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Case Report

Lung Cancer Screening in the Midwest of the US: When Histoplasmosis Complicates the Picture

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Abstract

Lung cancer screening with low-dose computed tomography (LDCT) in high-risk patients could significantly reduce lung cancer mortality. However, the high rate of false positive findings in endemic areas with histoplasmosis may represent a significant barrier for its implementation.

Keywords: *Histoplasmosis; Lung Cancer Screening; Lung Nodules*

Introduction

Lung cancer (LC) is the most common cause of mortality associated with malignancy in the US [1,2]. The average 5-year survival rate for LC patients is poor (17.7%), mostly because up to 84% of these patients have regional or distant metastasis at diagnosis [1]. LC patients with localized disease have a 5-year survival rate higher than 50% [1]. LC screening has been proposed as an efficient strategy to diagnose LC at early stages and reduce LC mortality. The National Lung Screening Trial (NLST) demonstrated that annual low-dose computed tomography (LDCT) in high-risk patients could significantly reduce lung cancer mortality [3]. In 2014, the USPSTF gave a class B recommendation for annual lung cancer screening with LDCT [4]. In 2015, the Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) that covers annual lung cancer screening with LDCT. However, one of the main limitations of LC screening is the high prevalence of lung nodules detected on LDCT (around 40% in the NSLT) and nearly all being false positives [3]. In the Midwest of the United States, an endemic area of histoplasmosis, the rate of false positive findings appears to be higher. It is unclear how this endemic mycosis would affect the efficacy of lung cancer screening. We present two cases that exemplify this problem.

Case 1

A 68-year-old white male with a history of severe COPD (FEV1: 1.2L - 34%) and heavy tobacco abuse (> 100 pack-year history, quit 2 years ago) presented with a newly discovered lung nodule of 1.8 cm in the right upper lobe (Figure 1A). The lung lesion was found on a LDCT during lung cancer screening. The CT chest also showed diffuse emphysematous changes and enlarged mediastinal/hilar lymphadenopathy (lymph node station 4R and 11R) both measuring 1.3 cm in short axis (Figure 1B). The patient reported chronic stable dyspnea on mild exertion and chronic productive cough with whitish sputum. Otherwise, the review of system was negative. The patient was born and raised in rural Iowa and worked as a mechanic for 10 years with some exposure to asbestos. He denied alcohol or illicit drug abuse and TB or animal contact. He had a brother who died of lung cancer. His physical exam showed normal vital signs and scattered bilateral wheezing on lung auscultation. The rest of the physical exam was unremarkable. A Positron emission tomography (PET)/CT was done and showed high FDG uptake of the lung nodule (SUV max 13.7) (Figure 2A) and mediastinal/hilar lymphadenopathy (SUV max 6.3) (Figure 2B).

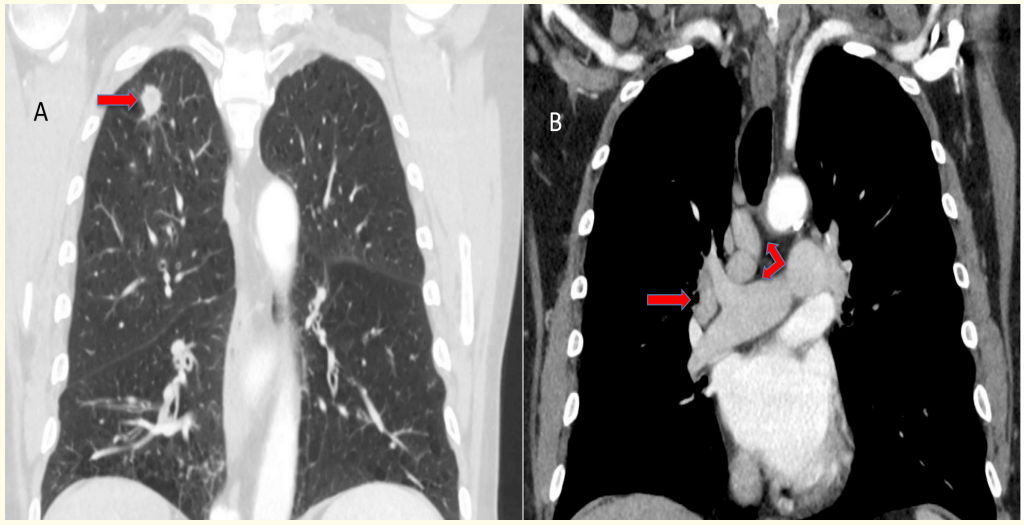

Figure 1: *Coronal view of the patient #1 CT chest with contrast at presentation. Panel A, lung window, shows the spiculated right upper lung nodule (arrow). Panel B, mediastinal window, shows the enlarged mediastinal (double arrow) and right hilar lymphadenopathy (single arrow).*

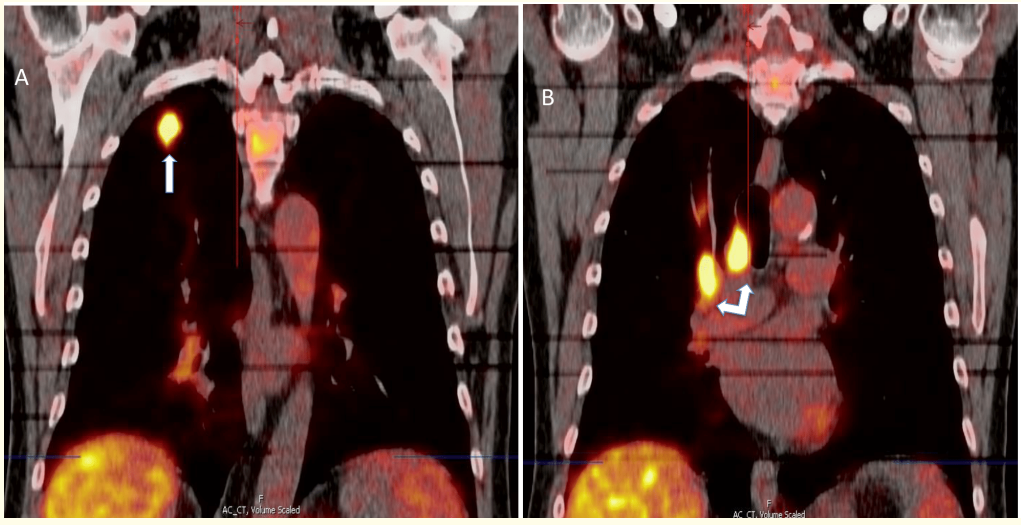

Figure 2: *Coronal view from the patient #1 PET/CT at presentation. Panel A shows high FDG avidity (arrow) of the spiculated right upper lobe lung nodule, evidenced by the bright yellow color. Panel B shows high FDG uptake (double arrow) from the mediastinal and hilar lymphadenopathy.*

The presence of risk factors for lung cancer (patient's age, history of tobacco abuse, emphysema, family history of lung cancer, size and location of the lung nodule) along with high FDG uptake of the lung nodule and mediastinal/hilar lymphadenopathy was very suggestive of lung cancer with spread to the mediastinum. The patient underwent a bronchoscopy with endobronchial ultrasound (EBUS) and fine needle aspiration of the lymphadenopathy (4R and 11R). The cytopathology examination showed necrotizing granulomas. The stains were negative for microorganisms. These findings supported the diagnosis of a chronic granulomatous process such as histoplasmosis, tuberculosis or sarcoidosis. In endemic areas of histoplasmosis, the presence of necrotizing granulomas in the mediastinum is very sup-

portive of pulmonary histoplasmosis, especially when the acid-fast bacteria stains are negative and clinical picture is not compatible with sarcoidosis. In this context, the right upper lobe lung nodule was also likely a granuloma related to histoplasmosis. The patient was started on empiric therapy with Itraconazole 200 mg twice a day for 6 weeks. A follow up CT chest three months later showed increasing size of the right upper lobe lung nodule, measuring now 2.7 cm compared to 1.8 cm three months prior (Figure 3A). The patient was referred to CT guided biopsy of the right upper lobe lung nodule to rule out malignancy. The pathology examination showed necrotizing granulomas; the stains were negative for any microorganisms; no malignant cells were observed. These findings supported the diagnosis of pulmonary histoplasmosis. Patient was followed with another CT chest after four months, which showed a decrease in size of the right upper lobe lung nodule (now measuring 1 cm) (Figure 3B). The initial worsening radiological changes likely represented ongoing inflammation triggered by the dying organisms after starting antifungal therapy.

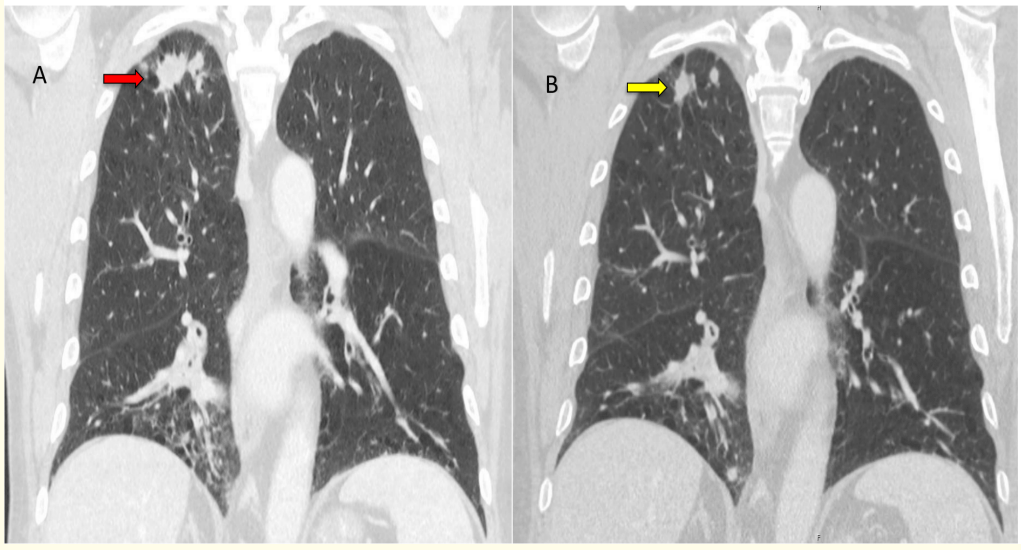

Figure 3: *Coronal view from the patient #1 CT chest. Panel A shows the right upper lobe nodule (red arrow) after the patient had finished Itraconazole therapy. Notice the increase in size compared to initial presentation (figure 1A). Panel B shows the decrease in size of the right upper lobe nodule (yellow arrow) 4 months after he had a negative CT guided biopsy.*

Case 2

56-year-old white female with a history of emphysema and heavy tobacco abuse (80 pack-year, on-going) presented for an evaluation of a 1.3 cm spiculated right upper lobe lung nodule discovered on a LDCT during a lung cancer screening (Figure 4A). The patient reported chronic stable dyspnea on moderate exertion and intermediate wheezing. Otherwise, the review of system was negative. The patient was born and raised in Iowa. She denied alcohol or illicit drug abuse, exposures to fumes, dust and asbestos, and any history of TB or animal contact. Her brother died of lung cancer. Physical exam showed normal vital signs and scattered bilateral wheezing on prolonged expiratory phase on lung auscultation. The rest of the physical exam was unremarkable. The estimated likelihood of malignancy for this lung nodule was considered very high based on the patient's age, history of tobacco abuse and emphysema, family history of lung cancer, and size and location of the lung nodule. A CT guided biopsy of the lung nodule was performed and showed necrotizing granulomas without the presence of malignant cells. The stains for microorganisms were negative. The negative biopsy decreased but did not exclude the likelihood of malignancy. The patient was followed with another CT chest three months later. This CT showed decrease in size of the right upper lobe lung nodule measuring now 0.6 cm (Figure 4B). This finding supported the diagnosis of benign granulomatous process-likely pulmonary histoplasmosis.

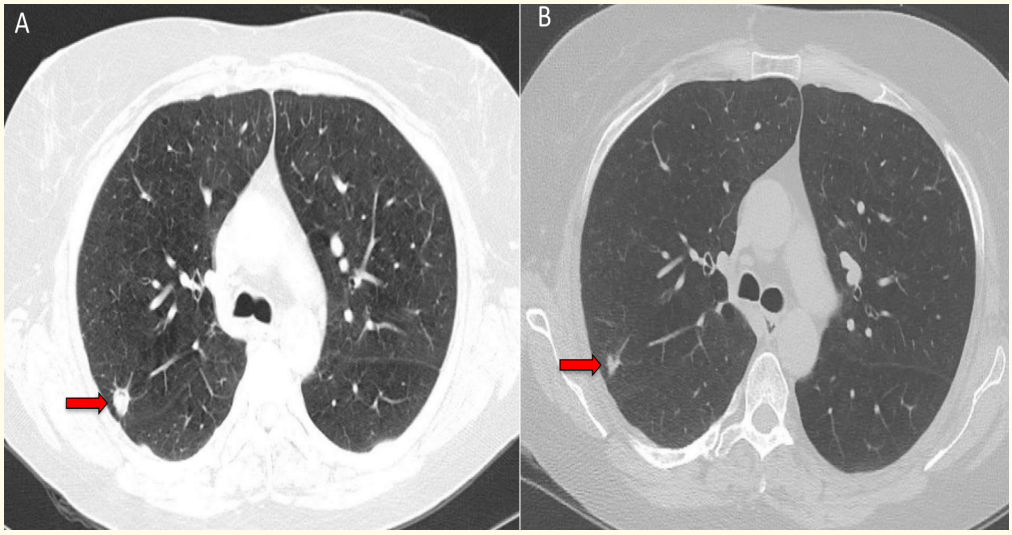

Figure 4: *Axial view from the patient #2 CT chest at presentation (A) and three months later (B). Panel A shows a spiculated, and partially cavitated lung nodule (red arrow) in the right upper lobe, measuring 1.3 cm. Panel B shows the same lung nodule but with significant decrease in size, measuring now 0.6 cm (red arrow).*

Discussion

We present two patients with significant risk factors for lung cancer that underwent LDCT for LC screening in an endemic area of histoplasmosis. Both were found to have lung nodules highly suspicious for malignancy and underwent tissue biopsy as recommended by the guidelines [5]. The CT guided biopsy in both cases did not provide a definitive diagnosis. According to the guidelines, a surgical biopsy would have been indicated following the CT guided biopsy. However, based on the pathologies of both cases, which showed necrotizing granuloma without malignant cells, imaging surveillance was chosen instead. In the end, a benign etiology was diagnosed in both cases. This scenario is not uncommon in the Midwest of the US, where the high prevalence of histoplasmosis exposure is associated with an elevated rate of pulmonary nodule detection on LDCT (up to 85%) [6]. In the NSLT, a 30% increase in positive findings on baseline LDCT screening was observed among patients living in histoplasmosis endemic areas [7].

Lung nodules from histoplasmosis are often indistinguishable from primary lung cancer on imaging and can also show high FDG uptake on PET/CT, as shown in the first case. Newer diagnostic modalities (exhaled breath volatile organic compounds, airway epithelial gene expression biomarkers or serum sampling for antibodies) and improved LC risk models have been developed to help assess the likelihood of malignancy on lung nodules [8,9]; however, tissue biopsy currently remains the gold standard to differentiate benign from malignant nodules. Tests used to diagnose invasive histoplasmosis in immunosuppressed patients include serology, fungal cultures and antigen detection in urine, blood or bronchoalveolar lavage. But these methods lack enough sensitivity and specificity in testing asymptomatic immunocompetent patients [10]. Distinction between primary lung cancer and benign etiology becomes even more difficult as granuloma formation can occur around malignant tumors as well, and concomitant granulomatous infections in lung cancer tumors (ie. tuberculosis, histoplasmosis) have also been reported [11-13].

In the NSLT, despite the high prevalence of false positive findings, less than 10% of patients with lung nodules underwent invasive testing and less than 1% of these patients had serious complications from invasive procedures [3]. However, physicians in the community are less conservative in following the guidelines and tend to perform more invasive procedures even without indications; up to 45 % of the lung nodules biopsied in the community have low risk for malignancy [14,15]. In the Veteran Health System, up to 45% of patients

evaluated for lung nodules received care inconsistent with the guidelines [16]. Furthermore, the rate of complications from CT guided biopsy in the community is also higher compared to the NSLT with a 15% incidence of pneumothorax and up to 6% requiring chest tube placement [17].

We suspect that in the Midwest of the US, lung cancer screening will result in higher rates of false positives. Subsequently, many of these patients will undergo invasive testing, some requiring more than one invasive procedure to prove a benign diagnosis such as the patient presented in the first case. A higher rate of invasive procedures may eventually result in a higher incidence of complications. Even if the false positive findings are only managed by imaging surveillance, this strategy will create a significant burden on the health care system and unnecessary anxiety and stress in these patients. Imaging surveillance also exposes these patients to significant amount of radiation; it has been calculated that a person requiring CT chest follow up over a 20 to 30-year period may experience a cumulative radiation exposure of up to 280 - 420 mSv, which exceeds the radiation exposure of nuclear workers and atomic bomb survivors [18]. These factors may decrease the benefits of lung cancer screening with LDCT observed in the NSLT. Further research needs to be done in endemic areas of histoplasmosis before a wide implementation of lung cancer screening programs in the Midwest of the US.

Conclusion

It is unclear if lung cancer screening with LDCT in the Midwest or other areas with endemic mycosis in the US would have the same benefits as observed in the NSLT.

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