTIC CHALLENGE

Histopathology

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ABSTRACT

Background: Pulmonary tuberculosis and lung cancer share overlapping clinical, radiological and epidemiological features, and their coexistence in the same lobe of lung remains a well-recognised but under-reported diagnostic challenge, particularly in tuberculosis-endemic regions such as India. **Case Presentation:** A 76-year-old male, a treated type 2 diabetic, presented with a two-month history of hoarseness of voice and dry cough followed by breathlessness, dysphagia and anorexia of two weeks' duration. Contrast-enhanced computed tomography of the neck and chest, performed over the preceding ten weeks at two centres, showed a left upper lobe mass with an abrupt bronchial cut-off, bilateral randomly distributed pulmonary nodules, left vocal cord medialisation, an incidental calcified thyroid nodule, an intraspinal calcified lesion at the C7-D1 level and a left pleural effusion with severe pulmonary arterial hypertension. Pleural fluid analysis showed a lymphocyte-predominant exudate with a borderline-elevated adenosine deaminase level and was cytologically negative for malignancy. Computed tomography-guided core biopsy of the left upper lobe mass revealed a malignant epithelial neoplasm with a predominantly lepidic growth pattern, morphologically favouring adenocarcinoma, together with well-formed granulomas containing epithelioid histiocytes and multinucleated giant cells and no necrosis. A GeneXpert MTB/RIF Ultra assay performed on the same biopsy tissue detected a trace amount of Mycobacterium tuberculosis complex DNA with indeterminate rifampicin resistance. The patient was managed symptomatically for hyponatraemia, anaemia and respiratory symptoms and was discharged in a stable condition with plans for multidisciplinary correlation and anti-tubercular and oncological work-up. **Conclusion:** This case highlights the need for a high index of suspicion for concurrent tuberculosis and malignancy in a solitary or dominant pulmonary mass, especially in tuberculosis-endemic settings, and underscores the value of adequate tissue sampling with combined histopathological, microbiological and molecular testing before committing a patient to either anti-tubercular therapy or oncological treatment alone.

KEYWORDS

Lung Adenocarcinoma; Lepidic Pattern; Pulmonary Tuberculosis; Granulomatous Inflammation; GeneXpert MTB/RIF Ultra; Vocal Cord Palsy; Case Report

INTRODUCTION

Lung cancer and pulmonary tuberculosis are both leading causes of respiratory morbidity and mortality worldwide, and India carries a disproportionate share of the global tuberculosis burden. Epidemiological and mechanistic evidence has increasingly implicated chronic tuberculous inflammation, fibrosis and scarring as contributors to carcinogenesis in the lung, a phenomenon historically termed "scar carcinoma," and population-based cohort studies have shown that prior pulmonary tuberculosis is associated with a significantly increased subsequent risk of lung cancer, particularly adenocarcinoma [1-4]. Conversely, active tuberculosis may coexist within or adjacent to a lung malignancy at the time of diagnosis, producing radiological and histopathological pictures that mimic each other and complicate management [5,6]. The revised international multidisciplinary classification of lung adenocarcinoma recognises a lepidic growth pattern, in which tumour cells grow along pre-existing alveolar septae without stromal, vascular or pleural invasion, as one of the five major histological patterns and the classic architecture of the entity formerly designated bronchioloalveolar carcinoma [7,8]. We report a case in which histopathological examination of a computed tomography-guided lung biopsy simultaneously demonstrated a lepidic-pattern malignant epithelial neoplasm and well-formed granulomatous inflammation, with molecular testing confirming trace Mycobacterium tuberculosis complex DNA in the same specimen, illustrating the diagnostic overlap between these two conditions in routine clinical practice.

Case Presentation

Patient Information and History

A 76-year-old man, a resident of southern India, presented with breathlessness and dysphagia of two weeks' duration, hoarseness of voice and dry cough of two months' duration, and loss of appetite for two weeks. He was a known type 2 diabetic of six years' duration, on oral hypoglycaemic agents which he had self-discontinued two months prior to presentation; he had no history of hypertension, coronary artery disease, asthma or known drug allergies. There was no history of prior tuberculosis, and no documented history of smoking or alcohol use was recorded in the case notes available for this report.

Clinical and Radiological Evaluation Prior to Admission

Approximately ten weeks before admission, a plain computed tomography of the neck performed for evaluation of hoarseness showed medialisation of the left aryepiglottic fold with widening of the ipsilateral pyriform fossa, raising suspicion of left vocal cord palsy, together with an incidental well-defined calcified nodule in the left lobe of the thyroid. On the same study, the visualised lung fields showed a large soft-tissue-density lesion measuring approximately 6.2×4.2 cm with internal calcific foci in the anterior segment of the left upper lobe and superior lingula, with abrupt cut-off of the left upper lobe bronchus, along with a few small randomly distributed nodules in both lung fields, suspicious for malignancy with possible metastatic nodules; correlation with contrast-enhanced computed tomography of the chest and histopathology was recommended. A repeat dedicated computed tomography of the neck two weeks later confirmed a tiny left vocal cord nodule with mild cord medialisation and re-demonstrated the calcified thyroid nodule. A subsequent plain computed tomography of the chest performed approximately one month before admission showed patchy consolidation in the basal segments of both lower lobes and the lateral segment of the right middle lobe, an enlarged prevascular lymph node measuring 15×9 mm, and a soft-tissue lesion with bronchial cut-off in the left upper lobe measuring 6.5×6 cm with areas of calcification; bronchoscopic and biopsy correlation was advised, with a differential of infective (tuberculous) versus neoplastic aetiology. A further contrast-enhanced computed tomography of the chest obtained shortly before admission showed progression to a heterogeneously enhancing calcified soft-tissue mass measuring 7.2×4.9 cm in the left upper lobe with abrupt bronchial cut-off and abutment of the pleural surface, ground-glass opacity nodules in the bilateral lung fields raising concern for contralateral metastasis, a left pleural effusion, and an intraspinal calcified lesion at the C7-D1 vertebral level; histopathological correlation was again recommended.

Admission, Examination and Investigations

The patient was admitted to the department of respiratory medicine for further evaluation of the left upper lobe mass, left vocal cord palsy and left pleural effusion. On examination he was conscious, oriented and afebrile, with no pallor, icterus, cyanosis, clubbing or pedal oedema, and no palpable peripheral lymphadenopathy. Vital parameters were stable (blood pressure 120/90 mmHg, pulse rate 86/min, oxygen saturation 98% on room air), and systemic examination, including

respiratory and cardiovascular systems, was unremarkable apart from the known effusion. Laboratory evaluation revealed a haemoglobin of 10.9 g/dL and hyponatraemia (serum sodium 125 mEq/L), which was managed as resolving hyponatraemia. Transthoracic echocardiography showed normal left ventricular size and systolic function (ejection fraction 61%) with grade I diastolic dysfunction, a sclerotic aortic valve, trivial aortic regurgitation, moderate (2+) tricuspid regurgitation and severe pulmonary arterial hypertension with an estimated pulmonary artery systolic pressure of 52 mmHg, without pericardial effusion or intracardiac clot.

Pleural Fluid Analysis

Ultrasound-guided diagnostic and therapeutic thoracentesis yielded clear, straw-coloured fluid. Fluid analysis showed a total nucleated cell count of 1,500 cells/cu.mm with a lymphocyte-predominant differential (96% lymphocytes, 4% neutrophils). Biochemical analysis demonstrated a protein of 4.5 g/dL and a lactate dehydrogenase of 474 IU/L, both consistent with an exudate by conventional criteria, a glucose of 248 mg/dL, and an adenosine deaminase level of 39.7 IU/L, marginally below the conventional cut-off used to favour a tuberculous aetiology. Gram staining showed occasional pus cells with no organisms, Ziehl-Neelsen staining for acid-fast bacilli was negative, and aerobic bacterial culture showed no growth on preliminary report. Cytological examination of the pleural fluid cell block showed lymphocytes, neutrophils and occasional reactive mesothelial cells in a proteinaceous background, with no atypical or malignant cells identified.

Tissue Diagnosis

In view of the persistent radiological suspicion of malignancy, an interventional radiology opinion was obtained and an ultrasound/computed tomography-guided core needle biopsy of the left upper lobe mass was performed, yielding three grey-white linear tissue cores measuring 0.8, 1.1 and 1.5 cm, entirely embedded in a single block. Histopathological examination revealed areas of lung tissue infiltrated by malignant epithelial carcinoma which showed atypical cuboidal to columnar cellular pattern in a lepidic growing pattern. Tumour cells were characterized by enlarged dark nuclei, mild to moderate pleomorphic features, and thin to moderate quantity of eosinophilic cytoplasm. Alveolar walls showed thickening due to chronic inflammation. Granulomas made of epithelioid cells and giant cells were formed in one of the alveolar walls. The overall impression was of a lung tumour with a predominant lepidic pattern together with granulomatous inflammation, favouring a diagnosis of adenocarcinoma with a lepidic pattern, subject to clinical and radiological correlation. In parallel, a separate biopsy specimen labelled as being from the left vocal cord region did not show diagnostic material beyond reactive changes.

Because of the co-existing granulomatous inflammation, a portion of the same core biopsy tissue was submitted for a GeneXpert MTB/RIF Ultra assay. This detected a trace amount of *Mycobacterium tuberculosis* complex DNA, with rifampicin resistance reported as indeterminate, a result that, per the assay's own performance characteristics, indicates a very low bacillary burden and does not permit definitive resistance profiling [9,10].

Diagnosis, Management and Outcome

The patient was given a composite discharge diagnosis of a left upper lobe mass for further evaluation, left vocal cord palsy, left pleural effusion with severe pulmonary arterial hypertension (52 mmHg), type 2 diabetes mellitus, resolving hyponatraemia and anaemia. During the four-day admission he was managed with intravenous antibiotics, anticoagulation, antiplatelet therapy, a statin, insulin, antihypertensive cover and supportive analgesic and bronchodilator therapy; his hyponatraemia improved and he remained haemodynamically stable throughout. He was discharged in an improved and stable condition with inhaled bronchodilator-corticosteroid combinations, an antihistamine-antitussive combination and a leukotriene receptor antagonist-antihistamine combination for symptomatic relief, pending the final histopathology and GeneXpert reports, with a plan for multidisciplinary (pulmonology, oncology and infectious disease) correlation to define the relative contributions of tuberculosis and malignancy before initiating either anti-tubercular therapy, oncological staging and treatment, or both.

DISCUSSION

This case illustrates the well-described but clinically difficult overlap between pulmonary tuberculosis and lung cancer. Epidemiological

studies from tuberculosis-endemic countries have consistently shown that a history of pulmonary tuberculosis approximately doubles the subsequent risk of lung cancer, an association attributed to chronic inflammation, oxidative DNA damage and fibrotic scarring within healed tuberculous foci that may act as a nidus for malignant transformation, most classically for adenocarcinoma arising in peripheral scars [1-4,11]. In the present case, however, the histological picture was of active granulomatous inflammation admixed with tumour tissue in the same core, together with a GeneXpert-positive result for *Mycobacterium tuberculosis* complex DNA, raising the alternative or additional possibility of a tuberculous focus arising within, or immediately adjacent to, an already-established malignancy, a pattern that has also been reported when tumour-related bronchial obstruction and post-obstructive changes create a permissive local environment for mycobacterial infection [5,6,12].

The lepidic growth pattern identified on histopathology is one of the five architectural patterns recognised in the current classification of invasive pulmonary adenocarcinoma, in which relatively bland-to-mildly atypical tumour cells spread along intact alveolar walls; a predominant lepidic pattern generally correlates with a more indolent clinical course than acinar, papillary, micropapillary or solid patterns, although an accurate distinction between a purely in-situ or minimally invasive lesion and a frankly invasive lepidic-predominant adenocarcinoma requires examination of a larger resection specimen rather than a small core biopsy [7,8]. The presence of well-formed, non-necrotising granulomas with multinucleated giant cells within the same specimen is a recognised, if less common, host response seen adjacent to some pulmonary carcinomas, and can reflect either a genuine sarcoid-like or foreign-body-type reaction to tumour antigens or, as appears more probable here given the GeneXpert result, a true co-existing mycobacterial infection [6,13].

The GeneXpert MTB/RIF Ultra assay used in this case has substantially higher sensitivity than the original Xpert MTB/RIF assay, particularly in paucibacillary specimens such as small tissue biopsies, but this increased sensitivity comes at the cost of an increased rate of "trace" calls, which represent detection of only a very small amount of *Mycobacterium tuberculosis* DNA and are frequently associated with an indeterminate or unassessable rifampicin-resistance result because insufficient DNA is amplified to interrogate all four *rpoB* melt-curve probes reliably [9,10]. A trace result therefore requires careful clinical correlation, and in an appropriate clinical context may still be considered a true positive warranting anti-tubercular therapy, but it does not, by itself, exclude the possibility of an alternative or coexisting diagnosis such as malignancy [9,10]. In the pleural space, the fluid profile in this patient - a lymphocyte-predominant exudate with an adenosine deaminase level just below the widely used cut-off of approximately 40 IU/L - illustrates the limitation of adenosine deaminase testing at borderline values; while pleural fluid adenosine deaminase has good overall sensitivity and specificity for tuberculous pleuritis, values close to the cut-off, and negative acid-fast bacilli smears and cultures (both negative here), are well recognised, and a malignant or paramalignant effusion secondary to bronchial obstruction remains part of the differential even when cytology is negative, since sensitivity of pleural fluid cytology for malignancy is itself limited [14,15].

Hoarseness of voice with radiologically confirmed left vocal cord medialisation in this patient is most consistent with a left recurrent laryngeal nerve palsy, which classically results from mediastinal lymphadenopathy, direct tumour extension, or entrapment of the nerve as it loops beneath the aortic arch, and is a well-recognised presenting or accompanying sign of an intrathoracic malignancy, particularly one involving the left upper lobe or aortopulmonary window [16]. The presence of this patient here, along with bilateral lymphadenopathy and its cerebral lesion, made us suspect locally-advanced or disseminated disease. Thus, tissue diagnosis is of utmost importance prior to the composition of a management plan since the differential diagnoses of this finding may also comprise disseminated granulomatous condition. The detection of this incidental calcified thyroid nodule in the patient population is common and should be flagged for possible ultrasound rather than implementation of an immediate intervention.

Practically, this case illustrates the following principles relevant to routine pulmonology and pathology practice in a tuberculosis-endemic area. First, dominant/pulmonary mass that exhibits imaging features suspicious for malignancy should not be treated as

tuberculosis automatically nor assume malignancy absent due to existing granulomas on biopsy tissue. Second, if there is limited tissue such as core biopsy, ideally a portion should be sent for molecular mycobacterial testing along with conventional histopathology to ensure maximum diagnostic yield without the need for further tissue acquisition. Third, indeterminate rifampicin resistance along with a trace GeneXpert should be interpreted among the complete clinical, radiological, and histopathological context and continues to carry obligation for completion of oncologic staging when a malignancy already has been detected morphologically [9,10,17]. Finally, multidisciplinary case conferences including pulmonology/pathology/microbiology/radiology and oncology must occur if TB treatment is begun as scheduling therapy appropriately may not be feasible with all specialties included since delays from either specialty could alter the outcomes negatively.

CONCLUSION

Coexistence of a lepidic-pattern pulmonary adenocarcinoma with granulomatous inflammation and trace *Mycobacterium tuberculosis* complex DNA in the same biopsy specimen is a rare but instructive presentation that reflects the broader epidemiological and pathobiological overlap between tuberculosis and lung cancer in endemic regions. A systematic diagnostic approach combining radiology, adequate tissue sampling, histopathology, microbiological smear and culture, and molecular testing is essential to avoid misattributing symptoms, radiological progression or a positive molecular test to a single disease process, and to ensure that patients such as this one receive timely, appropriately sequenced treatment for both conditions where they truly coexist.

Figures

Photomicrographs of the computed tomography-guided core biopsy from the left upper lobe mass (haematoxylin and eosin stain), demonstrating the coexistence of a lepidic-pattern malignant epithelial neoplasm and granulomatous inflammation within the same specimen.

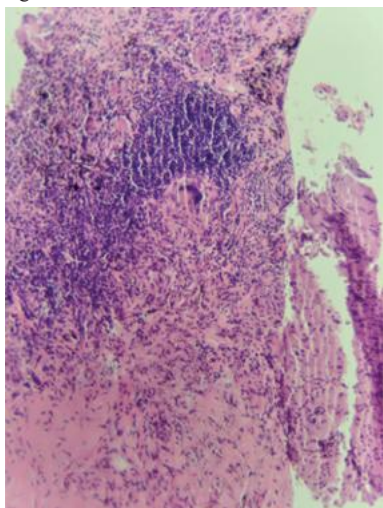


Figure 1. 40x view of a lung tissue core showing a dense granulomatous inflammatory focus with epithelioid histiocytes and admixed chronic inflammatory cells adjacent to alveolated lung parenchyma (H&E).

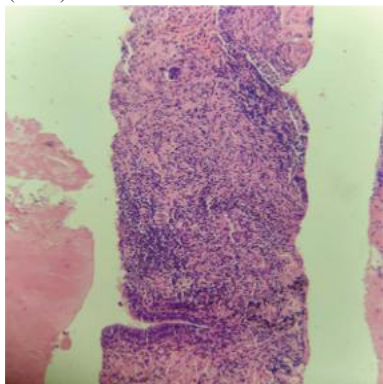


Figure 2. 10x view showing a well-formed granuloma bordered by

alveolar septae lined by atypical epithelial cells in a lepidic pattern, with surrounding chronic inflammatory infiltrate (H&E).

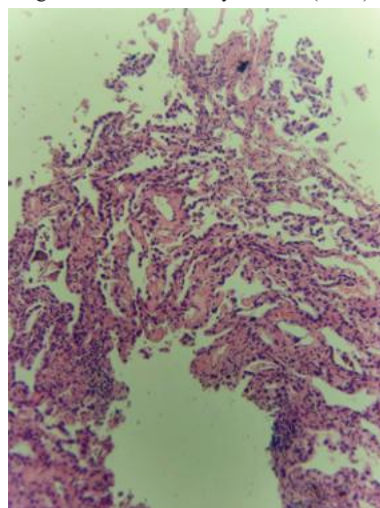


Figure 3. 40x view of alveolar septae lined by atypical cuboidal-to-columnar epithelial cells growing along pre-existing alveolar architecture, consistent with a lepidic growth pattern (H&E).

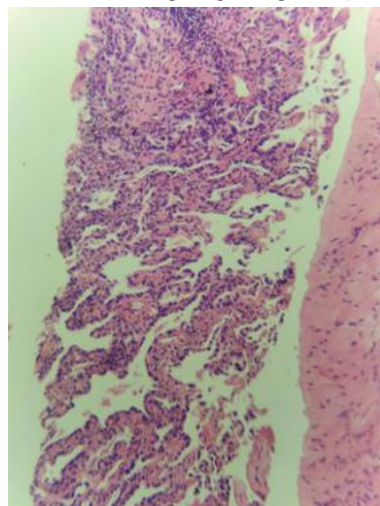


Figure 4. 10x view showing lepidic-pattern tumour cells with enlarged hyperchromatic nuclei and mild-to-moderate pleomorphism lining thickened alveolar septae (H&E).

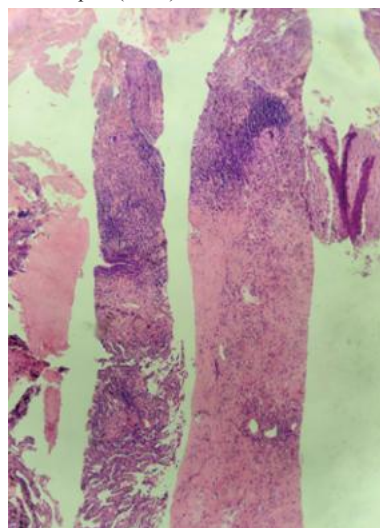


Figure 5. 4x view of two adjacent linear core fragments showing granulomatous inflammation (left core) and lepidic-pattern tumour tissue (right core), illustrating the coexistence of the two processes within the same biopsy (H&E).

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