

Extreme CYFRA 21-1 Elevation in Lung Adenocarcinoma is Uncommon: Evidence of Tumor Burden Over Histological Specificity

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ABSTRACT

Serum tumor markers are commonly used in lung cancer management, but interpretation may be difficult when levels are markedly elevated and discordant with histopathological findings. CYFRA 21-1 is typically associated with squamous cell carcinoma, whereas CEA is more characteristic of adenocarcinoma. We report a 43-year-old man presenting with generalized weakness, severe back pain, and inability to walk. Magnetic resonance imaging revealed a thoracic mass and extensive vertebral lytic-blastic lesions suggestive of disseminated skeletal metastases. Histopathology confirmed metastatic adenocarcinoma. Immunohistochemistry showed CK7 and TTF-1 positivity with CK20 negativity, supporting a diagnosis of lung adenocarcinoma. Serum markers showed markedly elevated CEA (>1000 ng/mL) and extremely high CYFRA 21-1 (>500 ng/mL), exceeding levels commonly reported in adenocarcinoma. The unusually high CYFRA 21-1 may reflect extensive tumor burden, diffuse bone metastases, and increased tumor cell turnover rather than histological subtype alone. This case highlights the importance of integrating tumor markers with radiological, histopathological, and immunohistochemical findings in advanced lung cancer.

Keywords: Cancer biomarker; CEA; CYFRA 21-1; Immunohistochemistry; Lung neoplasms

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide. More than 50% of global lung cancer cases occur in Asia, with nearly 60% of the overall disease burden borne by Asian countries. In Indonesia, lung cancer is the second most common malignancy in both sexes and is associated with a particularly high mortality rate, despite not being among the five most common cancers in women^{1, 2}. Approximately 85–90% of lung cancer cases in Indonesia are linked to active smoking and exposure to environmental tobacco smoke. Furthermore, non-smokers living with smokers have an estimated 20–30% increased risk of developing lung cancer. Most patients in Indonesia are

diagnosed at an advanced stage (stage III–IV), with adenocarcinoma is the predominant histopathological subtype³.

Lung cancer is classified into two main histological subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). This classification is based on histological differences, clinical behavior, and response to treatment. SCLC accounts for approximately 15–20% of all lung cancer cases and tends to show greater responsiveness to chemotherapy and radiotherapy. In contrast, NSCLC, especially adenocarcinoma, shows more heterogeneous biological characteristics and biomarker profiles, and this may complicate the diagnostic interpretation especially in advanced disease⁴.

Serum tumor markers such as carcinoembryonic antigen (CEA) and CYFRA 21-1 are commonly used in clinical practice to support diagnosis, predict prognosis, and therapy monitoring. CEA is typically elevated in adenocarcinoma, reflecting glandular differentiation, while CYFRA 21-1, a fragment of cytokeratin 19, is more commonly associated with squamous cell carcinoma. However, in advanced disease stages, tumor marker expression does not always follow classical histological patterns⁵.

We report a case of metastatic lung adenocarcinoma with an unusually extreme elevation of CYFRA 21-1, highlighting the importance of integrating clinical, radiological, histopathological, and biomarker findings to make an accurate diagnostic interpretation in advanced lung cancer.

CASE PRESENTATION

A 43-year-old male presented to the emergency department with progressive generalized weakness, severe lower back pain, and an inability to ambulate. The symptoms had worsened over time, significantly limiting his functional capacity. There was no reported history of similar illness, and no known family history of malignancy or hereditary disease.

Initial radiological evaluation was performed to investigate the underlying cause of his symptoms. Magnetic resonance imaging (MRI) of the entire vertebral column reveals abnormal signal intensity in multiple vertebral bodies, including T4, T7, T8, T11, T12, L1–L4, and S1. Lytic and destructive changes are noted in the vertebral bodies of T7, T8, T11, T12, and L1–L4 (Figure 1). These findings were consistent with a widespread metastatic bone disease.

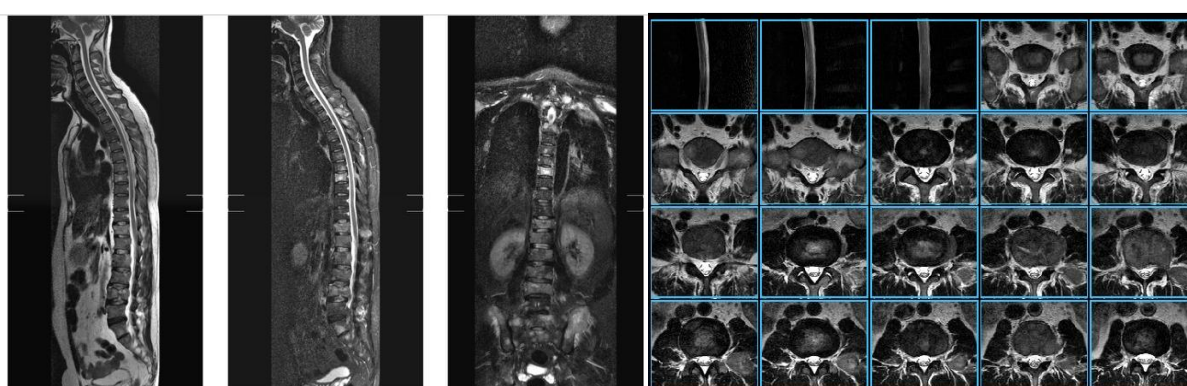


Figure 1. Magnetic resonance imaging (MRI) findings at initial evaluation. Thoracic MRI demonstrated a suspicious thoracic mass suggestive of either a primary lung lesion or mediastinal tumor, while whole-spine MRI revealed extensive mixed lytic–blastic metastatic involvement throughout the vertebral column from the cervical to sacral regions, consistent with disseminated skeletal metastases.

Based on the clinical and radiological findings, a working diagnosis of metastatic spinal disease was established, with differential considerations including malignancy and infectious processes, including tuberculosis. A comprehensive diagnostic workup was initiated to identify the primary tumor source. This included serum tumor marker evaluation and histopathological confirmation through tissue biopsy. The patient was also planned for posterior spinal fusion as part of the management of spinal instability.

Histopathological examination of the biopsy specimen revealed features consistent with metastatic adenocarcinoma (Figure 2). To determine the tissue of origin, immunohistochemical (IHC) staining was performed. The tumor cells showed positivity for thyroid transcription factor-1 (TTF-1) (Figure 3) and cytokeratin 7 (CK7) (Figure 4), and while cytokeratin 20 (CK20) was negative (Figure 5). This immunoprofile strongly supported a diagnosis of primary lung adenocarcinoma with spinal metastases.

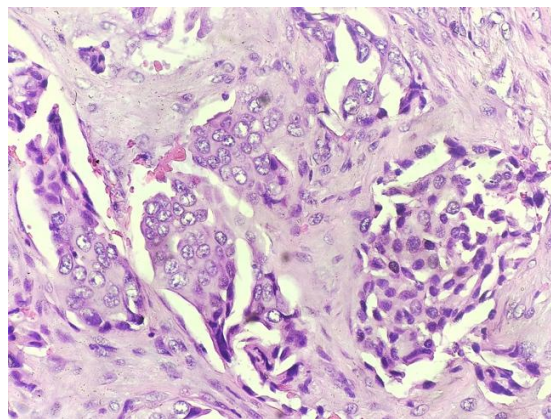


Figure 2. Histopathological examination of the biopsy specimen (hematoxylin and eosin staining) showing malignant epithelial cells arranged in irregular glandular structures, with nuclear pleomorphism, hyperchromasia, and prominent nucleoli, consistent with metastatic adenocarcinoma.

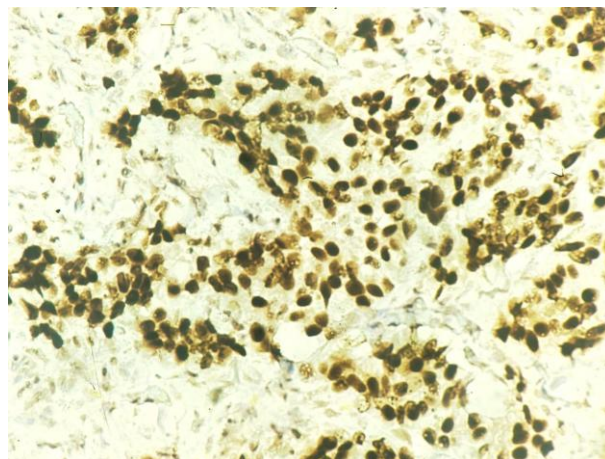


Figure 3. Immunohistochemical staining demonstrates diffuse nuclear positivity for thyroid transcription factor-1 (TTF-1) in tumor cells, supporting pulmonary adenocarcinoma origin.

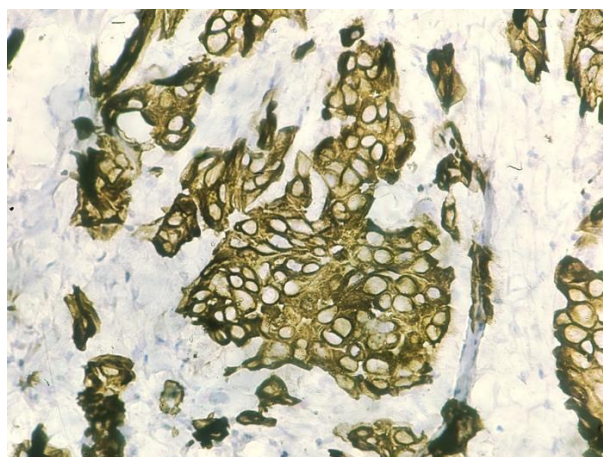


Figure 4. Immunohistochemical staining demonstrates diffuse cytoplasmic positivity for cytokeratin 7 (CK7) in tumor cells, supporting adenocarcinoma phenotype.

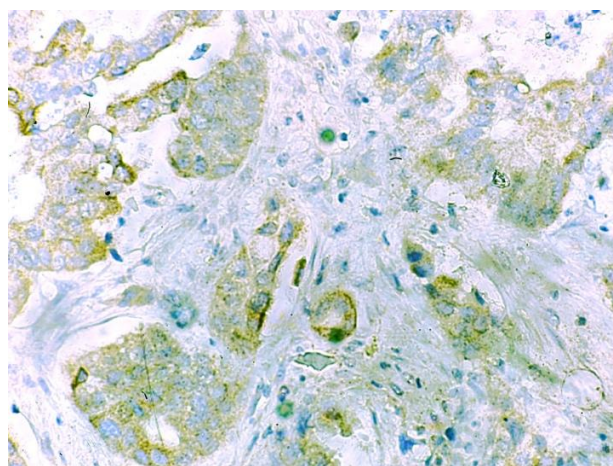


Figure 5. Immunohistochemical staining shows no significant cytoplasmic expression of cytokeratin 20 (CK20) in tumor cells

Serum tumor marker analysis demonstrated markedly elevated levels of carcinoembryonic antigen (CEA), exceeding 1000 ng/mL, and CYFRA 21-1, exceeding 500 ng/mL. It is important to note that no dilution was performed in accordance with the laboratory's standard operating procedures, indicating that the actual concentrations of both markers may have been substantially higher than reported. The degree of elevation, particularly for CYFRA 21-1, was striking and exceeded the levels typically observed in lung adenocarcinoma.

Taken together, the clinical presentation, radiological findings, histopathological confirmation, and immunohistochemical profile established the diagnosis of metastatic lung adenocarcinoma with extensive skeletal involvement. The unusually extreme elevation of CYFRA 21-1 in this case raised important considerations regarding the interpretation of tumor markers in the context of advanced disease and high tumor burden.

DISCUSSION

The case demonstrates a notable discrepancy between serum tumor marker expression and histopathological classification in advanced lung malignancy. Histopathological examination together with immunohistochemical staining conclusively established the diagnosis of pulmonary adenocarcinoma; however, the exceptionally high CYFRA 21-1 concentration was unusual because this

biomarker is classically linked to squamous cell carcinoma. In contrast, the markedly elevated carcinoembryonic antigen (CEA) level corresponded well with the glandular differentiation characteristic of adenocarcinoma. This finding suggests that serum tumor marker patterns do not invariably conform to their conventional histological associations and should therefore be interpreted within a broader diagnostic context.

One plausible explanation for the extraordinary increase in CYFRA 21-1 in this patient is the extensive metastatic burden demonstrated by diffuse spinal involvement on MRI. CYFRA 21-1 consists of soluble fragments of cytokeratin 19 that are released during epithelial cell degradation and turnover. In highly aggressive tumors, rapid proliferation, extensive invasion, and accelerated cellular destruction may result in substantial cytoskeletal disintegration, thereby increasing the release of cytokeratin fragments into the circulation. The widespread mixed lytic–blastic vertebral lesions observed in this patient further support the presence of biologically aggressive disease characterized by extensive tissue destruction and large tumor volume. Similar observations have been reported by Park et al., who demonstrated that elevated CYFRA 21-1 levels may also occur in lung adenocarcinoma, particularly in advanced-stage tumors, poorly differentiated lesions, and larger tumor masses. Moreover, elevated preoperative CYFRA 21-1 concentrations were associated with less favorable survival outcomes⁶. Increased CYFRA 21-1 levels have additionally been described in adenocarcinoma complicated by malignant pleural effusion and peritoneal metastasis, suggesting its potential utility in distinguishing malignant from benign effusions⁷.

Another mechanism that may contribute to markedly elevated CYFRA 21-1 levels is extensive tumor necrosis and apoptosis. Rapidly enlarging tumors frequently exceed their vascular supply, leading to hypoxia and subsequent cellular necrosis. This process promotes leakage of intracellular structural proteins, including cytokeratin-derived fragments, into the bloodstream. Consequently, the profound elevation of CYFRA 21-1 observed in this case is more likely to reflect aggressive tumor biology, extensive metastatic spread, and accelerated cellular turnover rather than squamous differentiation itself. Increasing evidence indicates that at very high concentrations, tumor markers may lose part of their histological specificity and instead mirror overall tumor dynamics and disease activity^{6, 8}.

Several clinically relevant points can be drawn from this case. First, interpretation of serum tumor markers should always be integrated with clinical presentation, imaging findings, histopathological examination, and immunohistochemical analysis rather than considered independently. Second, extremely elevated biomarker levels may not necessarily indicate a particular histological subtype, but instead signify extensive tumor burden and aggressive disease behavior. Third, biomarkers such as CYFRA 21-1 are more appropriately regarded as indicators of tumor activity, disease extent, and prognosis rather than definitive diagnostic tools for histological classification. Accordingly, their primary clinical value lies in monitoring disease progression, evaluating therapeutic response, and estimating prognosis. Finally, comprehensive molecular profiling, including assessment of EGFR, ALK, ROS1, BRAF, KRAS, and PD-L1 status, remains crucial in lung adenocarcinoma, particularly in younger patients, to guide personalized and targeted therapeutic approaches.

CONCLUSION

This case illustrates that markedly elevated serum tumor marker levels, particularly CYFRA 21-1, may not necessarily correspond to their traditional histopathological associations. Despite the exceptionally high CYFRA 21-1 concentration, histopathological and immunohistochemical evaluation clearly confirmed metastatic lung adenocarcinoma with extensive skeletal dissemination. The profound biomarker elevation in this patient is more likely attributable to massive tumor burden, diffuse metastatic involvement, and accelerated tumor cell destruction associated with necrosis and apoptosis rather than indicating squamous differentiation.

These findings emphasize the importance of interpreting tumor markers within an integrated diagnostic framework that incorporates clinical manifestations, radiological findings, histopathology, and immunohistochemistry. At extremely high concentrations, tumor markers may lose part of their subtype specificity and instead reflect biological aggressiveness, tumor activity, and disease extent. Therefore, biomarkers such as CYFRA 21-1 are likely to provide greater clinical utility for prognostic assessment, treatment monitoring, and evaluation of disease progression rather than serving as definitive indicators of tumor histology. In addition, comprehensive molecular characterization remains essential in patients with lung adenocarcinoma to support individualized therapeutic decision-making and targeted treatment strategies.

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