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CHEST

Rheumatoid pulmonary nodules: clinical and imaging features compared with malignancy

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Abstract

Objectives The objective of this study was to identify clinical and imaging features that distinguish rheumatoid lung nodules from malignancy.

Methods We conducted a retrospective review of 73 rheumatoid patients with histologically-proven rheumatoid and malignant lung nodules encountered at Mayo Clinic, Rochester, MN (2001–2016). Medical records and imaging were reviewed including a retrospective blinded review of CT and PET/CT studies.

Results The study cohort had a mean age of 67 ± 11 years (range 45–86) including 44 (60%) women, 82% with a smoking history, 38% with subcutaneous rheumatoid nodules, and 78% with rheumatoid factor seropositivity. Subjects with rheumatoid lung nodules compared to malignancy were younger (59 ± 12 vs 71 ± 9 years, $p < 0.001$), more likely to manifest subcutaneous rheumatoid nodules (73% vs 20%, $p < 0.001$) and rheumatoid factor seropositivity (93% vs 68%, $p = 0.034$) but a history of smoking was common in both groups ($p = 0.36$). CT features more commonly associated with rheumatoid lung nodules compared to malignancy included multiplicity, smooth border, cavitation, satellite nodules, pleural contact, and a subpleural rind of soft tissue. Optimal sensitivity (77%) and specificity (92%) (AUC 0.85, CI 0.75–0.94) for rheumatoid lung nodule were obtained with ≥ 3 CT findings (≥ 4 nodules, peripheral location, cavitation, satellite nodules, smooth border, and subpleural rind). Key ^{18}FDG-PET/CT features included low-level metabolism (SUV_{max} 2.7 ± 2 vs 7.2 ± 4.8, $p = 0.007$) and lack of ^{18}F-fluorodeoxyglucose (FDG)-avid draining lymph nodes.

Conclusion Rheumatoid lung nodules have distinct CT and PET/CT features compared to malignancy. Patients with rheumatoid lung nodules are younger and more likely to manifest subcutaneous rheumatoid nodules and seropositivity.

Key Points

- *Rheumatoid lung nodules have distinct clinical and imaging features compared to lung malignancy.*
- *CT features of rheumatoid lung nodules include multiplicity, cavitation, satellite nodules, smooth border, peripheral location, and subpleural rind.*
- *Key PET/CT features include low-level metabolism and lack of FDG-avid draining lymph nodes.*

Keywords Multidetector computed tomography · PET-CT scan · Multiple pulmonary nodules · Rheumatoid arthritis · Rheumatoid nodule

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Abbreviations

CCP	Cyclic citrullinated peptide
DLCO	Diffusing capacity for carbon monoxide
FEV_1	Forced expiratory volume in 1 s
FDG	^{18}F-fluorodeoxyglucose
FVC	Forced vital capacity
GGO	Ground glass opacity
HRCT	High-resolution computed tomography
IL-1	Interleukin-1
PET	Positron emission tomography
PFT	Pulmonary function test
RA	Rheumatoid arthritis
TLC	Total lung capacity

Introduction

Pulmonary nodules present a diagnostic challenge due to their common occurrence and concern for lung cancer. Moreover, the incidence of lung nodules appears to be increasing [1]. Guidelines for the management of lung nodules are based on clinical risk factors and radiographic characteristics but clinical decisions must be made on a case-by-case basis [2]. Patients with rheumatoid arthritis (RA) require additional diagnostic consideration since rheumatoid lung nodules can mimic lung cancer [3].

Rheumatoid lung nodules are historically described as ranging in size from millimeters to several centimeters, single or multiple, solid or cavitary, and generally located in a subpleural location [4]. However, current knowledge is based on limited data consisting mostly of case reports [5–10] and case series [11–13]. In some studies, the diagnosis of rheumatoid lung nodule was not confirmed histologically [14–16] or were performed prior to modern computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG)-PET imaging [17, 18].

The purpose of this study was to identify the clinical and radiographic features associated with rheumatoid lung nodules that may distinguish them from malignancy. In order to improve upon past studies, this study was conducted in a larger cohort of rheumatoid patients, all of whom had their lung nodules histologically diagnosed. In addition, imaging studies were reassessed in a blinded fashion.

Subjects and methods

Patient selection

The study was approved by the Mayo Clinic Institutional Review Board (IRB16-006571). We conducted a computer-assisted search for patients with RA and lung nodules encountered from January 2001 to June 2016 at Mayo Clinic, Rochester, Minnesota. According to Mayo Clinic institutional policy, patient information may be used for research purposes only with prior patient consent. All identified cases that fulfilled the 2010 Rheumatoid Arthritis Classification Criteria [19] were manually reviewed to confirm the presence of pulmonary nodule(s) on chest imaging. We identified 79 rheumatoid patients with biopsied/resected lung nodules including 23 patients with histologically-proven rheumatoid lung nodules. Rheumatoid lung nodule was defined histopathologically by the presence of necrotizing granuloma with or without palisading epithelioid histiocytes in the absence of evidence for infection on special stains and microbial cultures [20, 21]. The remaining 56 patients with non-rheumatoid lung nodules/masses had neoplasm ($n = 50$), infection ($n = 3$), and other benign lesion ($n = 3$). We excluded the latter six patients (3 histoplasmosis, 2 amyloid, and 1 respiratory bronchiolitis) from further analysis.

Clinical, laboratory, and radiologic findings

Medical records were reviewed for age, gender, smoking status, presenting symptoms, physical findings, laboratory results, pulmonary function testing, and findings on chest CT and ^{18}FDG-PET/CT scans.

A retrospective blinded CT and ^{18}FDG-PET/CT review of both rheumatoid and malignant pulmonary nodules was performed using standard clinical image review hardware and software. A range of techniques was utilized, given a 16-year span of performed exams. CT exams utilized helical technique with a minimum of four detectors, slice thickness between 3 and 5 mm, peak kilovoltage of 120–140, and a minimum milliamperes of 45. The diagnostic CT exams were performed with patients in inspiration breath hold. PET exams utilized 2D and 3D detectors, with a matrix of 128–192 and 3–5-min bed positions. Patients were in a minimum 6-h fasted state, prior to PET exams. After intravenous injection of 15–20 mCi ^{18}FDG, incubation time was about 60 min prior to initiating the exam. Imaging was reviewed for the purposes of this study, without knowledge of clinical and pathologic data, independently by a staff radiologist with board certification in diagnostic radiology (JRY) and a staff nuclear/thoracic radiologist with 10 years of clinical experience and board certification in radiology and nuclear medicine (GBJ). When multiple nodules were present, the nodule characteristics measured were for the largest and/or most FDG-avid nodule. CT imaging findings were defined according to accepted definitions in the literature [22, 23]. Rheumatoid lung nodule(s) and malignant nodule(s) were compared in the statistical analysis.

Statistical analysis

Data was analyzed using R version 3.2.3. Continuous variables were summarized using mean ± standard deviation (SD), median, and range, unless stated otherwise.

Categorical variables were summarized with frequency and percent. Comparison across groups was made using the chi-square test or Kruskal-Wallis test as appropriate. *P* values < 0.05 were considered statistically significant.

Results

Clinical characteristics of 23 patients with rheumatoid lung nodules and 50 patients with malignancy (46 primary lung cancers [40 non-small cell, 4 small cell, 2 carcinoid] and 4 metastatic [colon, melanoma, breast, adenocarcinoma of unknown origin, respectively]) are presented in Table 1. The mean age (± SD) for the entire cohort was 67 ± 11 years with 44 (60%) women; 60 (82%) had a history of smoking with 36 ± 28 pack-years exposure. Subcutaneous rheumatoid nodules were observed in 38%, rheumatoid factor positivity in 78%, and anti-cyclic citrullinated peptide (CCP) antibody positivity in 73%. A majority (77%) of patients presented with respiratory symptoms (dyspnea, cough, or chest pain) at time of lung nodule diagnosis. In five patients with lung malignancy, symptoms could be attributed to pneumonia (3 obstructive and 1 coincidental) and pleural effusion (n = 1). In three cases of rheumatoid lung nodule, symptoms were attributed to pneumonia (n = 1), pleural effusion (n = 1), and pneumothorax (n = 1). The remaining cases (23%) in the cohort were discovered incidentally in the absence of respiratory symptoms.

Compared to malignancy, patients with rheumatoid lung nodules were younger ($p < 0.001$), more likely to demonstrate subcutaneous rheumatoid nodules ($p < 0.001$) and rheumatoid factor seropositivity ($p = 0.034$), but less likely to have respiratory symptoms ($p < 0.001$). The majority of subjects in both groups had a smoking history ($p = 0.36$). There were no significant differences between the lung function parameters for patients with rheumatoid lung nodules compared to those with malignancy.

Radiographic features are presented in Table 2. Among the entire cohort, the mean number of nodules per patient was 6.2 ± 8.4 with a mean size (± SD) per nodule 21.3 ± 7.3 mm. CT features overall included smooth border (29%), spiculated border (39%), round shape (51%), cavitation (18%), air bronchogram (13%), semisolid appearance (13%), satellite nodules (25%), peripheral location (71%), subpleural location (54%), and subpleural rind of soft tissue (13%). Nodules

Table 1 Clinical features of rheumatoid lung nodules compared with malignancy

Feature	Total (n = 73)	Rheumatoid lung nodules (n = 23)	Malignancy (n = 50)	p value
Female gender	44 (60)	13 (57)	31 (62)	0.85
Age (year)	67 ± 11	59 ± 12	71 ± 9	< 0.001
Smoking history	60 (82)	17 (74)	43 (86)	0.36
Clinical presentation				
Respiratory symptoms[a]	56 (77)	12 (52)	44 (88)	< 0.001
Physical exam and serology[b]				
Subcutaneous nodules	24 (38)	16 (73)	8 (20)	< 0.001
Rheumatoid factor positivity	47 (78)	21 (96)	26 (68)	0.034
Anti-CCP antibody	32 (73)	16 (94)	16 (59)	0.029
Lung function[c]				
FEV_1% predicted	66 ± 20	67 ± 19	65 ± 21	0.64
FVC% predicted	79 ± 19	79 ± 20	80 ± 18	0.99
FEV_1/FVC	66 ± 14	70 ± 13	64 ± 14	0.14
TLC% predicted	102 ± 19	98 ± 18	104 ± 20	0.23
DLCO% predicted (corrected for Hgb)	62 ± 19	64 ± 19	61 ± 20	0.46

Data are summarized as n (%) for categorical variables, mean ± SD, median, and range for continuous variables. Comparisons across groups were made using the chi-square test or Kruskal-Wallis test as appropriate

FEV_1% forced expiratory volume in 1 s percent predicted, FVC% forced vital capacity percent predicted, TLC% total lung capacity percent predicted, DLCO% diffusing capacity for carbon monoxide percent predicted

[a] Respiratory symptoms include dyspnea, cough, and/or chest pain at the time of presentation

[b] Data missing for subcutaneous nodules (1 RA lung nodule and 9 malignancy), rheumatoid factor positivity (1 RA lung nodule and 12 malignancy), and anti-CCP antibody (6 RA lung nodules and 23 malignancy)

[c] Spirometry data was missing for four RA lung nodules and eight malignancy patients; TLC data missing for eight RA lung nodules and 14 malignancy patients and DLCO data was missing for five RA lung nodules and six malignancy patients

Table 2 Imaging findings of rheumatoid lung nodules compared with malignancy

CT features	Total, $n = 73$	Rheumatoid lung nodules ($n = 23$)[a]	Malignancy ($n = 50$)	p value
Solitary nodules	28 (38.9)	1 (4.5)	27 (54)	< 0.001
Mean number of nodules	6.2 ± 8.4	12.6 ± 10.7	3.4 ± 5.2	< 0.001
Mean size (mm)	21.3 ± 7.3	24.1 ± 8.4	20 ± 6	0.057
Smooth border	21 (29)	12 (55)	9 (18)	0.004
Spiculated border	28 (39)	3 (14)	25 (50)	0.008
Round shape	37 (51)	15 (68)	22 (44)	0.10
Cavitation	13 (18)	9 (41)	4 (8)	0.003
Air bronchogram	9 (13)	0	9 (18)	0.082
Semisolid	9 (13)	0	9 (18)	0.082
Calcification	3 (4)	1 (5)	2 (4)	> 0.99
Satellite nodules	18 (25)	12 (55)	6 (12)	< 0.001
Peripheral location	51 (71)	19 (86)	32 (64)	0.10
Subpleural location	39 (54)	16 (73)	23 (46)	0.066
Subpleural rind	9 (13)	6 (27)	3 (6)	0.033
^{18}FDG PET-CT[b]				
FDG-avid lymphadenopathy	5 (7)	0	5 (10)	0.30
SUV_{mean}	3.7 ± 2.2	1.8 ± 1.3	4.0 ± 2.2	0.011
SUV_{max}	6.6 ± 4.8	2.7 ± 2.0	7.2 ± 4.8	0.007

Data are summarized as n (%) for categorical variables, mean ± SD, median, and range for continuous variables. Comparisons across groups were made using the chi-square test or Kruskal-Wallis test as appropriate

FDG fluorodeoxyglucose (18F), *PET* positron emission tomography, *SUV* standardized uptake value

[a] Data for CT findings was missing for one patient with rheumatoid lung nodule who was evaluated by ^{18}FDG-PET only

[b] FDG PET-CT data was available to review among 47 malignancy and 7 rheumatoid lung nodules

appeared evenly distributed throughout the upper zone (45%), middle zone (34%), and lower zone (23%). Calcification (4%) was rare.

Distinguishing features of rheumatoid lung nodules compared with malignancy were multiplicity (12.6 ± 10.7 vs 3.4 ± 5.2, $p < 0.001$), smooth borders (55% vs 18%, $p = 0.004$), cavitation (41% vs 8%, $p = 0.003$), satellite nodules (55% vs 12%, $p < 0.001$), and subpleural rind (27% vs 6%, $p = 0.033$) (Figs. 1, 2, 3). To create an imaging *rheumatoid lung nodule score*, each of the key six findings suggestive of rheumatoid lung nodule present on a CT scan were summed (≥ 4 nodules, peripheral location, cavitation, satellite nodules, smooth border, and subpleural rind of soft tissue). A score of ≥ 3 maximized the sensitivity (77%), specificity (92%), and AUC 0.85 (CI 0.75–0.94) for a rheumatoid lung nodule. To create a combined clinical and imaging rheumatoid lung nodule score, each of the key eight findings suggestive of rheumatoid nodule was summed (subcutaneous rheumatoid nodule, seropositivity, ≥ 4 nodules, peripheral location, cavitation, satellite nodules, smooth border, and subpleural rind of soft tissue). A score of ≥ 4 maximized sensitivity (95%), specificity (85%), and AUC (0.90, CI 0.83–0.98).

Key ^{18}FDG-PET/CT features (per largest/most avid nodule) for rheumatoid lung nodule compared with malignancy included low-level metabolism (SUV_{mean} 1.8 ± 1.3 vs 4 ± 2.2, $p = 0.011$ and SUV_{max} 2.7 ± 2.0 vs 7.2 ± 4.8, $p = 0.007$). None of the rheumatoid lung nodule patients demonstrated FDG-avid mediastinal or hilar lymphadenopathy compared to five (10%) of malignancy (Fig. 4). PET-CT data was only available for 47/50 patients with malignancy and 7/23 patients with rheumatoid lung nodule(s), and therefore these findings were not added to the rheumatoid lung nodule score calculations.

Among the 23 patients with rheumatoid lung nodules, six patients (26%) were deceased at the time of study with a median survival of 11.9 years from diagnosis (95% confidence interval, 11.3 years-infinity). Among the 50 patients with malignancy, 28 patients (56%) were deceased at the time of study with a median survival of 5.3 years from diagnosis (95% confidence interval, 2.9–8.1 years). Patients with rheumatoid lung nodules had longer survival ($p = 0.001$, Fig. 5).

Discussion

This study describes clinical and imaging features associated with rheumatoid lung nodules in comparison to malignant lung nodules in rheumatoid patients. To the best of our

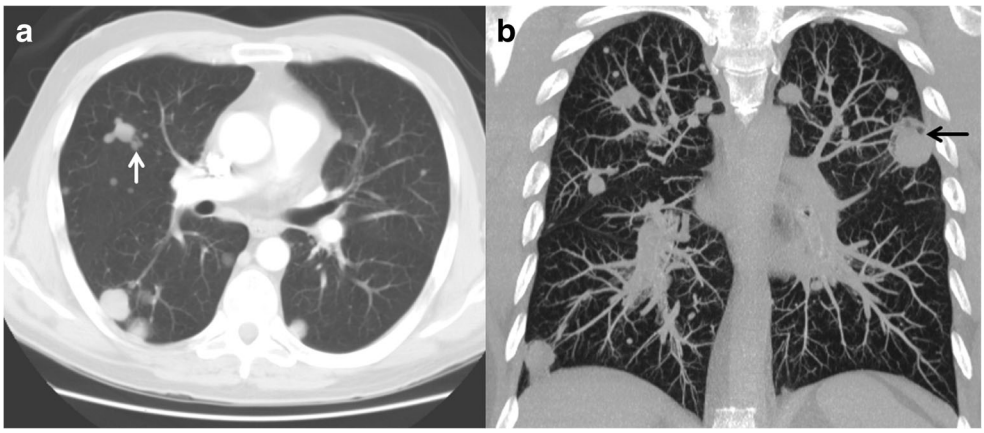

Fig. 1 CT appearance of rheumatoid lung nodules. Sixty-one-year-old male with rheumatoid arthritis. Axial (**a**) and coronal maximum intensity projection (**b**) CT images of the chest demonstrating multiple, well-circumscribed solid nodules. Surrounding satellite nodules (white arrow) and developing cavitation (black arrow) are noted

knowledge, this is the largest single study of histologically-proven lung nodules in patients with rheumatoid disease. The most striking imaging finding was multiplicity of nodules (mean of 13 nodules per patient) in those with rheumatoid lung nodules. The dominant rheumatoid lung nodules were nearly all peripheral in location or abutting the pleura. They were solid, typically round with smooth borders, and often associated with satellite nodules (Fig. 1). Subpleural rheumatoid nodules appeared to coalesce into a confluent subpleural rind of soft tissue (Fig. 2). Rheumatoid lung nodules may cavitate but calcification was rare (Fig. 3). Compared to malignancy, FDG avidity was low to moderate for rheumatoid lung nodules but there was an overlap in the degree of FDG uptake between rheumatoid lung nodules and malignancies. Rheumatoid lung nodules may present with a characteristic subpleural rind of hypermetabolic soft tissue thickening but were rarely associated with enlarged or FDG-avid draining lymph nodes and no such examples were seen in this study (Fig. 4).

Clinically, patients with rheumatoid lung nodules tended to be younger and more commonly manifest subcutaneous rheumatoid nodules and seropositivity. The majority in both groups had a smoking history. Most patients did not have symptoms or complications directly referable to rheumatoid lung nodules at the time of presentation and exhibited near-normal lung function measurements.

Several observations described here for rheumatoid lung nodule, such as multiplicity, peripheral location, and cavitation, have been previously described [4, 12, 13, 17, 24, 25]. In

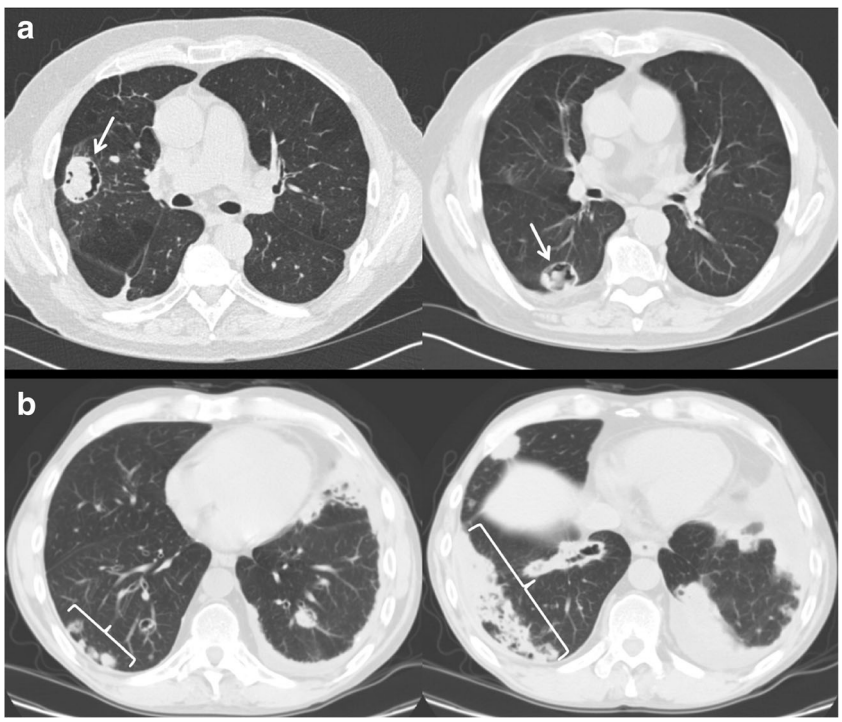

Fig. 2 Necrobiotic cavitary nodules. **a** Axial CT images of the thorax demonstrating two necrobiotic cavitary lesions with thick internal debris (arrows). Subpleural rind. **b** Axial CT images of the thorax demonstrating subpleural nodules (left panel) which coalesce into a thick subpleural rind of soft tissue (white bracket)

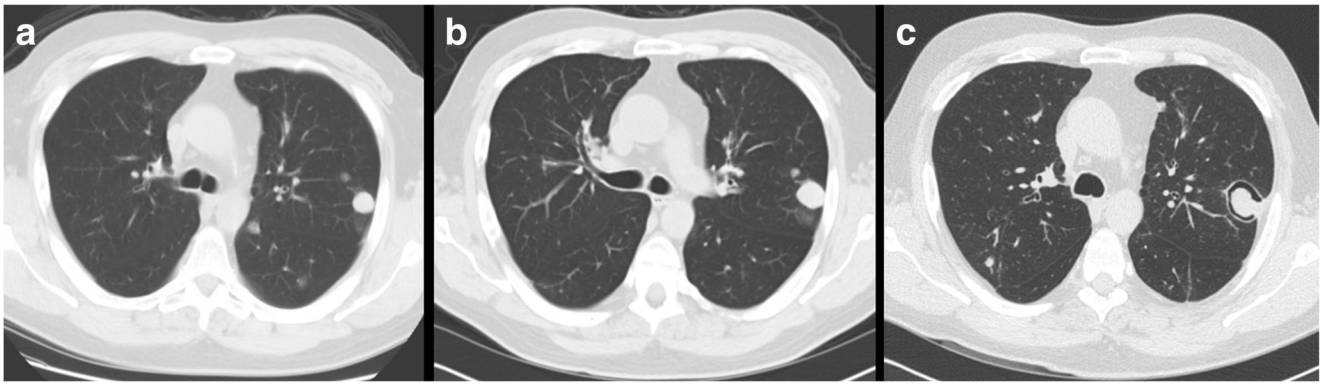

Fig. 3 Progression of rheumatoid lung nodule to cavitary disease. Sixty-seven-year-old male with rheumatoid arthritis. A left peripheral solid nodule (**a**) slowly enlarges over the course of 2 years (**b**). Five years later, that nodule has progressed into cavitary disease (**c**)

our study, most patients with rheumatoid lung nodule(s) had a history of smoking and elevated serum levels of rheumatoid factor which are also risk factors for subcutaneous rheumatoid nodules [26–28]. The majority of patients were female, supporting a recent report on higher female prevalence [12]. Most, albeit older, studies report a male predominance [13, 24, 25, 29]. The discrepancy may be explained by a higher prevalence of smoking among males compared to females in earlier cohorts and occupational exposures that may increase the risk of rheumatoid nodules [29, 30].

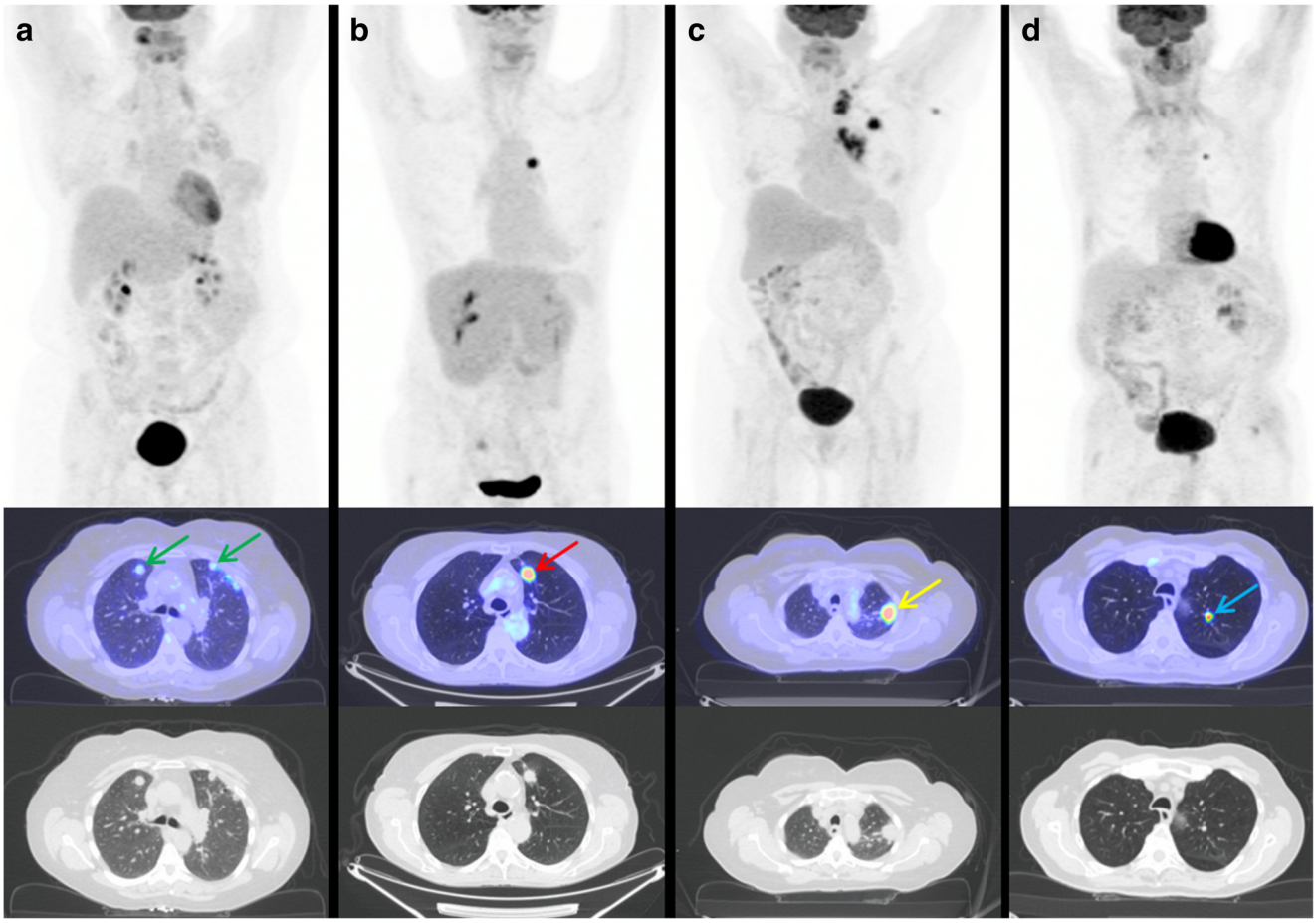

Fig. 4 PET/CT appearance of lung nodules (benign and malignant) in rheumatoid patients. Maximum intensity projection (top row), fusion (middle row), and computed tomography (bottom row) FDG PET-CT images of rheumatoid arthritis patients with histologically-proven pulmonary nodules. Rheumatoid nodules (**a**) presenting as multiple, well-circumscribed peripheral solid nodules with low FDG activity (green arrows). Squamous cell carcinoma (**b**) presenting as a solitary intensely FDG-avid solid nodule (red arrow). Adenocarcinoma (**c**) presenting as a solitary intensely FDG-avid solid nodule (yellow arrow) with several FDG-avid ipsilateral lymph nodes. Pulmonary carcinoid (**d**) presenting as a tiny solitary intensely FDG-avid peribronchovascular pulmonary nodule (blue arrow)

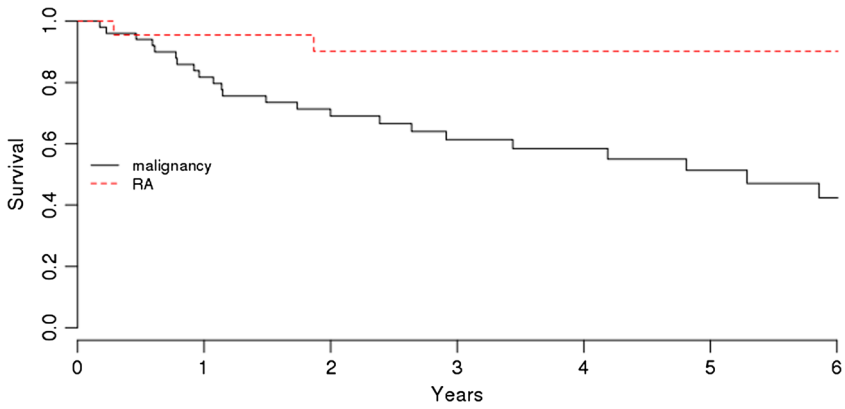

Fig. 5 Kaplan-Meier survival curve of rheumatoid patients with histologically-proven rheumatoid lung nodules compared with rheumatoid patients with lung malignancy (median survival 11.9 vs 5.3 years, $p = 0.001$)

The prevalence of lung nodules in rheumatoid patients depends on the method of detection. Among 516 consecutive patients with RA reported in the 1960s, lung nodules were rare and detected in less than 1% utilizing chest roentgenograms [18, 31]. As expected, the prevalence was higher among studies using CT scans (10–22%) [15, 16] as well as pathologic studies of lung in rheumatoid patients (30%) [17]. Few studies, if any, report associated mediastinal adenopathy with rheumatoid lung nodules. In our study, none of the PET scans demonstrated FDG-avid mediastinal or hilar lymphadenopathy.

Jolles et al described seven patients with seropositive RA with subcutaneous nodules who presented with a new pulmonary nodule(s) on chest radiography [3]. Although lung cancer was diagnosed in all patients, several observations deserve mention. All had a *new* nodule(s), three had extensive mediastinal disease, and the majority had new or worsening respiratory symptoms. In contrast, none of the patients in our cohort had mediastinal disease and the majority was asymptomatic at presentation.

Rheumatoid lung nodules appear to be associated with a good prognosis. In the study by Yousem et al [17] of lung biopsy in RA, all 11 patients who manifested rheumatoid lung nodules as the dominant pattern of lung involvement were alive with asymptomatic or stable disease (follow-up duration, 4 months to 8 years). In contrast, patients with RA-associated interstitial lung disease, such as organizing pneumonia or usual interstitial pneumonia, demonstrated increased mortality [17]. In our study, six patients with rheumatoid lung nodules were deceased with a median survival of 12 years from diagnosis. As expected, patients with rheumatoid lung nodules demonstrated significantly improved survival compared to those with malignancy (Fig. 5).

The main findings in our study have important clinical implications in the management of patients with RA and pulmonary nodules, especially in those with risk factors associated with lung cancer. Features characteristic of rheumatoid lung nodules may reduce the concern of cancer for such patients or guide nodule selection for invasive procedures, particularly when evaluating multiple nodules. Optimal sensitivity (77%) and specificity (92%) (AUC 0.85, CI 0.75–0.94) were obtained for rheumatoid lung nodule(s) with ≥ 3 imaging findings (≥ 4 nodules, peripheral location, cavitation, satellite nodules, smooth border, and subpleural rind). Results improved when clinical and imaging features were combined: 95% sensitivity and 85% specificity (AUC 0.90, CI 0.83–0.98) for rheumatoid lung nodule with ≥ 4 findings (subcutaneous rheumatoid nodule, seropositivity, ≥ 4 nodules, peripheral location, cavitation, satellite nodules, smooth border, and subpleural rind). Results for combined clinical and imaging features should be interpreted with caution due to missing clinical data (subcutaneous rheumatoid nodule and/or serologic data were incomplete for 16/50 subjects with malignancy). Nonetheless, these characteristic features of rheumatoid lung nodule may guide risk assessment of pulmonary nodules in rheumatoid patients.

There are limitations of our study which include those inherent in the retrospective design. The study did not aim to identify rheumatoid patients with pulmonary nodules whom were not referred for lung biopsy and the absence of such patients for comparison is a potential source for selection bias. Our findings are strengthened by the blinded fashion of radiologic interpretation without knowledge of clinical data or histologic diagnosis at the time of assessment. The ^{18}FDG-PET results should be interpreted with caution due to the small sample size. Prospective study of ^{18}FDG-PET in patients with rheumatoid arthritis and lung nodules may provide more definitive conclusions.

Conclusion

Rheumatoid patients with rheumatoid lung nodules are more likely to manifest subcutaneous rheumatoid nodules and seropositivity and tend to be younger than those with malignancy but a history of smoking is common in both groups. When compared to malignancies in the lung, rheumatoid lung nodules appear to have distinctive imaging features including multiplicity, smooth border, satellite nodules, cavitation, and

peripheral location with occasionally associated subpleural rind of confluent soft tissue. Rheumatoid lung nodules manifest low to moderate FDG avidity and are not associated with FDG-avid draining lymph nodes.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Jay H. Ryu.

Conflict of interest Dr. Johnson has received research funding from Pfizer which is not relevant to this work. None of the additional co-authors have relevant disclosures.

Statistics and biometry Mr. Paul A. Decker kindly provided statistical advice for this manuscript.

Informed consent The study was approved by the Mayo Clinic Institutional Review Board (IRB16-006571). According to Mayo Clinic institutional policy, patient information may be used for research purposes only with prior patient consent.

Ethical approval Institutional Review Board approval was obtained by the Mayo Clinic Institutional Review Board (IRB16-006571).

Study subjects or cohorts overlap None of the study subjects or cohorts have been previously reported except for abstract presentation at the American Thoracic Society International Conference 2017.

Methodology
- Retrospective
- Case-control study
- Performed at one institution

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