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AGGRESSIVE LUNG ADENOCARCINOMA PRESENTING WITH EXTENSIVE LYMPHADENOPATHY MIMICKING LYMPHOMA: A DIAGNOSTIC CHALLENGE

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ABSTRACT

Micropapillary adenocarcinoma represents uncommon but highly aggressive variant of non-small cell lung cancer (NSCLC), identified for a tendency for early micro metastasis, especially to mediastinal and extra thoracic lymph nodes. The report presents a case of a 61-year-old male diagnosed with lung adenocarcinoma, characterised by rapid clinical progression. The patient experienced two hospitalisations, with a diagnostic process that was both prolonged and complex. Initially, a suspected right lung mass was identified, which was subsequently reevaluated as a potential lymphoma. After three weeks of initial admission, the patient exhibited getting worse clinical and radiological signs, including superior vena cava syndrome (SVCS), requiring emergency intervention before a confirmed cancer diagnosis. Despite the performance of both bronchoscopy and an excisional biopsy of supraclavicular lymphadenopathy, a definitive diagnosis was not accomplished. Lung adenocarcinoma was eventually confirmed after two procedures of histopathological evaluation of fine-needle aspiration biopsy (FNAB) specimens. The patient's condition got worse, lead to death shortly after diagnosis, prior to the administration of chemotherapy. This case highlights the significant effects of diagnostic delay in aggressive lung cancer subtypes, emphasising the necessity of early identification and prompt treatment to enhance prognosis and survival outcomes.

Keywords: Adenocarcinoma, Micrometastasis, Micropapillary, Lymphadenopathy, Lymphoma

INTRODUCTION

Lung cancer continues to be a primary contributor to cancer-related mortality globally. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and is recognized for its capacity to spread micrometastases by blood vessels and lymphatic paths. Lymph node micrometastases are particularly frequent in NSCLC, especially within the adenocarcinoma subtype, occurring in about 30–40% of cases. Micrometastases are frequently challenging to detect in the early stages of disease and may act as preliminary indicators of aggressive tumor progression, occasionally occurring before the definitive diagnosis of lung adenocarcinoma. The detection of lymphatic micrometastases presents a considerable diagnostic challenge, potentially leading to delays in timely and accurate diagnosis.[1,2]

The role of lymph nodes is essential in the staging of lung cancer and is significantly associated with decreased patient survival rates. Lymphatic metastasis in pulmonary adenocarcinoma typically progresses at a slower rate compared to hematogenous spread, leading to earlier involvement of distant or extrapulmonary organs.[3] Wang et al. (2020) indicated that metastasis may arise in the early stages of lung adenocarcinoma, with a prevalence of 21.7%.[4] The observed discrepancy can be attributed to the histological diversity of lung adenocarcinoma, which includes various subtypes that exhibit distinct biological behaviors and metastatic patterns.[5]

Park et al. (2017) created a significant correlation of the histological subtype of lung adenocarcinoma and patient prognosis as well as overall survival. Adenocarcinoma subtype classification is correlated with the presence of lymph node micrometastases, irrespective of primary tumor size. The diverse histological characteristics of adenocarcinoma subtypes present a diagnostic challenge, particularly when significant lymph node involvement across various regions complicates the differentiation between lung adenocarcinoma and lymphoma.[5,6] We present the case of a 61-year-old male initially suspected to have lymphoma based on multiple lymphadenopathies spanning from the mediastinum to the inguinal regions. Further assessment validated the diagnosis of lung adenocarcinoma. The delay in accurate diagnosis adversely impacted the patient's prognosis, causing to a reduced survival duration prior to the initiation of appropriate therapy.

CASE

A 61-year-old heavy-smoking male was admitted twice within a three-month interval due to varying and progressively worsening clinical symptoms. Radiological discrepancies caused differential diagnoses of lung cancer and lymphoma. The patient's clinical and imaging decrease progressed, leading to a delayed diagnosis and delay of treatment initiation for three months. He initially came to the Pulmonology Clinic on January 27, 2024, indicating right-sided chest pain and a productive cough that had persisted for one week. The chest x-ray indicated right perihilar thickening, leading to a diagnosis of acute bronchitis (Figure 1a). The patient demonstrated clinical improvement after receiving symptomatic treatment.

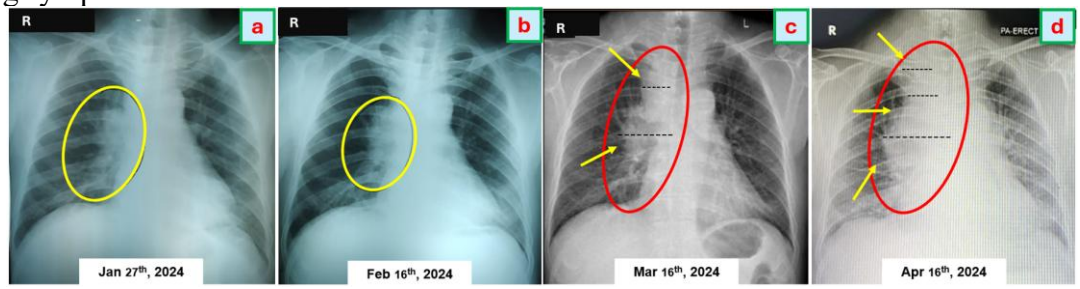

Figure 1. Serial Chest X-ray during Outpatient and Hospitalization

(a) and (b) CXR during outpatient care found hilum thickening on the right perihilar;
(c) First hospitalization showed worsening CXR with inhomogeneous consolidation from perihilar to right paratracheal;
(d) The second hospitalization showed an increase in the diameter of the homogeneous consolidation size from the perihilar to the right paratrachea which also extended to the supraclavicular right.

He returned on February 16, 2024, with current right chest pain and a productive cough, now associated with anorexia and weight loss. The repeat chest X-ray demonstrated consistent findings of right perihilar thickening (Figure 1b). Symptomatic treatment was administered, and additional diagnostic evaluation was advised. A contrast-enhanced thoracic CT scan was recommended based on the suspicion of a tumor in the right lung.

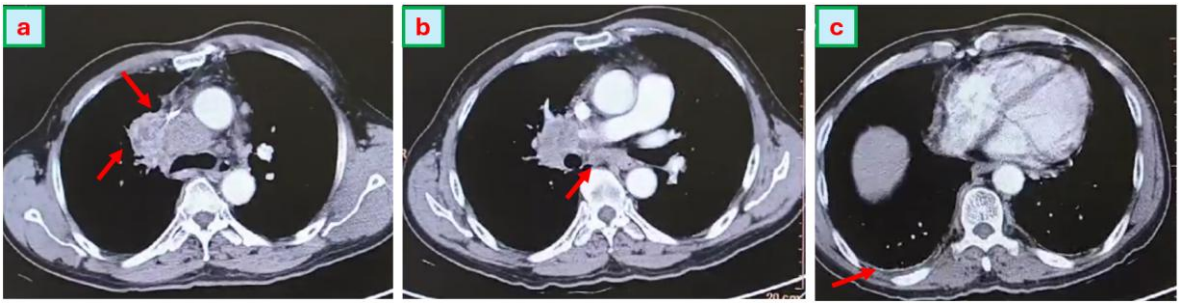

Figure 2. Thoracic CT scan with Contrast at First Hospitalization
(a) Lung mass measuring 3.8 × 4.0 cm right perihilar, along with ipsilateral perihilar lymphadenopathy (10R); (b) Lymphadenopathy of the subcarinal (7); (c) Minimal right pleural effusion

On March 16, 2024, the patient was admitted to Arifin Achmad General Hospital in Pekanbaru for advanced diagnostic evaluation. The patient reported present right chest pain, a productive cough, reduced appetite, and a weight loss of 9 kg over the last two months. A physical examination identified a 4 x 5 cm mobile; non-tender mass located in the right supraclavicular region. Vital signs were still stable: blood pressure 130/71 mmHg, pulse 88 beats per minute, respiratory rate 21 breaths per minute, temperature 36.7°C, and oxygen saturation 98% in room air. Lung auscultation showed normal vesicular breath sounds without any adventitious sounds.

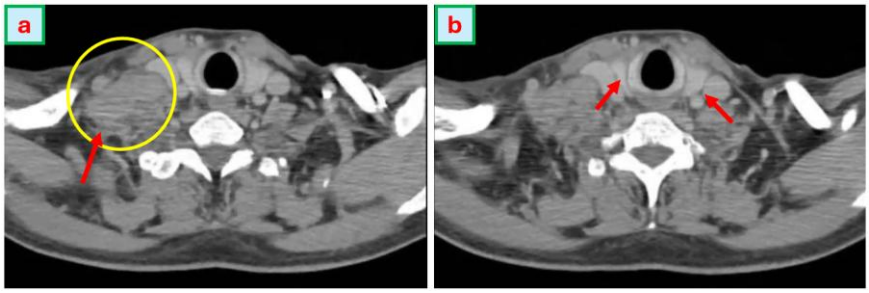

Figure 3. Neck CT scan with Contrast
(a) Solid mass, lobulated, irregular 5.6 x 5.6 x 4.1 cm in the supra clavicula dextra region; (b) Bilateral thyroid nodules, 5 mm on the right and 7 mm on the left

Chest X-ray showed inhomogeneous consolidation extending from the right paratracheal to the perihilar region, indicating radiological progression (Figure 1c). The CT scan of the thorax with contrast showed a 3.8 x 4 cm mass located in the anterior segment of the right lung, showing post-contrast enhancement. Additionally, lymphadenopathy was found subcarinal, perihilar, and right paratracheal regions, along with minimal right pleural effusion (Figures 2a–c). A neck CT with contrast showed a lobulated, irregular solid mass measuring 5.6 x 5.6 x 4.1 cm at right supraclavicular region, showing heterogeneous enhancement. In addition, bilateral thyroid nodules were identified, 5 mm on the right and 7 mm on the left (Figure 2). The brain CT scan with contrast showed no evidence of intracranial metastases (Figure 3). Abdominal ultrasound shown an absence of metastases in the liver, spleen, kidneys, lymphadenopathy of paraaortic and suprarenal (Figure 5a).

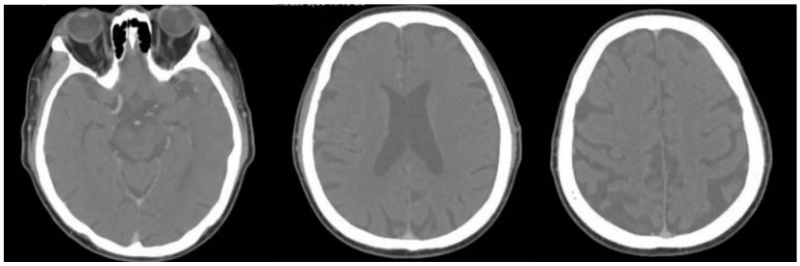

Figure 3. Brain CT scan with Contrast: No visible intracranial metastases

Bronchoscopy showed bilateral vocal cord edema and decompression stenosis at the orifice of the anterior segment (B3) of the right upper lobe (Figure 4). Forceps biopsy, bronchial washing, and brushing of B3 resulted in negative results for malignancy. The excisional biopsy of the right supraclavicular lymph node showed non-specific chronic lymphadenitis (Figure 7a). The patient got initial treatment for two weeks waiting histopathology results. The definitive diagnosis was right lung adenocarcinoma T4N3M1c1 (pleura, bilateral thyroid nodules) Stage IVB ECOG Performance Status 2.

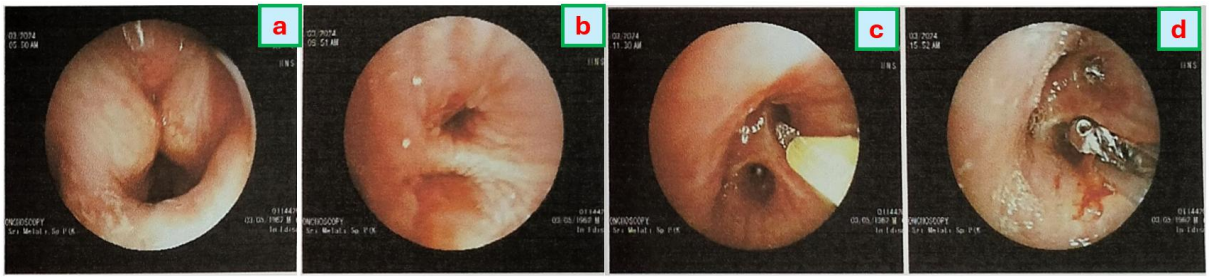

Figure 4. Bronchoscopy Procedure at First Hospitalization

(a) Bilateral vocal cord edema; (b) Hyperemic mucosa and decompression stenosis at the orifice of the anterior segment (B3) of the right upper lobe; (c) Brushing bronchial; (d) Forceps biopsy

The patient's condition got worse before follow-up and was eventually referred to Adam Malik General Hospital, Medan, on April 16, 2024. The patient showed progressive dyspnea over five days, bilateral limb swelling, and venous distension in the right subclavian region, suggestive of superior vena cava syndrome (SVCS). Other symptoms noticed was chronic cough, significant cancer-related pain (VAS 7), and dysphagia. Vital signs indicated blood pressure of 145/87 mmHg, heart rate of 121 bpm, respiratory rate of 28/min, temperature of 37°C, and oxygen saturation at 95% with 5 L/min via nasal cannula. The physical examination showed an enlarged right supraclavicular mass measuring 6 x 7 cm, venous distension in the right subclavian region, and bilateral limb edema.

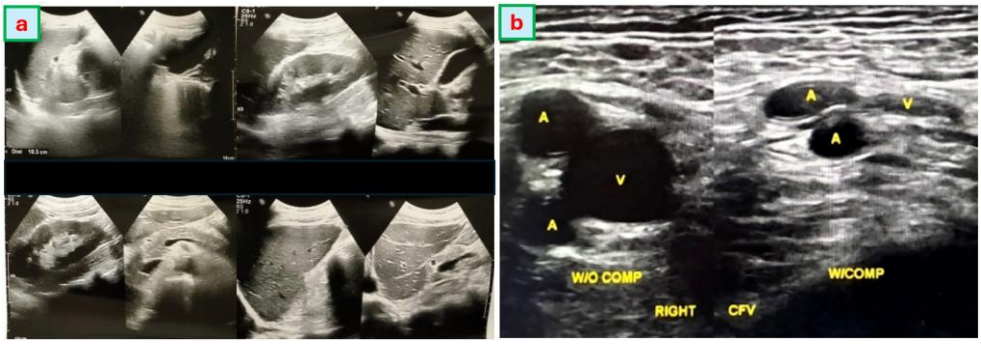

Figure 5. (a) Abdominal Ultrasound: No visible metastases in liver, spleen, kidneys, lymphadenopathy of paraaortic and suprarenal;
(b) Bilateral femoral and bilateral popliteal vein of DVT, Edema with bilateral popliteal venectases, Bilateral inguinal multiple lymphadenopathy

The chest X-ray showed an increase in homogeneous consolidation extending from the right paratracheal to the perihilar region if compared to previous examination (Figure 1d). The patient had urgent radiotherapy, completing 10 cycles for Grade 2 SVCS. Doppler ultrasound of the lower extremities showed bilateral deep vein thrombosis (DVT) in the femoral and popliteal veins, along with oedema, venous distension in the popliteal regions, and bilateral inguinal lymphadenopathy (Figure 5b). Tumour marker analysis indicated LDH at 246 U/L, AFP at 4.72 ng/mL, PSA at 4.1 ng/mL, CEA at 4.79 ng/mL, and Cyfra 21-1 at 11.2 ng/mL.

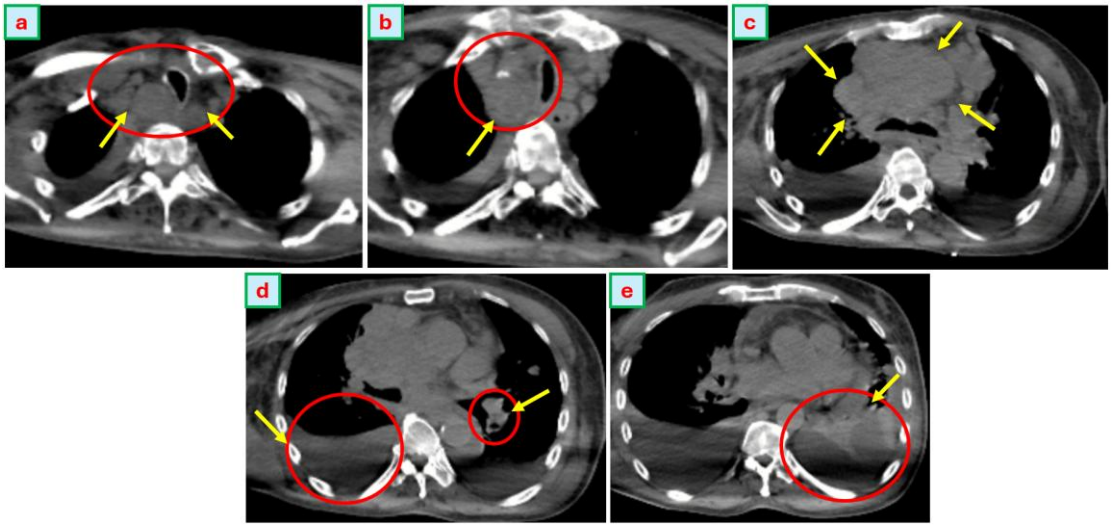

Figure 6. Thoracic CT scan with Contrast at Second Hospitalization
(a) Bilateral supraclavicular lymphadenopathy (1RL) and bilateral thyroid nodules
(b) Bilateral upper paratracheal (2RL) and subcarinal (7)
(c) Anterior mediastinal mass with necrotic component encasing superior vena cava and lymphadenopathy in bilateral lower paratrachea (4RL), ipsilateral perihilar lymphadenopathy (10R)
(d) Right pleural effusion with component of atelectasis in the lower lobe of the right lung and bilateral nodules 1-1.5 cm
(e) Left pleural effusion with a component of left lung lower lobe atelectasis with cardiomegaly and pericardial effusion

A subsequent contrast-enhanced thoracic CT scan performed after four cycles of radiotherapy in the second treatment course showed an anterior mediastinal mass with associated lymphadenopathy in the bilateral paratracheal, subcarinal, perihilar, para-aortic, and supraclavicular. The mass encased the superior vena cava. Bilateral upper lobe nodules measuring 1-1.5 cm appeared in segment 3 of both lungs. Bilateral pleural effusions and atelectasis in the lower lobes were noticed. Cardiomegaly, accompanied by left ventricular enlargement and pericardial effusion, was observed. The results show radiologic progression compared to the before thoracic CT scan and suggest lymphoma, as indicated by bilateral lower lobe atelectasis, bilateral pleural and pericardial effusions, and a contralateral left upper lobe nodule (Figure 6a-e).

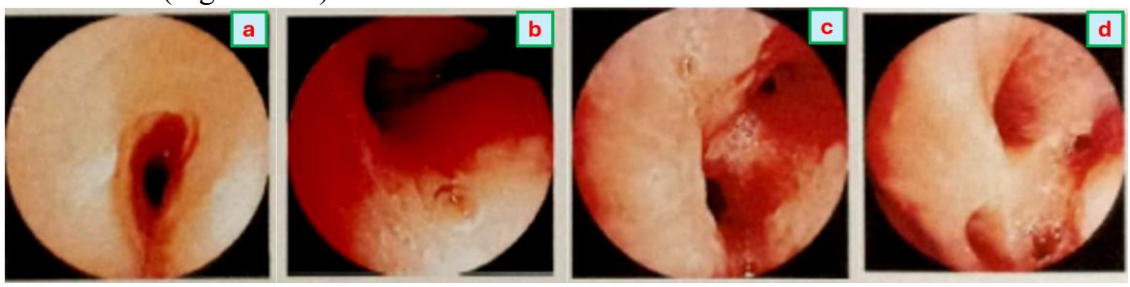

Figure 7. Bronchoscopy Procedure at Second Hospitalization
(a) Lumpy mucosa of the irregular trachea; (b) Blunt Karina;
(c) Open orifice and hyperemic mucosa; (d) Infiltrative stenosis in the right upper lobe

Following the fifth cycle of radiotherapy, a repeat bronchoscopy showed notable mucosal nodularity along the trachea, nodules present in the right bronchial branches, and infiltrative stenosis at the orifice of the right upper lobe (Figure 7a-d). Bronchial washing and forceps biopsy from the right upper lobe orifice showed squamous metaplasia accompanied by atypical cells. After the eighth cycle of radiotherapy, FNAB of the right supraclavicular region showed a malignant smear (C5) indicative of metastatic adenocarcinoma (Figure 8a). Histopathological slides had two reviews, confirming the presence of adenocarcinoma (Figure 8b).

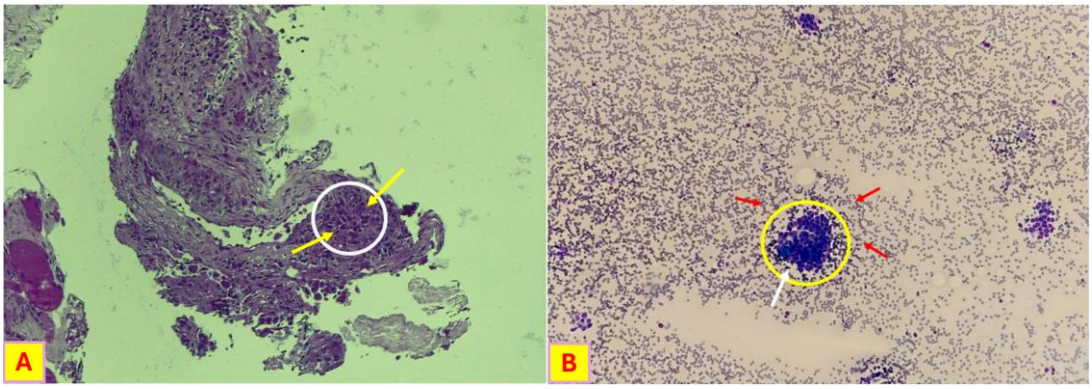

Figure 8. Anatomic Pathology Result of Right Supraclavicular Lymph Node
(a) Excision biopsy: Focus cells of circular shape are relatively large, hyperchromatin, and less cytoplasm;
(b) FNAB: Pleomorphic epithelial cells that are mostly acinar have round and oval enlarged cell nuclei, an irregular nuclear membrane, gross chromatin, and a smear background consisting of red blood cells

Integrating all clinical and diagnostic data, the patient was diagnosed with stage IVB right lung adenocarcinoma, T4N3M1c1, with pleural, pericardial, contralateral pulmonary, and bilateral thyroid involvement. He had ECOG performance status 2, Grade 2 SVCS, and concomitant DVT. Chemotherapy with carboplatin and paclitaxel was planned following completion of 10 radiotherapy cycles. Unfortunately, the patient died on day 21 of treatment due to type 2 respiratory failure shortly after the tenth radiotherapy session.

DISCUSSION

A significant difference was noticed between the patient's first and second hospitalizations about physical examination findings, radiological imaging, and anatomical pathology results. The rapid decrease in clinical status significantly contributed to the delaying of diagnosis and the initial start of treatment. The emergence of dyspnea with bilateral limb edema significantly confirmed the clinical diagnosis of superior vena cava syndrome, illustrating the necessity for quickly palliative radiotherapy. A comparative analysis of thoracic CT scans from the two hospitalizations indicated the development of ongoing mediastinal mass along with extensive lymphadenopathy impacting multiple nodes stations. The diagnosis was ultimately confirmed by FNAB, showing metastatic adenocarcinoma.

The case shows the histological variety of lung adenocarcinoma and the potential for early micrometastasis, even in the event of small primary lesions. Zhang et al. (2023) describe lung adenocarcinoma as a malignancy with different histological subtypes, each with different metastatic potentials, especially regarding early lymphatic promotion.[7] Micrometastasis indicates the spread of malignant cells across distant tissues or organs without the presence of a significant tumor nodule or visible clinical manifestations.[8] Several research studies show that lesion diameter and invasion depth, evaluated through radiologic modalities, can predict micrometastasis in lung adenocarcinoma, particularly in tumors categorized as T1 (<3 cm).[3]

Lung adenocarcinoma lesions generally located peripherally and infrequently show extensive lymphadenopathy involving mediastinal to infradiaphragmatic nodes. Several studies show no significant correlation between tumor location (central versus peripheral) and micrometastatic spread. Centrally located lung adenocarcinoma lesions show a higher propensity for mediastinal and extra thoracic lymph node metastasis, related to the solid nodes connect visible in the central lung region.[8-10] This case illustrates invasive lymphatic spread, with metastases exceeding bilateral inguinal lymph nodes, an atypical location given the infradiaphragmatic location. Inguinal lymph node metastasis is predominantly linked to primary tumors beginning from the genital, anorectal, cutaneous, or urinary tracts.[11]

Infradiaphragmatic nodes involvement in lung adenocarcinoma shows progressed and aggressive malignancy. Histologic subtype classification is a significant prognostic factor for lymph node metastasis in lung adenocarcinoma. Node metastases significantly impact patient survival and clinical outcomes.[8] Lung adenocarcinoma is categorized into six primary histologic subtypes: lepidic, acinar, papillary, micropapillary, solid, and variants. The micropapillary subtype is significantly correlated with an increased risk of mediastinal and extrathoracic (N2–N3) lymph node metastases. Initial radiologic examination focusing on tumor measurements and depth may assist in predicting nodes contribution.[8-10]

Circulating tumor DNA (ctDNA) analysis is increasingly suggested to improve early detection and monitoring of disease progression in NSCLC, particularly lung adenocarcinoma, to identify minimal residual disease and lymph node micrometastasis. Tumor markers assist in the characterization of the tumor load and metastatic potential. Cyfra 21-1, a fragment of cytokeratin 19, suggests effectiveness for assessing tumor location and metastatic spread, especially in mediastinal and lung lesions.[12,13]

In cases of enlarged lymph nodes, image-guided biopsy is an acceptable technique for confirming metastatic involvement and enabling diagnosis. Surgical resection is the primary treatment for early-stage lung adenocarcinoma (T1/T2), often followed by adjuvant chemotherapy or immunotherapy to decrease recurrence risk. Current research shows that patients with lung adenocarcinoma and lymphadenopathy (N2/N3) can profit from combined modality treatment, which integrates radiotherapy with systemic immunotherapy or chemotherapy, to target both local and micrometastatic disease. Several randomized controlled trials indicate that adjuvant immuno/chemotherapy, especially in micropapillary subtype lung adenocarcinoma at stages I and II, significantly increases 5-year survival rate ($p< 0.0004$).3,12,14 The above points to the importance of accurate diagnostic evaluation to identify micrometastasis early and educate aggressive multimodal approaches to treatment.

This case highlights the diagnostic challenges related to invasive small-sized lung adenocarcinoma that offers with extensive lymphadenopathy, which can resemble lymphoma. It points to the need for a multidisciplinary strategy involving clinical evaluation, advanced imaging, histopathology, and molecular diagnostics. Timely identification and comprehensive staging are essential for enhancing patient prognosis and survival rates. Future research should concentrate on advancing non-invasive biomarkers and imaging methods to improve the detection of micrometastases and adjust treatment strategies.

CONCLUSION

The case represents the diagnostic and therapeutic challenges associated with small-sized, invasive lung adenocarcinoma that presents with extensive lymphadenopathy, similar to hematologic malignancy. Although categorized as early-stage because of tumor size, these lesions may exhibit aggressive biological characteristics and show extensive micrometastatic spread, especially in histological subtypes such as the micropapillary variant. Conventional imaging frequently ignores illness degree, displaying the significance of including advanced diagnostic methods, such CYFRA 21-1 as serum tumor markers, focused on lymph node biopsy, and new methods such as ctDNA assays.

Recognizing that tumor size and location do not fully capture metastatic potential, this case highlights the pivotal role of a multidisciplinary approach in achieving accurate staging and expediting therapeutic decisions. Timely surgical resection remains the cornerstone of treatment, but in patients with nodal involvement or suspected micrometastases, systemic immunochemotherapy and radiotherapy are essential components to optimize outcomes. Early identification and comprehensive assessment of micrometastases is important for preventing treatment delays and educating personalized oncologic approaches. This case emphasizes the necessity for increased clinical alertness to identify small nevertheless innately aggressive lung adenocarcinomas, which may exhibit characteristics similar to non-lung malignancy such as lymphoma.

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CONFLICT OF INTEREST
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ETHICAL APPROVAL AND INFORMED CONSENT
Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY
The data supporting this research are available from the authors on reasonable request.

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AUTHOR'S CONTRIBUTION
ETMS and EMDS: literature search and manuscript preparation.
ETMS and EMDS: data collection.
SMM, AM, IFR, DK, and SE: review of manuscript.
All authors approval of the final version of the manuscript.

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