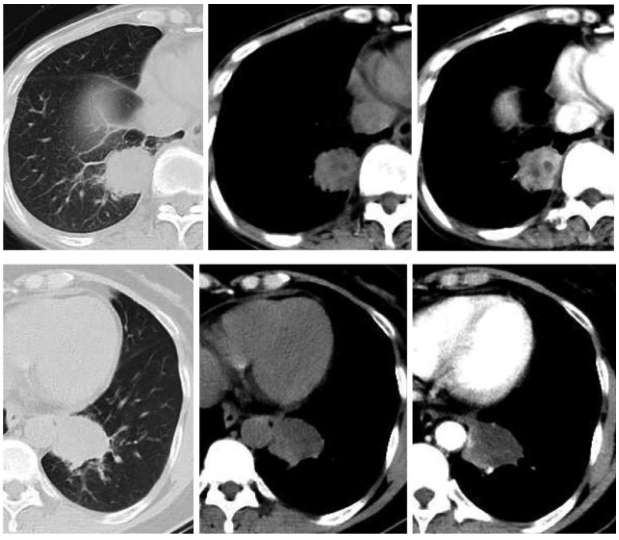
Radiology Science

Original Research

Differences in clinical manifestations and CT features between pulmonary actinomycosis and aspergillus nodules, as revealed by a solitary pulmonary nodule or mass

Graphical abstract



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Key points

- This study secondarily analyzed prospectively collected data for 17 patients with pulmonary actinomycosis and 25 patients with *Aspergillus* nodules. Pulmonary actinomycosis was more likely than pulmonary aspergillosis to occur in men.
- Patients with pulmonary actinomycetes were more likely to exhibit a mass, with bulky volume ill-defined margins, and interlobular septal thickening.
- Patients with *Aspergillus* nodules were more likely to exhibit cavitation, air-crescent sign, bronchiectasis, and calcifications.

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Differences in clinical manifestations and CT features between pulmonary actinomycosis and aspergillus nodules, as revealed by a solitary pulmonary nodule or mass

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Abstract

Background: Pulmonary actinomycosis is a rare bacterial disorder often misdiagnosed as other pulmonary diseases because of a lack of specific characteristics and radiographic findings. *Aspergillus* nodules, a common fungal infection and form of chronic pulmonary aspergillosis, have imaging findings that overlap with those of pulmonary actinomycosis. This study reviews patients' clinical and imaging data, to differentiate pulmonary actinomycosis from *Aspergillus* nodules.

Methods: This retrospective study included 17 patients with pulmonary actinomycosis and 25 patients with *Aspergillus* nodules diagnosed histopathologically in a tertiary Chinese hospital between June 2014 and January 2022. Data on age, sex, lesion types/locations, and CT findings were analyzed.

Results: No significant differences were found in age (mean age 58.2 ± 7.7 vs. 57.2 ± 11.9; $p = 0.76$), but statistically significant differences were found in sex (men 13 vs. women 10; $p = 0.02$), between groups. Common symptoms between groups included cough, hemoptysis, sputum production, fever, and chest pain, which showed no significant between-group differences ($p = 0.09$, $p = 0.28$, $p = 0.10$, $p = 1$, $p = 0.41$, respectively). Visual evaluation revealed that pulmonary actinomycosis lesions were more likely than pulmonary aspergillosis to appear mass-like ($p < 0.001$), with bulky volume ($p = 0.002$), ill-defined margins ($p = 0.045$), and interlobular septal thickening ($p = 0.008$). Pleural changes and mediastinal or hilar lymphadenopathy were more common in pulmonary actinomycosis than in *Aspergillus* nodules ($p = 0.037$, $p = 0.010$, respectively), whereas cavitation, an air-crescent sign, and bronchiectasis were more common in pulmonary aspergillosis ($p = 0.027$, $p < 0.001$, $p = 0.016$, respectively).

Conclusion: Distinguishing between pulmonary actinomycosis and *Aspergillus* nodules on the basis of clinical manifestations alone is difficult, although distinctive CT findings may differentiate the two diseases.

Keywords: *Aspergillus* nodules, computed tomography, differential diagnosis, pulmonary actinomycosis

1. INTRODUCTION

Actinomyces spp. are higher prokaryotic bacteria belonging to the family Actinomyceataceae. *A. israelii*, isolated in 1891, is the main species of *Actinomyces* responsible for human disease [1]. Pulmonary actinomycosis (*Actinomyces pneumoniae)* is the third most common form of human actinomycosis after cervicofacial and abdomino-pelvic actinomycosis [2]. Several factors, including improvements in oral hygiene, sensitivity to antibiotics, and common use of antibiotics, have made the presentation and incidence of pulmonary actinomycosis appear rarer than those in the pre-antibiotic era [2, 3]. Pulmonary actinomycosis is a chronic, slowly progressing disease that is difficult to diagnose, even by experienced physicians, because of its nonspecific symptoms and radiological findings.

Pulmonary aspergillus nodules are an uncommon subtype of chronic pulmonary aspergillosis, a slowly progressing pulmonary infection caused by *Aspergillus* species, typically *Aspergillus fumigatus* [4, 5]. Most *Aspergillus* nodules are rounded in appearance and smaller than 3 cm in diameter, and may display low attenuation or cavitation [5]. *Aspergillus* nodules may mimic many other benign or malignant lung diseases. In fact, most *Aspergillus* nodules are mistaken for lung cancer [6, 7], and some are misdiagnosed as pulmonary actinomycetes because of their similar computed tomography (CT) manifestations [7-9].

Although the clinical and imaging findings of pulmonary actinomycosis and *Aspergillus* nodules are similar, the treatment regimens vary widely. *Aspergillus* nodules can be definitively diagnosed only through histologic examination, and most patients choose to undergo lesion resection for detection and treatment of the disease; antifungal therapy after resection surgery is not recommended for immunocompromised patients [5]. However, the main principle of treatment for pulmonary actinomycosis is long-term high-dose intravenous penicillin. When surgery is the initial treatment, even if histology suggests complete resection, prolonged antibiotic therapy remains necessary, because surgery alone is usually not curative [2, 10, 11]. Therefore, early recognition and practical differentiation between diseases may enable prompt treatment and good prognosis. However, previous studies have been limited to case reports, which have suggested that the two diseases are often confused [7-9]. Hence, we retrospectively compared the clinical manifestations and CT features for more patients with pulmonary actinomycosis or *Aspergillus* nodules than reported previously, with an aim to differentiate pulmonary actinomycosis from *Aspergillus* nodules.

2. MATERIALS AND METHODS

2.1 Study design and setting

We retrospectively reviewed the medical records of consecutive patients with histopathologically confirmed pulmonary actinomycosis or pulmonary aspergillosis who were hospitalized and treated at the First Affiliated Hospital, Medical School of Zhejiang University, Hangzhou, China, between June 2014 and January 2022.

2.2 Inclusion and exclusion criteria

All cases were pathologically confirmed through biopsy with either surgical or nonsurgical methods. All patients underwent at least one chest CT before diagnosis, and imaging data were available. Patients with imaging findings of solitary pulmonary nodules or masses were screened via retrospective analysis of imaging data from the most recent scan before surgery or biopsy. Patients with aspergillomas and those with cavitating lung lesions, with or without fibrosis, were excluded. Patients with a diagnosis of invasive aspergillosis were also excluded.

2.3 Data collection

Patient data were extracted from inpatient electronic medical records. Patients' demographic and clinical data were collected, including age, sex, symptoms, and signs. The most recent chest CT images before surgery or biopsy were also reviewed. On the basis of size, lesions with round or round-like opacities no more than 3 cm in diameter were classified as nodules or masses. The lesion location (i.e., lobe) and accompanying CT signs (e.g., cavitation, central necrotic low attenuation, air-crescent sign, bronchiectasis, or calcifications) were recorded. Cavitation was defined as radiolucency within a nodular area or mass consolidation. The air-crescent sign was defined as crescent-like radiolucency within a nodular area or mass consolidation. Extrapulmonary findings, including pleural changes, pleural effusion, and mediastinal or hilar lymphadenopathy, were reviewed and analyzed on axial CT.

CT scans were obtained with a Phillips Brilliance 64-channel CT (Philips North America Corporation, Andover, MA, USA) and GE Lightspeed VCT System (GE Healthcare, Chicago, IL, USA) with 5 mm thick sections. The patients were scanned in supine position, and the scan range was from the apex to the base of the lung. The tube voltage was 120 kVp, and the tube current was automatically adjusted (150–200 mAs). The pitch was 1, and the FOV was 250 mm × 250 mm. A total of 23 patients underwent contrast-enhanced scanning, and contrast-enhanced chest CT images were obtained with a 30 s delay after injection of Lopromide (350 mg/ml, 1.2 ml/kg) at a rate of 4.3 ml/s with a power injector.

2.4 Statistical analysis

Categorical variables such as sex, lesion type, lesion location, and various CT signs were analyzed with Pearson's chi-square test or Fisher's exact test. Continuous variables are expressed as mean ± SD and were analyzed with two-sample t-tests. A p value < 0.05 was considered to indicate statistical significance. All analyses were performed in SPSS for Windows ver. 22.0 (IBM SPSS, Chicago, IL, USA).

3. RESULTS

The data for 42 patients (17 with pulmonary actinomycosis and 25 with pulmonary aspergillosis) were evaluated. The baseline characteristics and clinical manifestations of all patients are summarized in **Table 1**. The mean age in the pulmonary actinomycosis group was 58.2 ± 7.7 (range, 43–75), and 13 (76%) were men. The mean age in the pulmonary aspergillosis group was 57.2 ± 11.9 years (range, 22–71), and 10 (40%) were men. Compared with pulmonary aspergillosis, pulmonary actinomycosis was more likely to occur in men (76% vs. 40%, p = 0.02). Although older adults (> 65 years of

Table 1 | Baseline characteristics and clinical manifestations in patients with pulmonary actinomycosis and *Aspergillus* nodules.

Parameter	Pulmonary actinomycosis group	*Aspergillus* nodule group	p value
Mean age ± SD (range)	58.2 ± 7.7(43–75)	57.2 ± 11.9(22–71)	0.758
Sex			0.020
No. of men	13(76%)	10(40%)	
No. of women	4(24%)	15(60%)	
Clinical manifestations			
Cough	12(71%)	11(44%)	0.089
Hemoptysis	9(53%)	9(36%)	0.276
Sputum production	9(53%)	7(28%)	0.102
fever	2(12%)	3(12%)	1*
Asymptomatic	3(18%)	6(24%)	0.716*
chest pain	1(6%)	0(0%)	0.405*

Note: *Fisher's exact probability method was used.

age) are more susceptible to both actinomycetes and aspergillus, no statistical differences were found in age between groups in the present study.

The most common symptoms of patients in the pulmonary actinomycetes vs. *Aspergillus* nodules groups were cough (70.6% vs. 44%), followed by hemoptysis (52.9% vs. 36%) and sputum production (52.9% vs. 28%). Fever (11.8% vs. 12%, respectively) was relatively infrequent. Only one patient (5.9%) with pulmonary actinomycetes complained of chest pain. Some patients were asymptomatic with pulmonary actinomycetes (17.6%) or pulmonary aspergillus (24%). Nevertheless, no significant differences were found between groups in the symptoms listed above ($p = 0.089$, 0,276, 0.102, 0.716, 0.405, 1, respectively).

Compared with patients with pulmonary aspergillus, patients with pulmonary actinomycetes were more likely to exhibit masses (94% vs. 76%, $p < 0.001$) with bulky volume ($p = 0.002$), ill-defined margins ($p = 0.045$), and interlobular septal thickening ($p = 0.045$). No significant differences were found between groups in the distribution of lesions in the lung lobes. Results are shown in **Table 2**. One lesion in the pulmonary actinomycetes group grew across the lung lobes. The accompanying CT signs in the two groups indicated that patients in the pulmonary aspergillus group, compared with the actinomycetes group, were more likely to exhibit significant differences in the following characteristics: cavitation (44% vs. 12%, $p = 0.027$), air-crescent sign (6% vs. 24%, $p < 0.001$), bronchiectasis (6% vs. 40%, $p = 0.016$), and calcifications (18% vs. 28%, $p < 0.001$). The pulmonary actinomycetes group showed more central necrotic low attenuation, but the difference was not statistically significant (82% vs. 64%, $p = 0.300$). Significant differences were noted in some extrapulmonary findings, including pleural changes and mediastinal or hilar lymphadenopathy (**Table 2**), which were more common in the pulmonary actinomycetes group.

Nearly half the patients with pulmonary actinomycetes or aspergillosis were initially diagnosed with tumors or had no definite diagnosis; the remaining patients were initially diagnosed with inflammatory or infectious mass lesions. No specific infection type was given, except for two patients who were diagnosed with aspergillosis.

4. DISCUSSION

The pulmonary form of actinomycosis is a rare chronic disease characterized by necrosis and abscess formation, tissue fibrosis, and cavitation [12]. The disease is not clearly associated with an immunocompromised state, and it usually occurs in immunocompetent people but may sometimes occur in immunosuppressed people. People with human immunodeficiency virus have been reported to develop actinomycosis, although the reported incidence of actinomycosis in these patients has remained low [13, 14]. *Aspergillus* nodules are a less common form of chronic pulmonary aspergillosis, and other manifestations include chronic cavitary pulmonary aspergillosis, single aspergilloma, subacute invasive pulmonary aspergillosis, and chronic fibrosing pulmonary aspergillosis. Many different and typical presentations have been reported in different types of chronic pulmonary aspergillosis, and considerable overlap exists among different forms of the disease [15]. *Aspergillus* nodules are usually found in non-immunocompromised patients with prior or current lung disease [5]. Likewise, pulmonary actinomycosis is frequently observed as a secondary and localized infection, often with lung involvement, particularly in residual cavities or bronchiectasis [16].

Table 2 | CT findings in patients with pulmonary actinomycosis and *Aspergillus* nodules.

Parameter	Pulmonary actinomycosis group (%)	*Aspergillus* nodule group (%)	p value
Lesion type			0.000*
Nodules	1(6%)	6(24%)	
Masses	16(94%)	19(76%)	
Size (mm)	48.5 ± 14.8	34.0 ± 13.0	0.002
Lesion location			0.783*
RUL	5(28%)	11(44%)	
RML	2(11%)	2(8%)	
RLL	4(22%)	6(24%)	
LUL	4(22%)	4(16%)	
LLL	3(17%)	2(8%)	
Distribution			0.855
Inner one-third of lung	7(23%)	9(27%)	
Middle one-third of lung	13(42%%)	11(33%)	
Outer one-third of lung	11(35%)	13(40%)	
Accompanying CT signs			
Cavitation	2(12%)	11(44%)	0.027
Central necrotic low attenuation	14(82%)	16(64%)	0.300*
Ill-defined margin	6(35%)	2(8%)	0.045*
Irregular or spiculated edge	7(41%)	7(28%)	0.374
Interlobular septal thickening	8(47%)	2(8%)	0.008*
Air-crescent sign	1(6%)	6(24%)	0.000*
Bronchiectasis	1(6%)	10(40%)	0.016*
Calcifications	3(18%)	12(48%)	0.000*
Extrapulmonary findings			
Pleural changes	11(65%)	8(32%)	0.037
Pleural effusion	0	2(8%)	0.506
Mediastinal or hilar lymphadenopathy	7(41%)	3(18%)	0.019*
Initial diagnosis			0.440*
Tumor	6(35%)	5(20%)	
Inflammatory or infectious mass lesion	9(53%)	14(56%)	
No definite diagnosis	2(12%)	6(24%)	

Note: *Fisher's exact probability method was used. Abbreviations: RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe.

Data from the present study suggest a male predominance in patients with pulmonary actinomycosis, which has been reported to affect more than three times as many men as women [17, 18]. In the present study, the mean age of patients with pulmonary actinomycosis was in the 50s, in agreement with the findings of recent series [18-20]. Meanwhile, the present study showed a higher incidence of infection in women (women vs. men, 60% vs. 40%) with *Aspergillus* nodules, a proportion slightly higher than that reported in previous studies [6, 21]. Most *Aspergillus* nodules occurred in middle age in the present study, and no

differences were found in mean patient age between groups.

The clinical manifestations of pulmonary actinomycosis and *Aspergillus* nodules were nonspecific, and no significant differences were found between diseases in the present study, although cough, hemoptysis, and sputum production were the most common complaints in both disease groups. In the present study, compared with findings from European studies [20, 22], hemoptysis was more commonly seen, and fever and chest pain were less commonly seen, in patients with pulmonary actinomycosis; our findings are in agreement with the results of a single-center study conducted in China [18]. Thus, patients in different regions may have different clinical manifestations, and the disease may be more aggressive in the developing world. The high incidence of hemoptysis has been ascribed to the accompanying and underlying structural diseases of pulmonary actinomycosis [19]. *Aspergillus* nodules were not found to be associated with weight loss and dyspnea in the present study, although these symptoms have been common in other studies [6]. Both pulmonary actinomycosis or *Aspergillus* nodules can also be present in asymptomatic patients. Previous studies have suggested that the evolution of

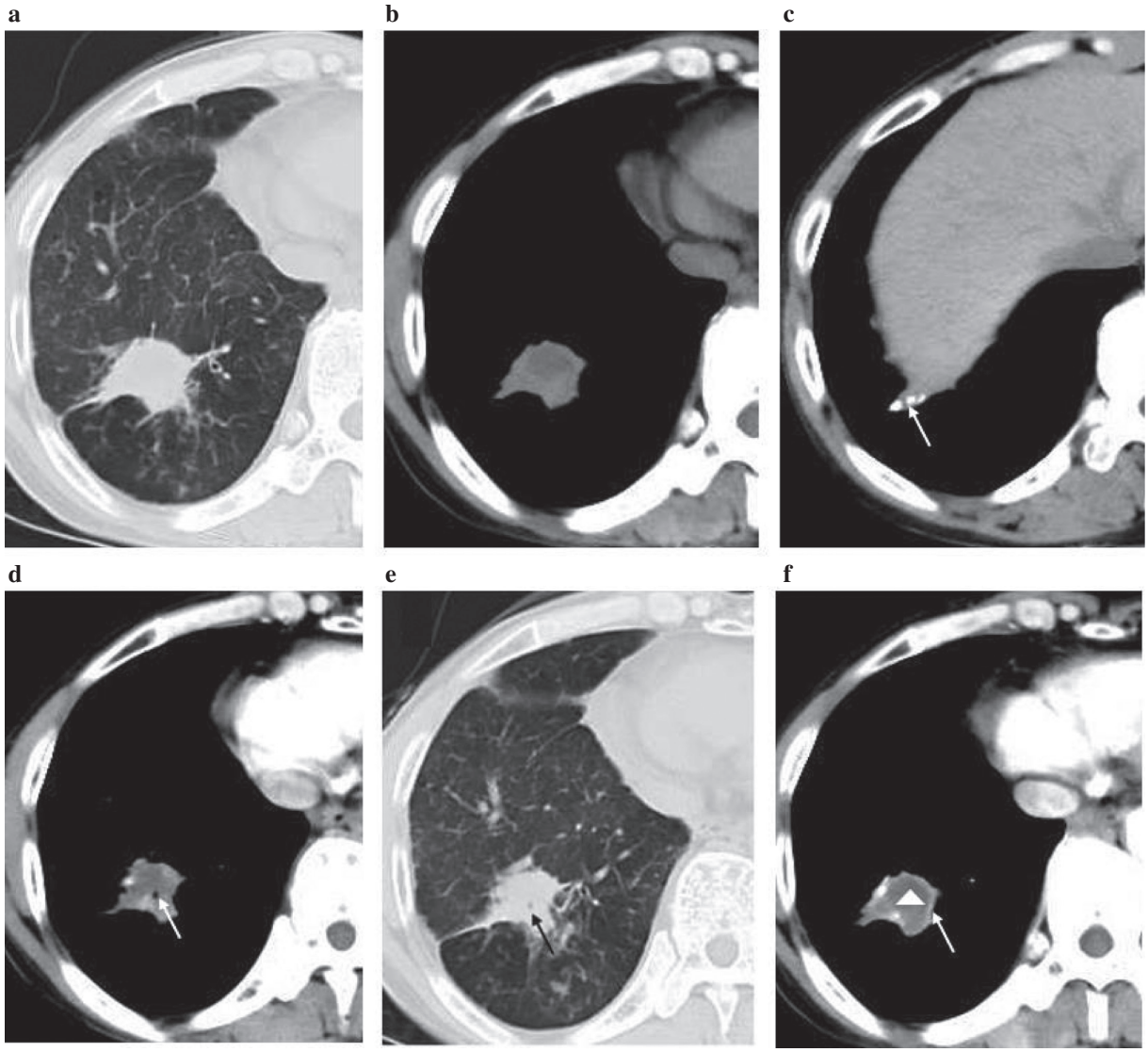

Figure 1 | A 52-year-old woman presented with a 4-week history of cough and hemoptysis.
a. CT image obtained with lung window settings, showing a solitary mass with a spiculated edge (size, 3.5 cm × 2.8 cm) **b** and **c**. CT image obtained with mediastinal window settings, showing a mass containing central low-attenuation area and calcifications (white arrow). **d** and **e**. Contrast-enhanced CT image obtained with mediastinal and lung window settings, showing a cavity (white and black arrow). **f**. Contrast-enhanced CT image, showing a central low-attenuation area (arrowhead) with no enhancement and brim enhancement (white arrow).

Aspergillus nodules correlates poorly with clinical course [23]. These findings allow objective radiological criteria to be used in disease diagnosis, to assess patients' therapeutic responses to treatment and to facilitate long-term monitoring [24].

In the present study, neither pulmonary actinomycosis nor *Aspergillus* nodules showed specific distinguishing features on chest CT, and the accuracy of initial diagnosis is relatively low, but several distinctive differences were still noted. Patients with *Aspergillus* nodules were more likely to exhibit cavitation, air-crescent sign, bronchiectasis, and calcifications as is shown in the Figures 1 and 2. The typical appearance of *Aspergillus* nodules involves single or multiple nodular lesions, with or without cavitation, most of which are solitary and smaller than 3 cm [5]. *Aspergillus* nodules also showed an upper lobe predominance in the present study, similarly to those reported in other studies [6]. However, lesions of pulmonary actinomycosis were located in the right, left, upper, middle, and lower lobes at similar rates. According to Kim et al. [25], the CT findings of pulmonary actinomycosis may vary at different stages of disease, and the lesions may gradually increase and manifest as a consolidation, which sometimes crosses the adjacent interlobar fissure or becomes a mass in later stages. A mass or nodosity with central necrotic low attenuation is a distinct CT feature of parenchymal actinomycosis. In the present study, pulmonary actinomycosis lesions were more likely to appear mass-like with bulky volume, ill-defined margins, and interlobular septal thickening (Figures 3 and 4). Various factors may account for the bulky volume, including the limited medical resources in areas of developing China, people's lack of awareness of seeking medical treatment or taboo of medical treatment. Pathological examination of the poorly defined margins indicates intra-alveolar fibrinous exudate with inflammatory cell infiltration [25]. The air-crescent sign was also seen in pulmonary actinomycosis lesions (Figure 5), albeit less frequently than in *Aspergillus* nodules. This sign can be considered to indicate disease progression to varying degrees. According to a prior study, with the slow progression of infection, pulmonary nodules—the early manifestations of disease—gradually increase in extent and present as an air-space consolidation or a mass [25].

Compared with those for *Aspergillus* nodules, extrapulmonary findings in CT scans of pulmonary actinomycosis indicated that some characteristics, pleural thickening and adhesion were more common in pulmonary actinomycosis. This difference might be associated with a decrease in invasiveness with respect to that in the pre-antibiotic era, and the peripheral predominance. In the pre-antibiotic era, the classic presentation of pulmonary actinomycosis was chest wall invasion and cutaneous fistulas discharging sulfur granules [2]. Hilar and/or mediastinal lymphadenopathy were observed more often on CT images in pulmonary actinomycosis in the present study, as confirmed by the presence of pathologically reactive hyperplasia lesions. The relevant literature has also indicated that mediastinal lymphadenopathy is common [2].

5. STRENGTHS AND LIMITATIONS

To our knowledge, this is the first relatively large series comparing the differences in clinical manifestations and CT features between pulmonary actinomycosis

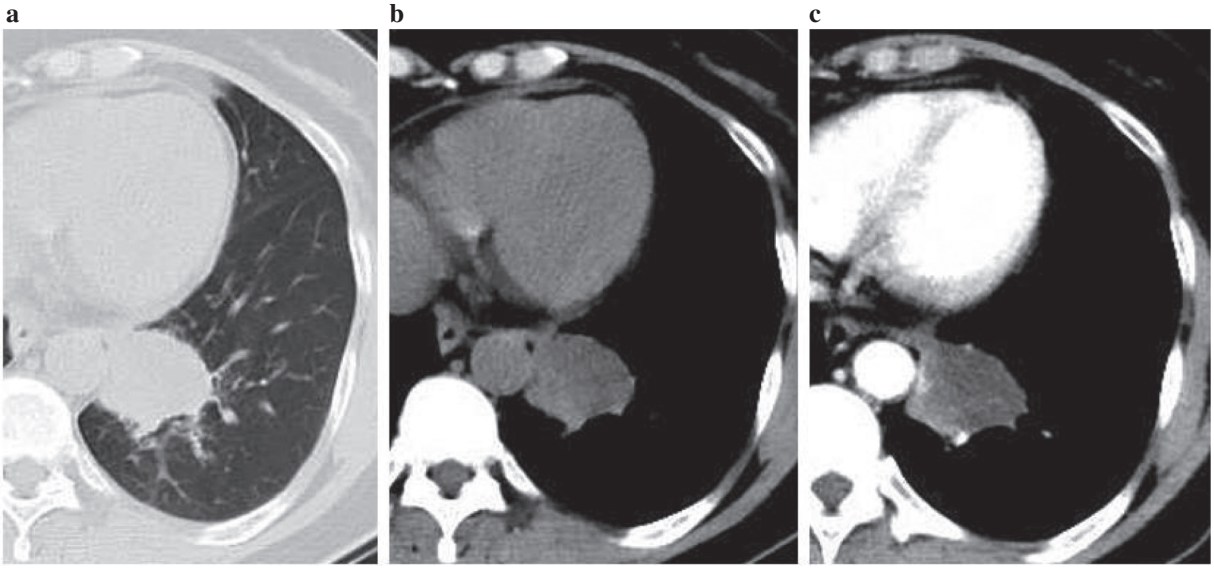

Figure 2 | A 52-year-old asymptomatic woman diagnosed with *Aspergillus* nodule.
a. CT image obtained with lung window settings, showing a solitary and circumscribed mass lesion (size, 3.0 cm × 3.5 cm). **b** and **c**. CT image obtained with mediastinal window settings, showing a mass containing a central low-attenuation area and minimal rim enhancement.

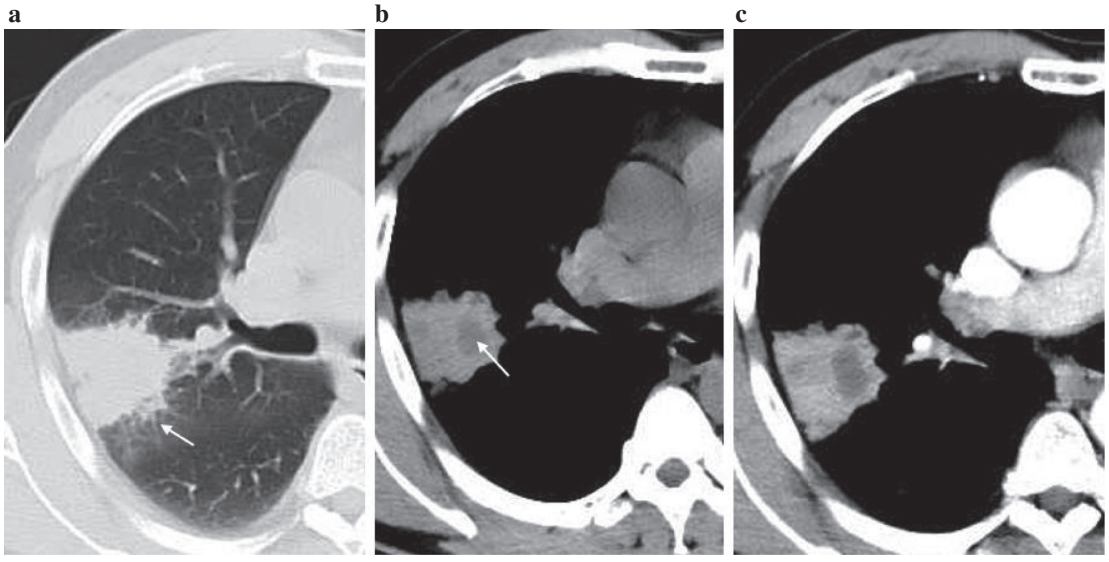

Figure 3 | A 51-year-old man diagnosed with pulmonary actinomycosis on the basis of surgical pathology, presented with a productive cough and sputum production for 4 weeks before surgery.
a. Contrast-enhanced CT image obtained with lung window settings, showing a poorly defined peripheral pulmonary mass in the right upper lobe (size, 4.3 cm × 3.9 cm). Surrouding areas of thickened interlobular septa (white arrow) are indicated. **b.** Image of A obtained with mediastinal window settings, showing a low-attenuation area in the lesion (white arrow). **c.** Contrast-enhanced CT image obtained with mediastinal window settings, showing a central low-attenuation area with a peripherally enhanced portion.

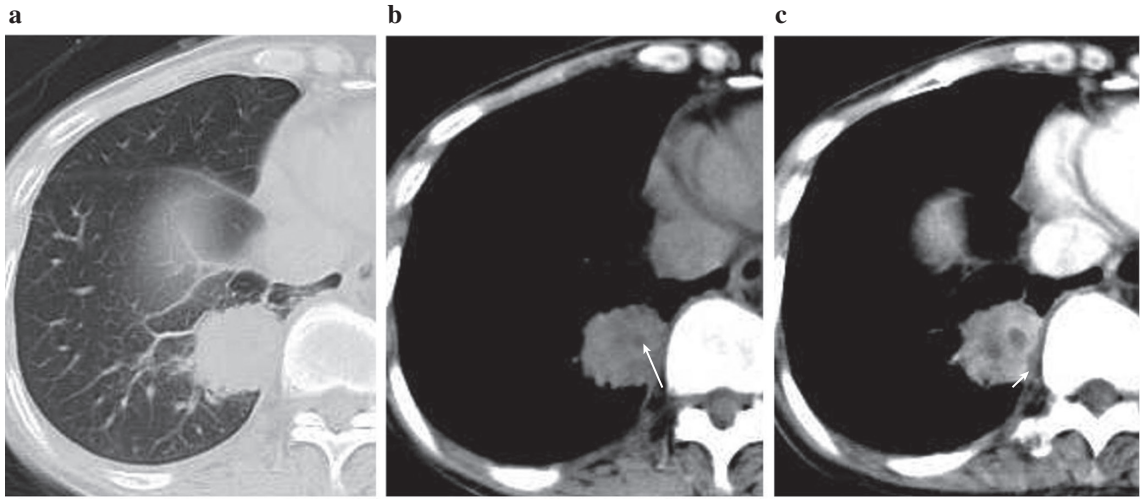

Figure 4 | A 60-year-old woman with pulmonary actinomycosis presented with a 2-week history of cough, sputum, and hemoptysis.
a. Axial computed tomographic images obtained in the pulmonary window, showing a peripheral mass with a partial poorly defined margin (size, 3.6 cm × 2.8 cm). **b.** Axial computed tomographic images obtained in the mediastinal window, showing a low-attenuation area in the lesion (white arrow). **c.** Contrast-enhanced CT image obtained with mediastinal window settings, showing a low-attenuation area with peripheral slight contrast enhancement and adjacent pleural thickening (white arrow).

and *Aspergillus* nodules. The results revealed several differences in clinical and imaging manifestations between diseases, which may aid in clinical diagnosis and treatment. However, this study has several limitations. First, the retrospective single-center nature of this study prevents selection bias form being ruled out, thus potentially influencing the significance and generalizability of our results. Second, the images we analyzed were not of a state of natural disease progression. Since we analyzed the last imaging data before pathological examination, some patients had been treated with drugs already. However, the effect of drugs on

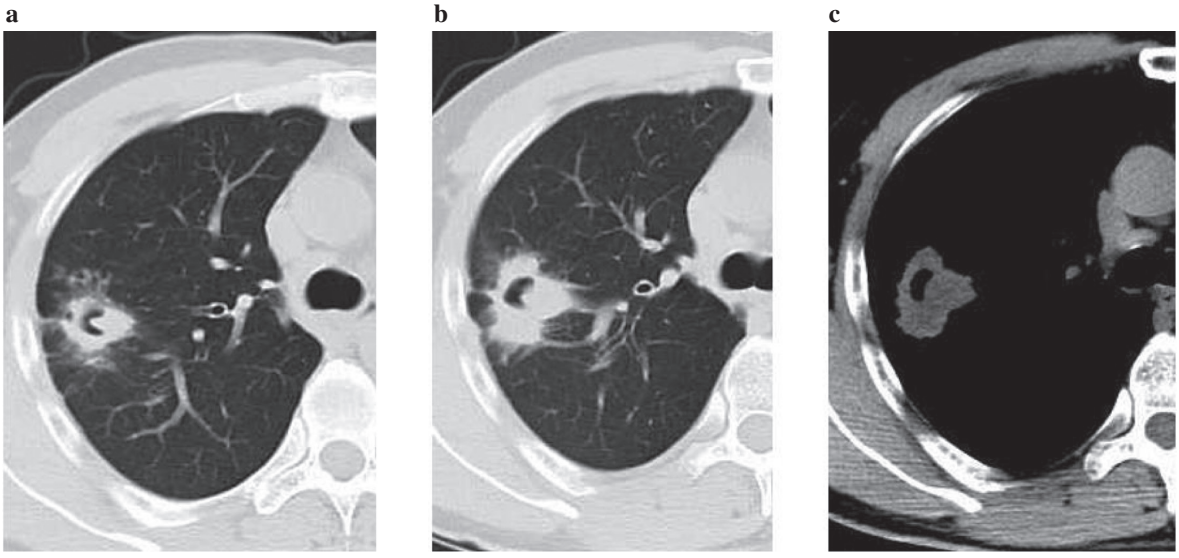

Figure 5 | A 46-year-old man with pulmonary actinomycosis presented with a 3-week history of cough and sputum production. **a** and **b**. CT images obtained with lung window settings, showing a mass lesion with air-crescent sign and ill-defined margin. **c**. CT image obtained with mediastinal window settings, showing a mass containing central low-attenuation area.

the lesion is still unknown. Third, we did not evaluate outcomes of the two diseases in the included patients. Further longer-term prospective studies are needed to confirm the results of the present study.

6. CONCLUSION

Distinguishing between pulmonary actinomycosis and *Aspergillus* nodules is difficult on the basis of clinical manifestations alone, because of their common features. However, CT findings may help differentiate the two diseases. Pulmonary actinomycosis lesions are more likely to appear mass-like with bulky volume, ill-defined margins, interlobular septal thickening, pleural changes, and hilar and/or mediastinal lymphadenopathy. Patients with *Aspergillus* nodules are more likely to exhibit cavitation, air-crescent sign, bronchiectasis, and calcifications on CT.

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