Subcentimeter lymphadenopathy portended advanced lung adenocarcinoma diagnosed via endobronchial ultrasound: a case report

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Background: Low dose computed tomography (LDCT) screening and the Lung Imaging Reporting and Data System (RADS) system have led to earlier diagnoses of lung cancer, a leader of cancer mortality. However, no guidelines direct management of incidental subcentimeter lymphadenopathy on LDCTs, which may portend spread of malignancy, especially when enlarged to ≥1.0 cm. Clinical significance of incidental mediastinal lymphadenopathy is even less certain without a suspicious parenchymal lesion. We report endobronchial ultrasound (EBUS) sampling of enlarging subcentimeter mediastinal lymphadenopathy on LDCT without parenchymal lesions to diagnose advanced non-small cell lung carcinoma (NSCLC).

Case Description: A 74-year-old African American man with chronic obstructive pulmonary disease (COPD) and a 20 pack-year smoking was found to have a 3.8 cm × 4.9 cm thin-walled cyst in the right lower lobe among emphysematous changes and was deemed Lung RADS category 1s on LDCT screening. The patient reported only mild cough, without dyspnea, and was exacerbation-free for over one year. Subsequent LDCT demonstrated 4 and 5 mm right upper lobe subpleural nodules, enlargement of paratracheal lymph nodes measuring up to 8 mm, and stability of the parenchymal cyst. Findings were categorized as Lung RADS 3. Reporting weight loss as well, the patient underwent EBUS. Histopathology from 2 of 4 lymph node stations confirmed poorly differentiated lung adenocarcinoma. Positron emission tomography (PET) scanning staged the patient as stage IIIB, who then completed weekly carboplatin [area under the curve (AUC) 2] and paclitaxel (45 mg/m^2) for 7 weeks, followed by two, weekly-administered consolidation doses, followed by 30 fractions of 200 cGy (total 6,000 cGy) over 50 days. The patient then began maintenance immunotherapy with durvalumab 1,500 mg intravenous (IV) every 4 weeks. Follow-up fifteen months later revealed improved symptoms on continued maintenance durvalumab.

Conclusions: While LDCT significantly improved the rate of detection of lung lesions suspicious for malignancy, conventional guidelines have not supported sampling of subcentimeter lymphadenopathy. Our patient's diagnosis of stage IIIB adenocarcinoma of the lung with subcentimeter lymph nodes, absent a suspicious lung nodule, emphasizes the importance of clinical judgment in evaluating the risk of malignancy in evolving mediastinal lymphadenopathy.

Keywords: Lymphadenopathy; endobronchial ultrasound (EBUS); low dose computed tomography (LDCT); case report; lung cancer

Received: 21 March 2023; Accepted: 09 April 2024; Published online: 06 June 2024.

doi: 10.21037/amj-23-189

View this article at: https://dx.doi.org/10.21037/amj-23-189

Introduction

Background

Lung cancer is the leading cause of cancer-related mortality globally (1). US Preventive Services Task Force (USPSTF) guidelines promoting low dose computed tomography (LDCT) have allowed for earlier diagnoses and treatment for patients with lung cancer, resulting in improved survival (2). Occasionally, pathological enlargement of the lymph nodes of the mediastinum will be detected on LDCT and may be the first sign to portend malignancy or its spread. While LDCT has been established to risk stratify lung nodules, there are no clear guidelines on the management and follow up of isolated mediastinal lymphadenopathy (IML) incidentally found in these patients.

Convex-probe endobronchial ultrasound (CP-EBUS) describes a flexible fiberoptic bronchoscope with 7.5 MHz convex side-viewing transducer which is used to visualize lymphadenopathy at anatomically typical locations. CP-EBUS allows for transbronchial needle aspiration (TBNA) by deploying a 19–22-gauge (3) biopsy needle into the visualized lymph node. EBUS with TBNA is considered a relatively low risk procedure, typically performed in the outpatient setting (4).

Highlight box

Key findings

- A 74-year-old African American man with a 20-pack-year smoking history had new mediastinal lymphadenopathy measuring up to 8 mm as well as 4 and 5 mm subpleural nodules. By way of endobronchial ultrasound (EBUS) with transbronchial needle aspiration (EBUS-TBNA), histopathology of 2 of 4 sampled lymph node stations confirmed the diagnosis of stage IIIB adenocarcinoma of the lung.

What is known and what is new?

- Low dose computed tomography (LDCT) can detect early stages of lung cancer, but there is less information regarding management of subcentimeter mediastinal lymphadenopathy in the absence of overtly suspicious lung parenchymal lesions.
- High risk patients with constitutional symptoms who present with subcentimeter lymphadenopathy on LDCT may have advanced cancer, and prioritizing tissue sampling with EBUS-TBNA can lead to earlier detection and treatment of non-small cell lung carcinoma (NSCLC).

What is the implication, and what should change now?

- Advanced cancer may present as less-suspicious pulmonary nodules and subcentimeter lymphadenopathy. This case report suggests new guidelines should be developed to incorporate lymphadenopathy seen on LDCT into clinical decision-making. Additional risk stratification and classification tools as well as increased clinician awareness may lead to improved early detection of NSCLC.

Rational and knowledge gap

EBUS with TBNA biopsy is the standard of care in pulmonary medicine to assess tumor invasion, mediastinal lymph node enlargement, and obtain tissue samples of suspicious nodes. A retrospective review (5) of the National Lung Screening Trial demonstrated the increased risk of malignancy with lymphadenopathy using a size criteria cut off of ≥1.0 cm in diameter. However, there are no evidence-based guidelines establishing when subcentimeter mediastinal lymph nodes should undergo biopsy by invasive procedures, especially in minimally symptomatic patients. We report the use of EBUS-guided biopsy of mediastinal and hilar lymph nodes to diagnose and stage the presence of lung adenocarcinoma despite no suspicious parenchymal lesions on LDCT.

Objective

We aim to demonstrate the need for additional study and characterization of the clinical significance of subcentimeter lymphadenopathy in patients at high risk for lung malignancy. We present this case in accordance with the CARE reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-189/rc).

Case presentation

A 74-year-old African American male with a past medical history of hypertension, chronic obstructive pulmonary disease (COPD), myocardial infarction, cerebral vascular accident, opioid use disorder, and a 20-pack-year smoking history who quit in 2020, and no personal nor family history of cancer, had his first LDCT scan performed in April 2021. This scan was the first in an intervention cascade detailed in *Figure 1*.

The April 2021 LDCT revealed a 3.8 cm × 4.9 cm thin-walled cyst in the right lower lobe, bilateral paraseptal emphysema, and no parenchymal lung nodules. The scan was designated category Lung Imaging Reporting and Data System (Lung RADS) 1s per American College of Radiology guidelines. His second LDCT was performed in June 2022, which revealed two new subpleural nodules in

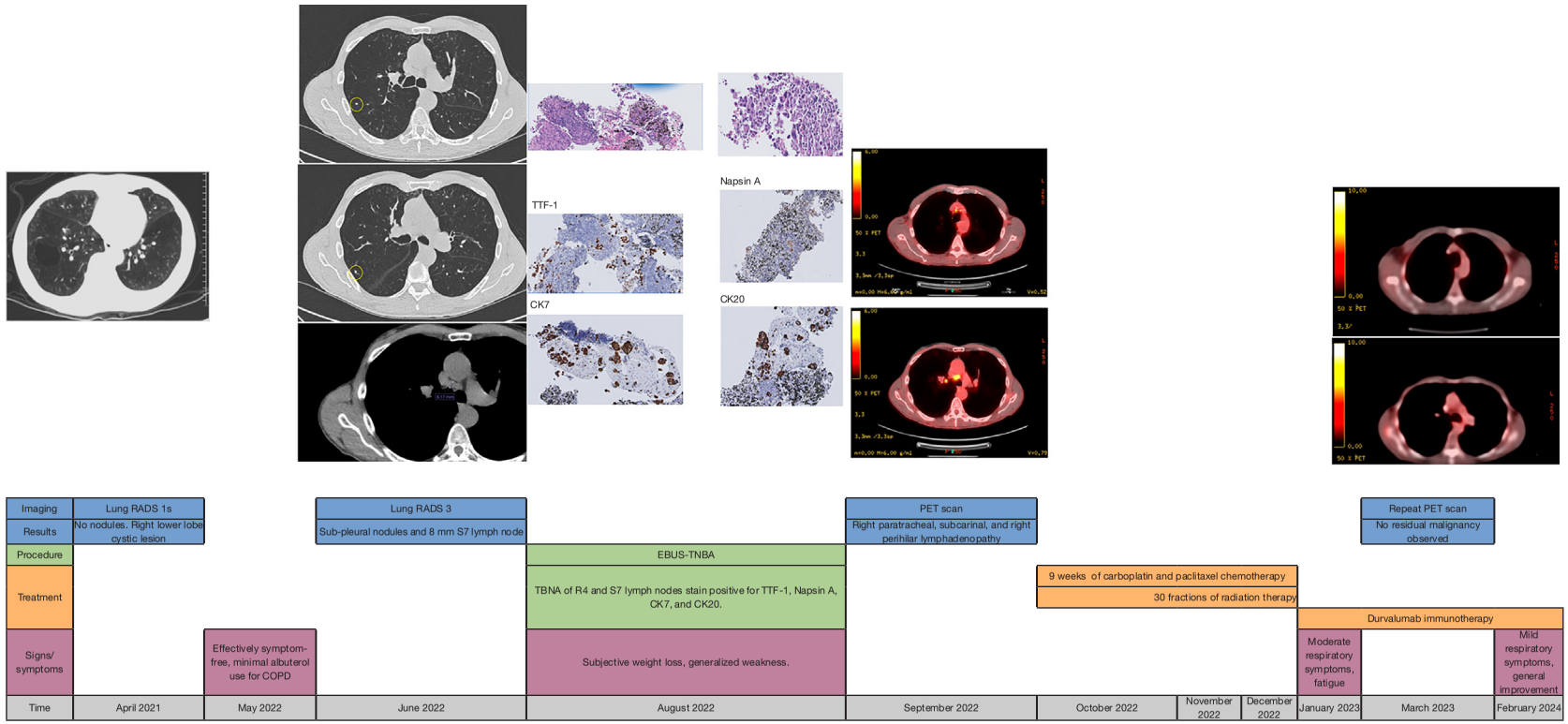

Figure 1 Timeline of patient interventions from April 2021 to February 2024. (Leftmost): April 2021, thin-walled cyst 3.8 cm × 4.9 cm in right lower lobe, Lung RADS 1s. (Second from left): June 2022, subpleural nodules 4 mm (top) and 5 mm (middle) (highlighted by yellow circles) with 8 mm paratracheal lymph node (bottom), Lung RADS 3. (Third from left, top): August 2022, transbronchial biopsy (left) with magnified view (right) demonstrating prominent glandular cells. (Third from left, middle and bottom): August 2022, TBNA biopsy of R4 and S7 lymph nodes stain positive for CK7, CK20, Napsin A, and TTF-1 (labeled). (Fourth from left): September 2022, PET scan demonstrating PET-avid right paratracheal (top) as well as subcarinal and perihilar lymphadenopathy (bottom). (Rightmost): March 2023, Resolution of PET-avidity of the right paratracheal (top) as well as right hilar and subcarinal (bottom) lymphadenopathy. Lung RADS, Lung Imaging Reporting and Data System; COPD, chronic obstructive pulmonary disease; EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration; CK7, cytokeratin-7; CK20, cytokeratin-20; TTF-1, thyroid transcription factor-1; PET, positron emission tomography.

the right upper lobe, measuring 4 and 5 mm, with multiple upper and lower paratracheal lymph nodes the largest of which measuring 8 mm. The previously seen thin-walled cyst was unchanged, and the scan designated Lung RADS 3.

At a follow up appointment August 2022, the patient had reported subjective weight loss, therefore after thorough discussion with the patient regarding risk of malignancy, he agreed to undergo EBUS-TBNA of the lymph nodes over continued surveillance with chest CT scans. Later that month, utilizing a BF-UCF180F Model CP-EBUS scope and a 21-G Boston Scientific Acquire EBUS needle, TBNA was performed of left hilar lymph nodes L10 and L11, the subcarinal lymph node, S7, and a right paratracheal (R4) lymph node under general anesthesia. Additional ultrasound scanning did not reveal adequate targets for TBNA biopsy. Histopathology of lymph nodes S7 and R4 showed minute foci of poorly differentiated non-small cell carcinoma. Immunostaining confirmed tumor cells positive for cytokeratin-7 (CK7) and cytokeratin-20 (CK20), as well as thyroid transcription factor-1 (TTF-1) and Napsin A while negative for p40, confirming the diagnosis of poorly differentiated lung adenocarcinoma. The left hilar lymph nodes revealed only lymphoid tissue.

A positron emission tomography (PET) scan subsequently obtained in September, 2022 demonstrated hypermetabolic mediastinal and hilar lymph nodes and a 1.1 cm superior mediastinal lymph node without the presence of a primary tumor and increased size of the paratracheal lymphadenopathy.

Per the 8th edition of the TNM (tumour-node-metastasis) classification method for non-small cell lung carcinoma (NSCLC), the patient was diagnosed as TxN3M0, stage IIIB poorly differentiated adenocarcinoma. In October 2022, the patient began weekly carboplatin [area under the curve (AUC) 2] and paclitaxel (45 mg/m^2) for 7 consecutive weeks, followed by two, weekly-administered doses of consolidation chemotherapy, and subsequently maintenance durvalumab 1,500 mg intravenous (IV) every 4 weeks. Beginning November 2022, the patient also underwent radiation therapy of 200 cGy administered at 30 fractions for a total of 6,000 cGy over a 50-day period finishing in December 2022. During routine clinic follow-up in January 2023 the patient reportedly tolerated treatment well, though had moderate dyspnea on exertion. Follow up PET scan performed March of 2023 demonstrated dramatic response to treatment and no residual lesions suggestive of active malignancy.

At the patient's clinic visit in February 2024, the patient reported feeling generally well, with only mild intermittent dyspnea. No adverse or unanticipated events were experienced by the patient during biopsy nor subsequent treatment. He continues on maintenance durvalumab therapy.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Key findings

Given that LDCT is used as a screening tool for lung cancer per USPSTF guidelines for patients at elevated risk, incidentally found lymphadenopathy, even in the absence of a pulmonary mass or nodule, is more likely to represent metastatic disease than in the general population. Additional inquiry is needed to properly characterize the additional risk of malignancy from isolated subcentimeter lymphadenopathy.

Our case describes how patients enrolled in LDCT screening programs who have IML may have a higher pretest probability for malignancy than previously thought. Though the utility of EBUS-TBNA has been firmly established as a sensitive and minimally invasive approach for diagnosis and staging of NSCLC, there are currently no clear guidelines for its use to sample mediastinal lymphadenopathy in absence of a suspicious lung nodule or mass. The importance of this is highlighted in a retrospective analysis of the National Lung Cancer Screening Trial (NLST) reported by Chalian *et al.* (5). In this study, mediastinal lymph node enlargement was defined as being greater than or equal to 1.0 cm in the shortest axis. Among NLST study participants, 1.6% were described as having approximately four times higher the risk of being diagnosed with lung cancer in the next 7 years than participants with no lymph node enlargement (17.1% *vs.* 3.9%, respectively). Expectedly, the presence of mediastinal lymphadenopathy correlated positively with earlier detection of lung cancer diagnosis, higher stage at time of diagnosis, and higher overall and lung cancer-related mortality. These findings emphasize the importance of prompt diagnosis and intervention if warranted for patients with significant

mediastinal lymphadenopathy. Notably, the participants in this study had pulmonary parenchymal lesions suspicious for malignancy, absent in the patient in this case report.

Strengths and limitations

A few limitations of the report were noted. This single-patient case report lacks the weight to change any professional societal guideline, however our aspiration is that it would add to a potentially growing body of data to better characterize the clinical significance of subcentimeter lymphadenopathy in the proper clinical context. Also of note, LDCTs are non-contrast studies that may underestimate the size and prevalence of lymphadenopathy. The interpreting radiologist of the patient's first LDCT included the (s) designation, included in approximately 10% of Lung RADS-categorized scans to suggest a potentially significant finding not necessarily related to malignancy (6). Current Lung-RADS classification criteria does not provide specific recommendations for follow up of IML absent other pulmonary abnormalities suggestive of malignancy, yet the (s) designation may have influenced the pretest probability of EBUS-TBNA in diagnosing malignancy. Similarly, contrary to the recommendations of Chalian *et al.* (5) of a whole-body PET/CT scan within 3 months of IML before tissue sampling, the patient underwent EBUS-TBNA first and subsequent PET scanning was performed for staging purposes. If obtained before the biopsy, the PET scan may have strengthened the clinical indication and increased pretest probability of the biopsy as well. Though the clinical decision to proceed with biopsy rather than serial imaging likely led to more prompt diagnosis and treatment halting further spread of the malignancy.

Comparison with similar research

Current American College of Chest Physicians (ACCP) guidelines recommend sampling lymph nodes greater than 5 mm when diagnosing and staging lung cancer. ACCP guidelines note that negative ^{18}F-fluorodeoxyglucose (^{18}F-FDG) avidity is valid for mediastinal lymph nodes even if they are less than 1 cm in the short axis, however, tissue sampling is recommended when lymph nodes are PET-avid, the tumor is central, hilar lymph nodes are PET-avid, or for any mediastinal node is larger than 1 cm in the short axis (regardless of ^{18}F-FDG avidity) (7).

Some studies have investigated the use of EBUS-TBNA to evaluate IML. Velu *et al.* (8) performed biopsies on patients with mediastinal or hilar lymph node enlargement >1 cm without the presence of an obvious associated malignancy. In these cases, EBUS-TBNA was used to diagnose malignancy in 25% of the sampled population. Features suspicious for, but not diagnostic of malignancy were identified in 8 cases (6%), and further procedures were necessary to diagnose malignancy in 5 of these cases. Three additional cases of cancer were diagnosed after additional testing in patients where EBUS-TBNA was negative for malignancy, and no clear histopathological diagnosis could be made in 72 cases (57%). This study suggests a limitation in the sensitivity of EBUS-TBNA for detecting cancer in mediastinal lymphadenopathy without additional radiographic findings.

Another area EBUS-TBNA has been shown to play a key diagnostic role is in evaluating a radiologically unremarkable mediastinum (9). To determine the sensitivity and specificity of EBUS in such a patient, Herth *et al.* (9) evaluated 100 patients who presented with a T1 to T4 parenchymal lung mass without mediastinal findings on CT scan. Among the cohort, 119 lymph nodes averaging 8.1 mm in diameter were sampled by EBUS-TBNA, including at least one from each patient. All patients subsequently underwent thoracotomy or mediastinoscopy. Malignant lymph node transformation was observed in 19 of 100 studied patients and the authors reported an EBUS-TBNA sensitivity of 92.3% and specificity of 100% for detecting malignancy. The negative predictive value was reported as 96.3%.

Subsequent study by Herth *et al.* (10) in 2008 of 100 patients with high suspicion of NSCLC that had a radiographically normal mediastinum on PET scan as well as CT scan revealed similar results. The sensitivity for detecting malignancy was 89%, with a specificity of 100%, and a negative predictive value of 98.9%. This result is predictable given the lower resolution of PET scans compared to CT.

Explanation of findings

The above two studies by Herth showed the excellent diagnostic yield of EBUS-TBNA in mediastinal lymph nodes <1 cm in diameter when associated with lung nodules and masses. This capability to provide a diagnosis in mildly enlarged lymph nodes was well-demonstrated in the patient described in this case report. However, what still remains unaddressed is clear guidelines for the evaluation of

lymphadenopathy without an obvious primary lung tumor, such as our case described above.

Implications and actions needed

This case suggests a potential advantage in early detection of advanced NSCLC by using EBUS-TBNA as the initial procedure for sampling enlarging, though still subcentimeter mediastinal lymphadenopathy, even in the absence of a primary pulmonary mass or nodule. Our results with this case highlight the need to develop guidelines to address IML in LDCTs even in the absence of a primary lung nodule or mass.

Conclusions

Lung cancer screening with LDCT combined with the precision of EBUS-TBA to sample small lymphadenopathy is changing the way we characterize incidentally-found mediastinal lymphadenopathy. Based on the key finding of this case report, that even subcentimeter mediastinal lymphadenopathy can prompt the consideration of advanced lung adenocarcinoma, we recommend that regardless of pulmonary parenchymal findings on LDCT, clinicians should perform a thorough risk stratification and consider EBUS with TBNA to evaluate for malignancy when mediastinal lymphadenopathy is demonstrated on LDCT. Our clinical practice has evolved to include cautious review for mediastinal lymphadenopathy of all of our LDCTs with the expectation of a forthcoming case series of subcentimeter lymphadenopathy without suspicious parenchymal lesions that lead to a diagnosis of malignancy. Ultimately, additional data from LDCT screening programs that opt for tissue sampling in subcentimeter mediastinal lymphadenopathy may aid in developing evidence-based guidelines and advance efforts for early detection of lung cancer.

Acknowledgments

Routine facility support from SUNY Downstate Health Sciences Univerisity.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Jonathan Kurman and Bryan S. Benn) for the series "Diagnostic & Therapeutic Bronchoscopy" published in *AME Medical Journal*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-23-189/rc

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-23-189/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-23-189/coif). The series "Diagnostic & Therapeutic Bronchoscopy" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/amj-23-189
Cite this article as: Elayaperumal P, Daribayeva E, Sonde S, Ikinya LM, Idowu A, Arancibia R. Subcentimeter lymphadenopathy portended advanced lung adenocarcinoma diagnosed via endobronchial ultrasound: a case report. AME Med J 2024;9:36.