

Identifying lung cancer in patients with active pulmonary tuberculosis

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Abstract: The diagnosis of lung cancer can be delayed in patients with a history of infection with pulmonary tuberculosis that present with new lesions on chest imaging, due to a high initial index of suspicion for mycobacterium tuberculosis complex rather than malignancy. This may lead to diagnosis of malignancy at a more advanced stage of the disease with subsequent increased morbidity and mortality. We reviewed the current literature to evaluate various methods of differentiating between a diagnosis of lung cancer and tuberculosis including radiography, computerized tomography (CT), positron emission tomography (PET) and various biological markers. We included only papers published in English. Based on current data, we recommend that patients established as high risk, according to the American Association of Thoracic Surgery, patients with age greater than or equal to 55 years and a smoking history of greater than or equal to 30 pack years, should be assessed with CT for underlying malignancy prior to beginning tuberculosis treatment, even in the presence of a clinical or microbiologic diagnosis of tuberculosis. In patients with equivocal CT findings, we recommend examination of tumor markers miR128, miR210, miR126 along with CEA, if these tests are at the clinician's disposal.

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Introduction

Lung cancer is one of the most common malignancies in the world, with an incidence of 1.8 million and 1.6 million deaths, annually, according to the World Health Organization's most recent cancer report (1). The 5-year survival rate is poor at approximately 15% (1). Mortality is greatly increased at later stages of diagnosis, as evidenced by the National Cancer Institute's Surveillance, Epidemiology, and End Results program publication in 2012, showing a 5-year survival rate of 52.5% in localized cancer confined to primary site of malignancy compared with 3.7% for metastatic cancer (2). Approximately 57% of patients with

lung cancer are diagnosed with stage IV disease and only 16% are diagnosed when their disease remains localized, confined to the primary cancer site with no regional lymph node involvement (2). The high occurrence of late-stage diagnosis is likely due to the asymptomatic nature of early disease or nonspecific symptoms such as cough, shortness of breath, and dyspnea (3). Lung cancer is most amenable to treatment at an early stage; therefore, it is important to have a high index of suspicion for malignancy when evaluating suspicious radiographic lesions in high-risk patients with non-specific symptoms.

Pulmonary tuberculosis can present a challenge for clinicians when ruling out malignancy in a patient, and

the diagnosis of lung cancer in patients with a history of mycobacterial tuberculosis complex infection, a tuberculin skin test (TST) or interferon gamma release assay (IGRA), and radiographic pulmonary lesions may be delayed as malignant lesions may be mistaken for active pulmonary tuberculosis. According to the 2015 Centers for Disease Control Annual Tuberculosis Surveillance Report, there are over 9,000 new confirmed cases of active tuberculosis in the United States annually, with many more people with latent disease at risk for reactivation (4). Although the incidence in the United States decreased from 2015 to 2016 by 2.7%, at the current rate of decline, the goal of eradication of tuberculosis in the United States will not occur during this century (5). Globally, tuberculosis infection continues to be a major health threat with an estimated incidence of 10.4 million in 2016 and an estimated 1.674 million deaths of attributable to the disease in 2016 according to the World Health Organization 2017 global tuberculosis report (6). This diagnostic dilemma is one that will continue to plague physicians for many decades.

The differentiation between active pulmonary tuberculosis, lung cancer or the identification of coexistence of the two disease processes during diagnostic evaluation of a patient with a pulmonary lesion is of particular significance because it has been shown that active pulmonary infection with mycobacterium complex is more likely to occur in patients with lung cancer (7-9) and that the morbidity and mortality of a pulmonary malignancy is increased when accompanied by an active pulmonary tuberculosis diagnosis (10,11). Therefore, it is not only more likely that a patient presenting with what appears to be tuberculosis will concurrently have a pulmonary malignancy than someone who does not have a tuberculosis infection, but also that it is of greater urgency to make an expedited diagnosis of the malignancy.

This is especially problematic because it is acceptable to make a clinical diagnosis of tuberculosis infection when a patient has an assessment suggestive of active pulmonary tuberculosis based on chest radiography and clinical symptoms such as cough, shortness of breath, hemoptysis, night sweats, weight loss and fatigue, which are shared between mycobacterial infection and pulmonary malignancy (2,4) as well as positive testing with TST or IGRA. This not only may result in the misdiagnosis of active pulmonary tuberculosis in patients with cancer and latent infection, prior infection or a history of false positive TST due to history of Bacillus Calmett-Guérin (BCG) vaccination, but also would fail to identify patients with

both active tuberculosis infection and an occult pulmonary malignancy. It is common practice to empirically treat patients with a clinical diagnosis of tuberculosis with serial re-assessment of the lesion following treatment. The duration of treatment necessary for active pulmonary tuberculosis, six months minimum with extended therapy for cavitary disease, may lead to a significant delay in tissue sampling and diagnosis if there is an underlying malignancy. Furthermore, partial response to antibiotic therapy on plain radiographs may limit further imaging that may otherwise have identified growth due to occult malignancy. Below, we review current literature on identification of lung cancer in patients with active or chronic pulmonary tuberculosis.

We performed a review of current literature and policies available via the Brown University online library. Literature and policies regarding the diagnosis of lung cancer and pulmonary tuberculosis were reviewed, with particular attention given to those that examined specificity of a method for one of these pathological states over the other. Publications were excluded if they were not available in English.

Radiography

Studies investigating chest radiography as a screening technique for lung cancer have found it to be neither sensitive nor specific based on inability to visualize small lesions and non-specific features indistinguishable from other etiologies, including those of an infectious nature (12-15). Pulmonary malignancy is commonly not visible on chest radiography early in the disease under one centimeter (cm) in diameter, and as the disease progresses, it may present as a non-specific focal consolidation with irregular borders and commonly with calcifications and usually with a solid component versus a ground glass appearance (16). Although there are some classic findings highly suggestive of tuberculosis, it can also be quite variable, sometimes revealing non-specific findings such as parenchymal consolidations in primary disease, fibrosis and scarring with parenchymal and nodal calcifications in inactive disease and more poorly defined, patchy consolidations in reactivated disease (17), all of which could also be consistent with a lung cancer diagnosis.

Computerized tomography (CT)

CT is currently recommended by the Association for Thoracic Surgery as the imaging modality of choice

in screening for pulmonary malignancy in high risk populations (18), based on studies showing that it may identify potentially malignant lesions earlier and is able to reduce lung cancer mortality by 20% compared with screening with radiography (18). The major weakness of low-dose CT, though, is that it is not very specific and therefore has a high rate of false positives due to the presence of benign lesions, including those from previous infection, such as tuberculosis, inflammatory conditions or fibrosis from other causes (18). Several studies have examined the value of differentiating between malignant and benign pulmonary disease based on CT radiodensity as defined by Hounsfield units (HU). Swensen *et al.* performed a multicenter study to examine the ability to differentiate benign from malignant pulmonary nodules based on the premise that malignant lesions are significantly more vascular and therefore will exhibit increased enhancement. They found that they could diagnose malignancy using enhancement greater than 15 HU with 98% sensitivity and 54% specificity—indicating that this would better establish a nodule as benign, rather definitively diagnose a lesion as malignant. With regards to mycobacterial tuberculosis complex infection, they found that inactive tuberculomas were easily distinguished based on lower levels of enhancement, but active lesions with active inflammation could not be differentiated on this basis (19). This finding was in agreement with other previously held studies (20,21). Xie built upon this study and examined the efficacy of differentiating between benign inflammatory processes and malignant disease based on radiodensity on enhanced rather than plain CT and found that lung cancer enhancement is generally moderate (HU 46.5–79.5) and inhomogeneous, while pulmonary tuberculosis enhancement was slight to moderate (HU 38.2–67.5) and also inhomogeneous (22). This indicates that while lesions that display moderately high radiodensities on enhanced CT are more likely to be malignant, there is overlap between pulmonary tuberculosis and malignant lesions. Enhanced CT alone thus is not sufficient to differentiate between the two diseases.

Positron emission tomography (PET)

Many studies have looked to PET scans and PET/CT scans to differentiate between benign inflammatory disease and non-small lung cancer lesions. Lindell *et al.* found PET to be inferior to CT for detecting malignant lesions smaller than one centimeter in diameter (23). Additionally, Zheng *et al.* found that there is similar 18F-fluoro-2-

deoxy-D-glucose (18F-FDG) uptake in tuberculosis, especially active tuberculosis, and malignancy, making the differentiation between pulmonary tuberculosis and malignancy using 18F-FDG PET difficult (24). A 2001 meta-analysis found that 18F-FDG PET is very effective in identifying a malignant lesion—with a sensitivity of 96.8%, but has a specificity of 77.8%, but the analysis did not comment on the proportion of studies included that were in tuberculosis-endemic areas or the accuracy when specifically attempting to differentiate between malignant and active tuberculosis etiologies (25). A recent study by Niyonkuru *et al.* examined the use of 18F-FDG PET/CT in the evaluation of lung nodules in populations with a high prevalence of tuberculosis and found that there is a high rate of false positives leading to unnecessary invasive tissue collection and resections in these populations (26). Therefore, although 18F-FDG PET/CT is a sensitive tool in establishing a lung cancer diagnosis with lesions greater than one cm in size, it does not have sufficient specificity to identify lung cancer in a patient with pulmonary tuberculosis.

Biological markers

In addition to radiographic evaluation, there has been significant interest in the ability to use biomarkers in order to differentiate between benign and malignant disease, and numerous markers have been examined to date.

A study examining the use of carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (CYFRA 21-1) as diagnostic tools to differentiate between benign and malignant pulmonary disease found the use of elevated levels of each of these tumor markers for the diagnosis of malignancy to be insensitive (CEA 69%, CYFRA 21-1 43%) with only marginal specificity (CEA 68%, CYFRA 21-1 89%) when they are each used individually. Additionally, when the markers were used together—with elevations of both markers used to establish the diagnosis of a malignancy, specificity improved to 95% with an associated drop in sensitivity to 33% (27). Therefore, the simultaneous elevation of both CEA and CYFRA 21-1 is highly indicative of a malignant etiology, but would result in many false negatives.

Ghosh *et al.* looked at CEA, carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA19-9) and carbohydrate antigen 125 (CA125) from both serum and bronchoalveolar lavage (BAL) samples in the diagnosis of lung cancer and had more encouraging results, particularly

from BAL samples, with a sensitivity and specificity respectively of 91.3% and 90% for CEA, 89.13% and 45% for CA 15-3, 91.3% and 77.5% for CA19-9 and 89.13% and 75% for CA 125 (28). This study did not specifically examine the levels for these markers in active pulmonary tuberculosis, and Kim *et al.* found that CA 125 is significantly elevated in the serum of patients with tuberculosis and non-tuberculosis mycobacterial infections (29), potentially limiting the usefulness of this marker in the identification of lung cancer in a patient with tuberculosis. Squamous cell carcinoma antigen (SCC Ag) has been shown to be increased in patients with squamous cell carcinoma of the lung (30), but levels have not been specifically examined in patients with active pulmonary tuberculosis infection.

A recent meta-analysis examined serum human epididymis protein 4 (HE4) also known as whey acid protein type four disulphide core 2 (WFDC2) levels as a potential marker for pulmonary malignancy, and found that HE4 levels have a high specificity in diagnosing lung cancer and levels tend to increase with the severity of disease, but that the sensitivity in identifying pulmonary malignancy is poor (31). An earlier study by Liu *et al.* specifically examined serum HE4 levels as a method to differentiate between pulmonary tuberculosis and malignancy and found levels to be significantly higher in patients with non-small cell lung cancer (NSCLC), but not in those with tuberculosis or in healthy individuals (32). This suggests that in a patient with tuberculosis a positive result on serum HE4 testing would suggest that the simultaneous presence of malignancy, but that a negative result would not be sufficient to rule it out.

Abd-El-Fattah *et al.* examined the expression of various forms of micro-ribonucleic acid (miR) based on the expression levels found in the serum of patients with pulmonary malignancy and benign disease, including tuberculosis and found that miR-182 was significantly elevated in NSCLC, but not in patients with pulmonary tuberculosis (33). A more recent study also evaluated serum levels of miR-182 in patients with NSCLC and found them to be elevated, allowing them to differentiate between the serum of patients with NSCLC versus individuals without the disease with a sensitivity of 63.4% and specificity of 80%. This study also found that patients with NSCLC had elevated levels of miR-183, miR-210 and CEA as well as decreased levels of miR-126 in patients with NSCLC when compared with controls. Using this panel of elevated miR-182, miR-183, miR-210 and CEA with decreased miR-126, sensitivity and specificity were improved to 88.5% and 92.5%, respectively. This study did not specifically

evaluate the use of this panel in patients with tuberculosis; so further investigation is required to determine if this specificity holds in population with a high prevalence of tuberculosis (34).

Finally, studies have recently been focused on the identification and quantification of cancer cell-free DNA (cfDNA) in the serum in order to identify NSCLC in the early stages. This technique separates and amplifies cfDNA via polymerase chain reaction (PCR)—separating out short and long fragments. The short and long chain fragments, as well as the total concentration of cfDNA is then quantified and used as a marker for malignancy with higher total concentration and longer fragments found in the serum of those harboring a malignancy (35). Leng *et al.* recently evaluated it specifically in order to distinguish between NSCLC and tuberculosis. This study found that the evaluation for cfDNA is more sensitive and specific in differentiating NSCLC from tuberculosis than CA125, NSE and CEA (35). This method relies on the ability to amplify the cfDNA via PCR in order to obtain levels amenable to detection, as well as many other molecular techniques of evaluation such as digital PCR, next-generation sequencing, and beads, emulsion, amplification and magnetics when undergoing qualitative analysis of the cfDNA for specific mutations (36). These approaches are currently costly with a low throughput; however, these techniques are becoming more efficient and inexpensive, such that it may soon be feasible that this could be a test in the pocket of many front-line clinicians.

Conclusions

In a patient with signs and symptoms of active pulmonary mycobacterial tuberculosis infection, it is imperative that a diagnosis of lung cancer be excluded with a reasonable degree of certainty prior to beginning a lengthy treatment regimen for tuberculosis. Mutual symptomology, the increased incidence of lung cancer in patients with active infection and associated inflammation with pulmonary tuberculosis (37) and the increased incidence of active tuberculosis in patients with an underlying malignancy leading to an immunodeficient state result in a diagnostic challenge (10). We recommend that for patients established as high risk for lung cancer (age >55 years and a smoking history of >30 pack years) be assessed with chest CT scan for underlying malignancy prior to initiating tuberculosis treatment, even in the presence of a clinical or microbiologic diagnosis of tuberculosis. In patients with

equivocal CT findings, these tests—examination of tumor markers miR128, miR210, miR126 along with CEA—are at the clinician's disposal. HE4 may also prove as a good test to establish a diagnosis of malignancy if the index of suspicion for malignancy is high. CfDNA is unlikely to be affordable or timely enough for the average provider to use as a diagnostic tool, but shows promise as technologies evolve to make the test more practical. For those who do not have access to test for tumor markers, in patients with equivocal CT findings, we recommend early repeat CT at six months in order to evaluate for a response to tuberculosis treatment. In the absence of response, we recommend a tissue diagnosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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