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AGGRESSIVELY QUICK: A CASE OF NEGATIVE RADIOGRAPHIC EVIDENCE PROGRESSING TO A LARGE LOBULATED LUNG MASS IN SIX MONTHS

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ABSTRACT

We present the case of a 61-year-old male with a past medical history of diabetes, hypertension, obstructive sleep apnea, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD), who developed a rapidly growing lung mass after previously having no radiographic evidence of cancer 6 months earlier. The patient initially presented for what appeared to be a COPD exacerbation, and imaging at that time showed no sign of any lung mass. Six months later, the patient returned with dyspnea and was found to have a large lobulated lung mass, possibly extending into the mediastinum. Lung malignancies include small cell carcinomas and non-small cell carcinomas. In this case, the patient developed an indeterminate differentiation of a non-small cell carcinoma, which rapidly progressed from negative radiographic findings to a 9.7 cm mass at its largest dimension within 6 months.

KEYWORDS

Lung cancer, non-small cell carcinoma, lung malignancy, volume doubling time

LEARNING POINTS

- Recognize the significance of highly proliferative lung cancer with volume doubling time metric.
- Review and understand lung cancer screening, tumor differentiation, and prognostic factors.

INTRODUCTION

Lung cancer has been a leading cause of death in the United States for several years, with a 5-year survival rate of roughly 20%[1]. Smoking, both firsthand and secondhand, has been undeniably shown to increase the risk of lung cancer[2]. Other risk factors include occupational hazards such as asbestos exposure, idiopathic lung fibrosis, and other lung pathologies like chronic obstructive pulmonary disease[2]. Lung cancers are predominantly categorized into small cell carcinoma, adenocarcinomas, large cell carcinomas, and squamous cell carcinoma, each with different characteristics and prognoses[2,3]. The proliferative factors vary based

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on the molecular and genetic makeup[3]. One important measure used to assess the aggressiveness of a cancer is volume doubling time (VDT), which refers to the time a cancer mass takes to double in size[4]. VDT varies among different malignancies and individual patients. In the United States, screening begins at age 50 with low dose computed tomography (CT) imaging, based on individual risk factors such as smoking history[1]. Despite these known risk factors and screening efforts, lung cancer remains a leading cause of death in the USA[1]. In this report, we present a case of a man who initially had no radiographic evidence of lung malignancy, but 6 months later was found to have a highly proliferative and aggressive lung cancer.

CASE REPORT

The patient was 61-year-old male with a past medical history of insulin-dependent diabetes mellitus, hypertension, obstructive sleep apnea, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease. He initially presented to the emergency department with fatigue and lethargy. A CT scan of the head was unremarkable, and laboratory work revealed CO_2 retention, with an arterial blood gas (ABG) showing a pH of 7.33 and a pCO_2 of 63. While hospitalized, the patient was treated for acute respiratory hypercapnic failure with bi-level positive airway pressure (BiPAP), and his mental status improved over 1 day. To rule out other causes of dyspnea, he also underwent a CT scan of the chest, which showed subpleural fibrosis in the upper lobes and along the subpleural mediastinum, as well as thickening of the interstitium suggestive of interstitial lung disease. After clinical improvement, the patient was discharged with instructions to follow up with pulmonology. Over the following months, the patient presented to the emergency department with chronic back pain. Six months after his initial presentation, he began complaining of neck pain, intermittent neck spasms, difficulty swallowing, and worsening dyspnea. During this visit, the patient was hypertensive (161/90 mmHg), had a heart rate of 118 bpm, and was saturating at 94% on room air. A CT chest angiogram and a CT of the neck were ordered to rule out a pulmonary embolism and investigate the neck symptoms. The CT of the neck revealed bulky lymphadenopathy within the mediastinum, while the CT chest showed a large mass exerting a mass effect on surrounding structures. The lobulated mass measured 9.7 × 6.1 cm and was located along the left hilar, suprahilar region, mediastinum, and upper lobe. The mass closely abutted the main pulmonary trunk and left pulmonary artery, and it possibly infiltrated the aortic arch.

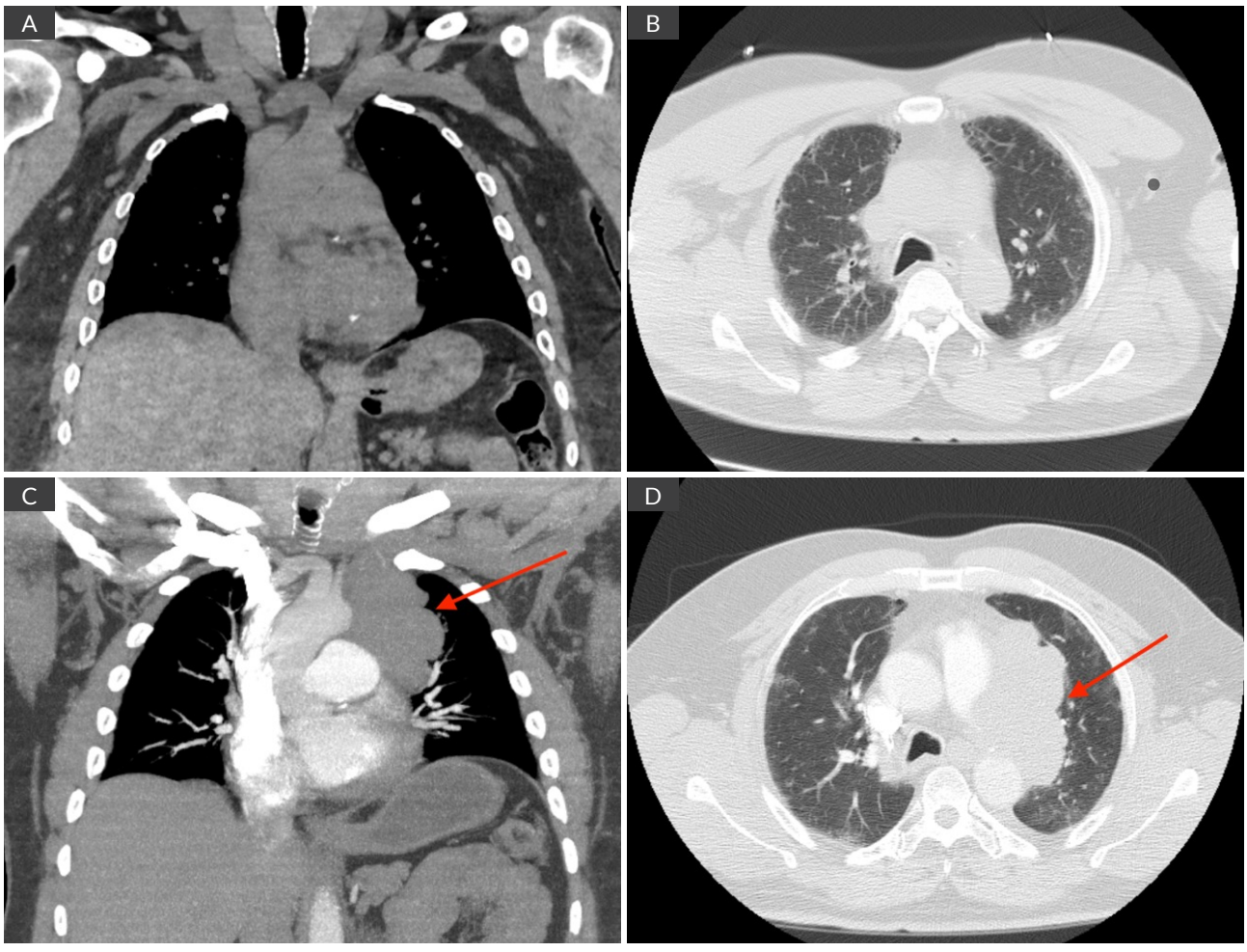

Figure 1. A) Computed tomography scan of the chest coronal cut showing no apparent mass; B) Computed tomography scan of the chest axial cut showing no apparent mass; C) Computed tomography scan of the chest coronal cut 6 months later showing large lobulated mass (red arrow); D) Computed tomography scan of the chest axial cut 6 months later showing large lobulated mass (red arrow).

A review of the CT chest done 6 months earlier showed no evidence of a mass *(Fig. 1)*.

A positron emission tomography (PET) scan revealed no evidence of distant metastasis but demonstrated a lobulated hypermetabolic mass extending from the apical lung region to the left mediastinum and left suprahilar regions, with a maximum standardized uptake value (SUV) of 21.7. There was uncertainty regarding whether the mass was extending into the mediastinum or if the cancer originated from the mediastinum. The mass encased the left upper pulmonary artery and bronchus and displaced the trachea and superior mediastinum to the right of the midline. A core biopsy revealed poorly differentiated non-small cell carcinoma *(Fig. 2 and 3)*. Immunohistological analysis showed positive staining for pan-cytokeratin (CK), CK7, synaptophysin, chromogranin, and a high proliferative index (Ki67 ~ 50%) *(Fig. 4 and 5)*. TTF-1 and CD 45 were negative. The specimen was sent to an outside facility for a second opinion, which confirmed the diagnosis of non-small cell carcinoma with indeterminate differentiation based on morphology and markers. The final diagnosis was stage IIIc (T4, N3) poorly differentiated non-small cell carcinoma, not otherwise specified. The patient was treated with paclitaxel, carboplatin, and radiation therapy, and later started on maintenance therapy with durvalumab.

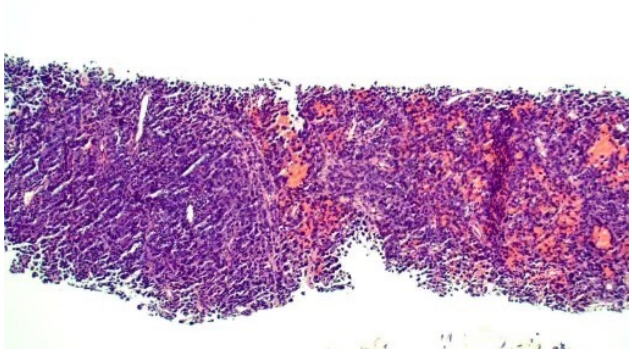

Figure 2. Low power view showing poorly differentiated neoplasm.

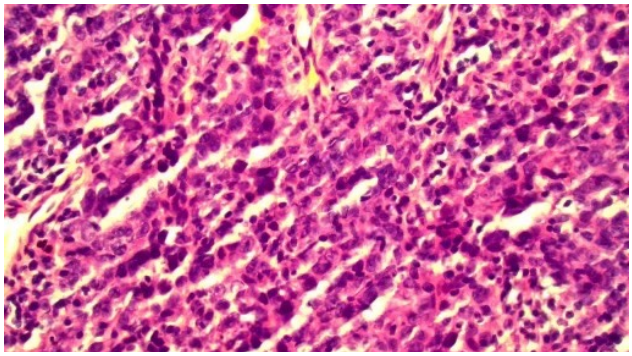

Figure 3. High power view shows atypical cells with round nuclei containing nuclei.

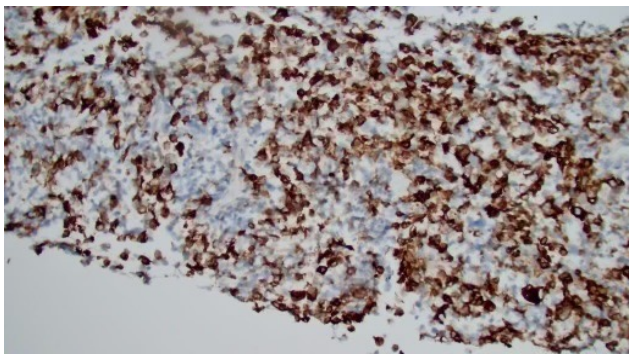

Figure 4. Immunostaining for synaptophysin positive in many malignant cells.

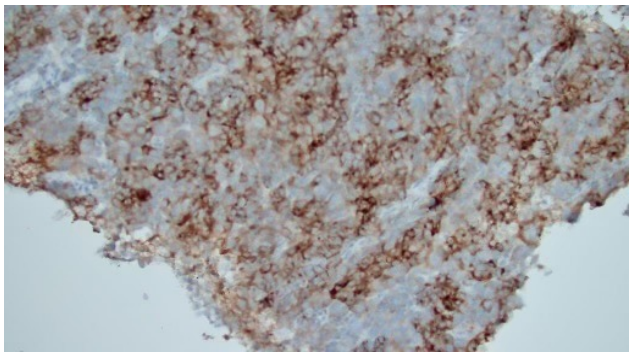

Figure 5. Immunostaining for pan-cytokeratin positive in many malignant cells.

DISCUSSION

Lung cancer remains a leading cause of death in the United States, with well-documented modifiable risk factors, such as smoking[2]. Despite being well derstood, it continues to have a significant impact, with an average 5-year survival rate of 15-20%[1,2]. Lung cancers are broadly classified into small cell carcinoma and non-small cell carcinoma[2]. Non-small cell carcinomas are further subdivided into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma[2]. Early detection is critical in improving survival rates. In the USA, screening for lung cancer using low-dose CT imaging is recommended for patients aged 50-80 with a smoking history of more than 20 pack-years, or for those who quit smoking within the last 15 years, unless they have exclusion factors like limited life expectancy[1,5]. Despite these efforts, screening only reduces lung cancer mortality by up to 20%[1]. Lung cancers have varying growth rates, which are assessed using VDT[6]. VDT measures how long it takes for a mass to double in size[4]. These growth rates, along with other factors, influence treatment options and prognosis. For instance, non-small cell carcinomas like adenocarcinoma and large cell carcinoma may require surgery for initial treatment, but more advanced cases often need additional treatment, such as chemotherapy and radiotherapy[2]. Even with surgery, some cancers, such as large cell lung carcinoma, have high recurrence rates, with 64% recurring within 1 year and 91% within 3 years[7].

In this case, the rapid progression of the cancer was significant. The patient initially had no evidence of a lung mass, but 6 months later, imaging revealed a 9.7 cm lobulated mass. Although rare, very rapid cancer expansions have been documented, such as a case where a lung nodule expanded significantly over 7 months with a VDT of 36 days[6]. Our patient's VDT was estimated at 30 days based on the size of the mass. In a retrospective study of VDT in surgically

resected non-small cell lung cancer, the VDT for lung adenocarcinoma was 261 days, squamous cell carcinoma was 70 days, and large cell neuroendocrine carcinoma was 45 days. Even before the biopsy results, it was clear our patient had an aggressive tumor.

Another notable aspect of this case was the inability to definitively categorize the tumor type based on histopathological findings. Initially, large cell neuroendocrine carcinoma was suspected due to the tumor's rapid growth, location, and aggressiveness. However, histological analysis showed large nuclei with minimal cytoplasm, which argued against that diagnosis. The tumor cells were positive for markers like AE1/AE3 (focal, patchy), CK7 (weak, patchy), synaptophysin, and chromogranin (rare), while negative for CK20, P40, TTF-1, and CD45, which are commonly used to differentiate types of lung cancer[8,9]. The rare pattern of synaptophysin and chromogranin positivity, without clear neuroendocrine morphology, made the diagnosis of neuroendocrine carcinoma unlikely[10]. This may be a case of t a poorly differentiated carcinoma, possibly a thoracic SMARCA4-deficient or undifferentiated tumor, which can present with similar immunohistochemical staining patterns. The tumor's poor differentiation likely contributed to its rapid progression, as poorly differentiated tumors often exhibit more aggressive behavior and a higher proliferation rate.

Limitations in this case included the inability to confidently diagnose the specific cancer type or determine the tumor's origin. It was unclear whether the mass originated from the mediastinum or extended into it. After discussion with the patient, it was decided to treat the case as stage IIIc (T4, N3) poorly differentiated non-small cell carcinoma and avoid further biopsy sampling.

CONCLUSION

In this case, a patient with no prior radiographic evidence of a lung mass developed a poorly differentiated and highly proliferative carcinoma over several months. The lack of clear immunohistochemical differentiation posed challenges in both treatment planning and prognosis. This case highlights the need for ongoing discussion about lung cancer screening, tumor differentiation, and prognostic factors, especially in cases of rapidly growing, poorly differentiated tumors. Further research is needed to better understand the aggressive nature of such cancers and to refine diagnostic and treatment strategies.

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