

Not All Pulmonary Nodules in Smokers are Lung Cancer

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Diagnosis of pulmonary nodules requires an in-depth workup, including clinical evaluation, laboratory and pulmonary functions tests, and imaging, which helped to identify in this patient pulmonary rheumatoid arthritis, an important factor in patient mortality.

Identification of pulmonary nodules in older adults who smoke immediately brings concern for malignancy in the mind of clinicians. This is particularly the case in patients with significant smoking history. According to the National Cancer Institute in 2019, 12.9% of all new cancer cases were lung cancers.¹ Screening for lung cancer, especially in patients with increased risk from smoking, is imperative to early detection and treatment. However, 20% of patients will be overdiagnosed by lung cancer-screening techniques.² The rate of malignancy noted on a patient's first screening computed tomography (CT) scan was between 3.7% and 5.5%.³

Rheumatoid arthritis (RA) is an autoimmune inflammatory condition that mainly affects the joints. Extraarticular manifestations can arise in various locations throughout the body, however. These manifestations are commonly observed in the skin, heart, and lungs.⁴ Prevalence of pulmonary rheumatoid nodules ranges from < 0.4% in radiologic studies to 32% in lung biopsies of patients with RA and nodules.⁵

Furthermore, there is a strong association between the risk of rheumatoid nodules in patients with positive serum rheumatoid factor (RF) and smoking history.⁶ Solitary pulmonary nodules in patients with RA can coexist with bronchogenic carcinoma, making their diagnosis more important.⁷

CASE PRESENTATION

A 54-year-old woman with a 30 pack-year smoking history and history of RA initially presented to the emergency department for cough and dyspnea for 5-day duration. Her initial diagnosis was bronchitis based on presenting symptom profile. A chest CT demonstrated 3 cavitary pulmonary nodules,

1 measuring 2.4 x 2.0 cm in the right middle lobe, and 2 additional nodules, measuring 1.8 x 1.4 and 1.5 x 1.4 in the left upper lobe (Figure). She had no improvement of symptoms after a 7-day course of doxycycline. The patient was taking methotrexate 15 mg weekly and golimumab 50 mg subcutaneously every 4 weeks as treatment for RA, prescribed by her rheumatologist.

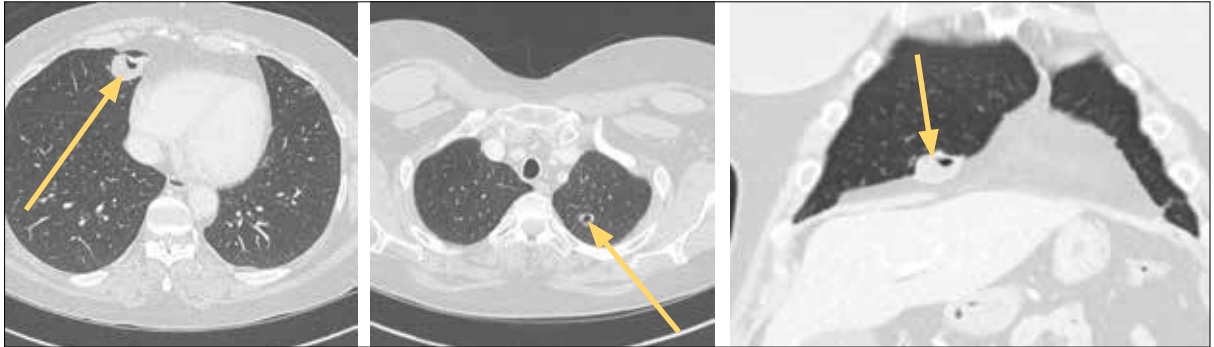
Pulmonology was consulted and a positron emission tomography-CT (PET-CT) confirmed several cavitary pulmonary nodules involving both lungs with no suspicious fluorodeoxyglucose (FDG) uptake. The largest lesion was in the right middle lobe with FDG uptake of 1.9. Additional nodules were found in the left upper lobe, measuring 1.8 x 1.4 cm with FDG of 4.01, and in the left lung apex, measuring 1.5 x 1.4 cm with uptake of 3.53. CT-guided percutaneous fine needle aspiration (PFNA) of the right middle lobe lung nodule demonstrated granuloma with central inflammatory debris. Grocott methenamine silver (GMS) stain was negative for fungal organism, acid-fast bacteria (AFB) stain was negative for acid-fast bacilli, and CD20 and CD3 immunostaining demonstrated mixed B- and T-cell populations. There was no evidence of atypia or malignancy. The biopsy demonstrated granuloma with central inflammatory debris on a background of densely fibrotic tissue and lympho-plasmatic inflammation. This finding confirmed the diagnosis of RA with pulmonary involvement.

Outpatient follow-up was established with a pulmonologist and rheumatologist. Methotrexate 15 mg weekly and golimumab subcutaneously 50 mg every 4 weeks were prescribed for the patient. The nodules are being monitored based on Fleischner guidelines with CT imaging 3 to 6 months

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FIGURE Chest Computed Tomography

Arrows indicate cavitary rheumatoid nodules.

TABLE Patient Laboratory Test Results

Tests	Results
Nuclear antibody	Negative
Rheumatoid factor	46 (range 0-15)
Histoplasma antibody	Negative
Coccidioides antibody	Negative
Quantiferon tuberculosis	Negative
Acid-fast bacilli	Negative

following initial presentation. Further imaging will be considered at 18 to 24 months as well to further assess stability of the nodules and monitor for changes in size, shape, and necrosis. The patient also was encouraged to quit smoking. Her clinical course since the diagnosis has been stable.

DISCUSSION

The differential diagnosis for new multiple pulmonary nodules on imaging studies is broad and includes infectious processes, such as tuberculosis, as well as other mycobacterial, fungal, and bacterial infections. Noninfectious causes of lung disease are an even broader category of consideration. Noninfectious pulmonary nodules differential includes sarcoidosis, granulomatous with polyangiitis, hypersensitivity pneumonitis, methotrexate drug reaction, pulmonary manifestations of systemic conditions, such as RA chronic granulomatous disease and malignancy.⁸ Bronchogenic carcinoma was suspected in this patient due to her smoking history. Squamous cell carcinoma was also considered as the lesion was cavitary. AFB and GMS stains were

negative for fungi. Langerhans cell histiocytosis were considered but ruled out as these lesions contain larger numbers of eosinophils than described in the pathology report. Histoplasma and coccidioides laboratory tests were obtained as the patient lived in a region endemic to both these fungi but were negative (Table). A diagnosis of rheumatoid nodule was made based on the clinical setting, typical radiographic, histopathology features, and negative cultures.

This case is unique due to the quality and location of the rheumatoid nodules within the lungs. Pulmonary manifestations of RA are usually subcutaneous or subpleural, solid, and peripherally located.⁹ This patient's nodules were necrobiotic and located within the lung parenchyma. There was significant cavitation. These factors are atypical features of pulmonary RA.

Pulmonary RA can have many associated symptoms and remains an important factor in patient mortality. Estimates demonstrate that 10 to 20% of RA-related deaths are secondary to pulmonary manifestations.¹⁰ There are a wide array of symptoms and presentations to be aware of clinically. These symptoms are often nondescript, widely sensitive to many disease processes, and nonspecific to pulmonary RA. These symptoms include dyspnea, wheezing, and nonproductive cough.¹⁰ Bronchiectasis is a common symptom as well as small airway obstruction.¹⁰ Consolidated necrobiotic lesions are present in up to 20% of pulmonary RA cases.¹⁰ Generally these lesions are asymptomatic but can also be associated with pneumothorax, hemoptysis, and airway obstruction.¹⁰ Awareness of these symptoms is important for diagnosis and monitoring clinical improvement in patients.

Further workup is necessary to differentiate malignancy-related pulmonary nodules and other causes; if the index of suspicion is high for malignancy as in our case, the workup should be more aggressive. Biopsy is mandatory in such cases to rule out infections and malignancy, as it is highly sensitive and specific. The main problem hindering management is when a clinician fails to include this in their differential diagnosis. This further elucidates the importance of awareness of this diagnosis. Suspicious lesions in a proper clinical setting should be followed up by imaging studies and confirmatory histopathological diagnosis. Typical follow-up is 3 months after initial presentation to assess stability and possibly 18 to 24 months as well based on Fleischner guidelines.

Various treatment modalities have been tried as per literature, including tocilizumab and rituximab.^{11,12} Our patient is currently being treated with golimumab based on outpatient rheumatologist recommendations.

CONCLUSIONS

This case demonstrates the importance of a careful workup to narrow a broad differential. Medical diagnosis of pulmonary nodules requires an in-depth workup, including clinical evaluation, laboratory and pulmonary functions tests, as well as various imaging studies.

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Ethics and consent

The authors report that this patient provided informed consent.

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