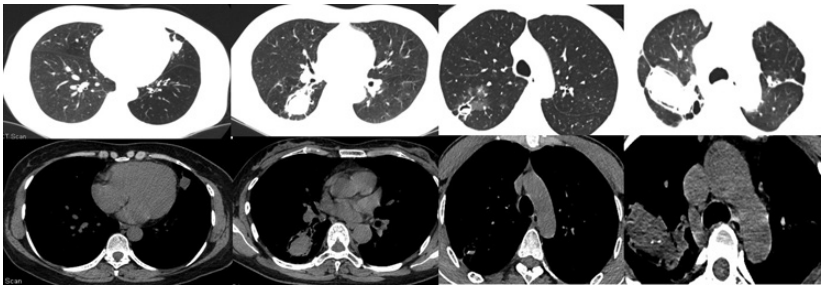
Radiology Science

Original Research

Radiological features of aspergillomas and surrounding areas after pulmonary tuberculosis

Graphical abstract



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Key points

- Most patients with aspergilloma had a history of hemoptysis, and some once had severe hemoptysis.
- Patients who experienced hemoptysis-associated events had radiological manifestations of perilesional GGO surrounding the aspergilloma, which were indistinguishable from those in patients without hemoptysis-associated events.
- Aspergilloma in patients with prior TB is characterized by nodules or consolidation, or nodules with cavities located in "the golden area."
- Importantly, the characteristics of areas surrounding aspergillomas—including perilesional GGO, perilesional calcification, perilesional bronchiectasis, and pleural thickening—are not distinguishable between patients with prior TB and those without a history of TB.

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Radiological features of aspergillomas and surrounding areas after pulmonary tuberculosis

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Abstract

Objectives: Although pulmonary tuberculosis (TB) may be effectively treated, destruction of the lung parenchyma can lead to recurrent infections including aspergilloma. Hemoptysis is a serious complication of aspergilloma. However, the relationship between aspergillomas and surrounding areas after TB has not been comprehensively investigated. Herein, CT scans were used as the primary method of investigation.

Methods: A retrospective study on patients with aspergilloma was performed. Twenty patients with prior tuberculosis infections were compared with 27 individuals who had never been infected with tuberculosis. The Mann-Whitney U-test was used for direct comparison of aspergilloma volume and cavity thickness between the TB group and the non-TB group. Fisher's exact test was used to compare aspergilloma calcification and location; perilesional ground-glass opacity (GGO), calcification, and bronchiectasis; and pleural thickening between groups. To facilitate the localization of aspergilloma, the apical and posterior segments of the upper lobe or the superior segment of the lower lobe were defined as "the golden area."

Results: A total of 76.60% patients (36/47) had a history of hemoptysis, and 13.89% (5/36) had previously experienced severe hemoptysis. Patients who had hemoptysis-associated events were significantly more likely to have considerable perilesional GGO around the aspergilloma than those who did not experience such events (77.78% vs 36.36%, P=.027). In the TB group, all aspergillomas were situated in "the golden area" (100.00% vs 77.78%, P=.031). However, no statistically significant differences were observed in aspergilloma amount or volume, or the thickness of the cavity between groups (P >.05). Furthermore, no significant differences were observed between groups regarding aspergilloma calcification, perilesional GGO, perilesional calcification, perilesional bronchiectasis, or pleural thickening (P >.05).

Conclusions: Hemoptysis caused by aspergilloma is frequently encountered in clinical settings, and the presence of perilesional GGO on CT images is strongly suggestive of hemoptysis. Patients with prior tuberculosis often have aspergillomas located in "the golden area." Images obtained from CT scans may be used to guide therapy.

Keywords: Pulmonary tuberculosis; Aspergilloma; Radiological features; Surrounding areas.

1. INTRODUCTION

In recent years, developing nations have seen an increase in the incidence of pulmonary tuberculosis (TB) [1]. According to some studies on the epidemiology of TB in mainland China, the prevalence of TB has decreased by more than 50% during the past 20 years [2, 3]; nonetheless, the number of new cases of China in 2017 ranked second worldwide despite ongoing interventions [4]. People with TB, regardless of whether they receive treatment, are at risk of developing several sequelae, including permanent loss of lung parenchyma, and irreversible destruction of airways and pleura [5]. These irreversible thoracic alterations after TB may be associated with an increased risk of a variety infections including aspergilloma [5]. Hemoptysis is an important

complication associated with aspergilloma. In patients with aspergilloma, severe hemoptysis-associated events is common and has been reported to reach 28.9% in long-term follow-up [6]. However, the relationships between the radiological characteristics of aspergillomas and the alterations in surrounding areas as a result of prior TB have not been comprehensively confirmed. Here, we discuss and illustrate the imaging features of aspergilloma after thoracic TB in terms of the sequelae and complications affecting the lung parenchyma, airways, and pleura. Aspergilloma is a fungal infection that can develop after thoracic TB. Evaluation of the radiological aspects of aspergilloma associated with hemoptysis is important.

2. METHODS

2.1 Study population and design

We analyzed clinical data for patients treated at Xinqiao Hospital between January 2012 and December 2021. All participants were diagnosed with pulmonary aspergilloma according to the Aspergillosis treatment guidelines developed by the Infectious Diseases Society of America in 2008 [7]. The diagnosis of all patients was confirmed on the basis of agreement between two respiratory physicians. The CT scans were evaluated by two radiologists. In cases of inconsistent interpretation of CT images, two radiologists discussed the final results. In bronchoalveolar lavage (BAL) samples, none of the patients had positive bacterial blood or sputum cultures, or positive PCR test results for respiratory viruses or Pneumocystis jiroveci. Patients who had mixed etiologies of lung infection, as well as negative galactomannan antigen results from serum blood or BAL tests, were not included in this research [8]. The protocol for the research was approved by the Ethics Committee at Xinqiao Hospital, and each patient provided consent to participate after receiving sufficient information. In total, 47 patients with a diagnosis of pulmonary aspergilloma were included in this study after the diagnoses were verified on the basis of comprehensive information in compliance with the diagnostic criteria. The hospital medical records were searched to retrieve data on patient demographics, imaging results, and treatments. Patients were separated into two groups: those with TB (TB group) and those without TB (non-TB group). Patients in the TB group had previously been diagnosed with TB but showed no evidence of active forms of the disease [9], whereas patients in the non-TB group did not have a previous history of TB. Radiological characteristics were compared and analyzed between groups. On the basis of the assumption that aspergilloma is an ellipsoid, the volume formula was $V=4/3\pi$ (length/2 × width/2 × height/2) [6]. Visual inspection was used to estimate the cavity wall thickness. The apical and posterior segments of the upper lobe or the superior segment of the lower lobe were defined as "the golden area" to facilitate aspergilloma localization. According to the findings from cavitary lung diseases [10], a thick-walled cavity was defined by a width exceeding 4 millimeters.

2.2 Statistical analysis

SPSS 26.0 was used to perform the statistical analysis (IBM Corporation, Armonk, NY, USA). For data with a non-normal distribution, the median and interquartile range were used to describe the data, whereas the mean and standard deviation were used for data with a normal distribution. The characteristics of the study groups were compared with unpaired t-test or Mann-Whitney U-test, as appropriate, for continuous variables. Fisher's exact test was used for categorical variables, such as the appearance of aspergilloma, the number of aspergillomas, and perilesional ground-glass opacity (GGO). These tests were performed on continuous variables. In each test, the threshold for significance was set at $P < .05$.

3. RESULTS

3.1 Clinical characteristics of the participants

The clinical features of the participants are detailed in Table 1.

There were 22 male patients, making up 46.8% of the total, and the average age of all patients was 49.6 years. Hemoptysis was the most prevalent respiratory symptom, occurring in 76.6% of cases. In addition, several patients complained of other respiratory symptoms such as purulent sputum (17.0%), chest pain (6.4%), dyspnea (2.1%), or fever (2.1%), or the diagnosis of aspergilloma was made during doing routine physical examinations (8.4%). In the follow-up period, two patients underwent BAE, and 33 patients underwent surgical removal of aspergillomas.

3.2 Radiological manifestations of aspergillomas in patients with a history of TB

The imaging manifestations according to patient history of pulmonary TB are presented in Table 2.

A total of 20 of 47 patients were diagnosed with TB, whereas the other 27 patients did not have the disease. The number of nodules that included cavities was the same in both the TB and non-TB groups, at 13 (65.0%) and 13 (48.1%), respectively. In contrast to patients without a history of TB, all patients with a history of TB had aspergillomas found in the top portion of the lobe (Figures 1 and 2) (100.0% vs 77.8%, P=.031). In addition, perilesional calcification and fibrosis were among the most prevalent findings and were observed more frequently in the TB group than the non-TB group (65.0% vs 18.5%, P=.001).

No significant differences in the presence of aspergilloma (P=0.374) or the quantity of aspergilloma (P=0.241) were observed between groups. Mann-Whitney U-tests also indicated no difference in aspergilloma volume between the TB group and non-TB group. In addition, we observed no statistically significant differences between groups in aspergilloma calcification,

Table 1 | Clinical characteristics of participants.

Clinical characteristics, n (%)	TB group (n=20)	Non-TB group (n=27)	Total patients (n=47)
Male	8(40.0)	14(51.9)	22 (46.8)
Age	52. 4±2.3	45. 9±2.7	49. 6± 12. 4
Clinical characteristics			
Hemoptysis	16(80.0)	20(74.1)	36 (76.6)
Dyspnea	0(0.0)	1(3.7)	1(2.1)
Cough	7(35.0)	13(48.1)	20(42.5)
Fever	0(0.0)	1(3.7)	1(2.1)
Purulent sputum	3(15.0)	5(18.5)	8(17.0)
Identification in routine physical examination	3(15.0)	1(3.7)	4(8.5)
Chest pain	2(10.0)	1(3.7)	3(6.4)
BAE	1(5.0)	1(3.7)	2(4.3)
Surgical removal	16(80.0)	17(63.0)	33(70.2)

Table 2 | Radiological manifestations of patients with aspergilloma in the TB group and non-TB group.

Imaging manifestations, n (%)	TB group (n=20)	Non-TB group (n=27)	P-value
Appearance of aspergillosis			0.374
Nodule or consolidation	7(35.0)	14(51.9)	
Nodule with cavity	13(65.0)	13(48.1)	
Number of aspergillomas			
Single	15(75.0)	23(85.2)	0.241
Double	3(15.0)	4(14.8)	
Multiple	2(10.0)	0(0)	
Located in "the golden area"	20(100.0)	21(77.8)	0.031
Volume of aspergillosis (cm^3)	9.2(3.5,17.7)	7.1(1.2,9.9)	0.098
Calcification	8(40.0)	6(22.2)	0.214
Thick-walled cavity	10(50.0)	7(25.9)	0.089
Perilesional GGO	11(55.0)	21(77.8)	0.122
Perilesional bronchiectasis	6(30.0)	8(29.6)	0.978
Pleural thickening	12(60.0)	10(37.0)	0.148

thick-walled cavities, perilesional GGO, perilesional bronchiectasis, or pleural thickening (Figure 3) (P >.05).

3.3 Imaging features of hemoptysis

Table 3 presents the radiographic characteristics of individuals who recently presented with a complaint of hemoptysis. In a previous study of 47 patients, 36 patients (76.6%) reported having hemoptysis, and 5 patients (13.9%) reported having severe hemoptysis at some point in their lives. Radiological examinations indicated that perilesional GGO surrounding the aspergilloma (Figure 4) was significantly more prevalent in patients who had experienced hemoptysis-associated events than in patients who had not (77.8% vs 36.4%, P=.027). In contrast, no discernible differences were observed in the number of aspergillomas, the location of aspergillomas, perilesional bronchiectasis, or pleural thickening between patients with or without hemoptysis.

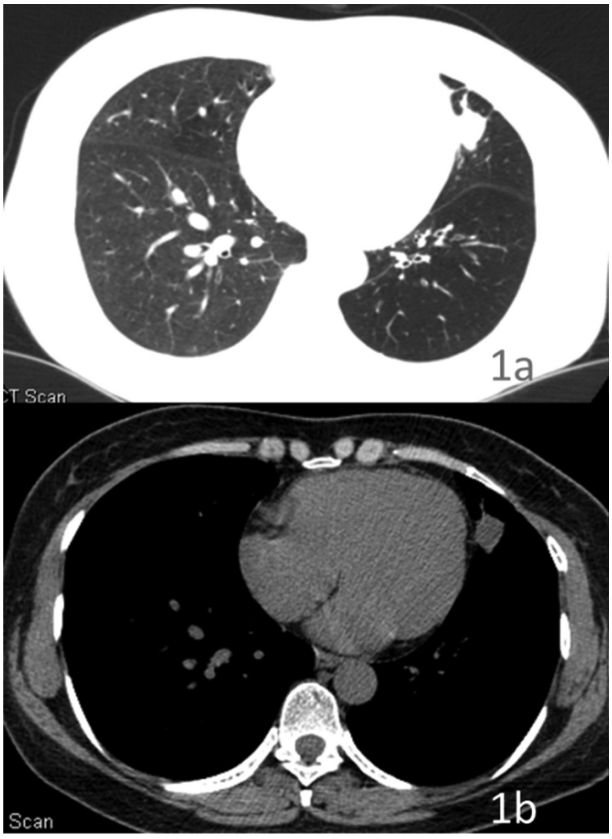

Figure 1 | Aspergilloma in a 46-year-old woman without a history of TB.
1a, 1b CT scan showing a well-defined, round, solid nodule with fibronodular scarring in the sublingual segment of the left upper lobe of the lung.

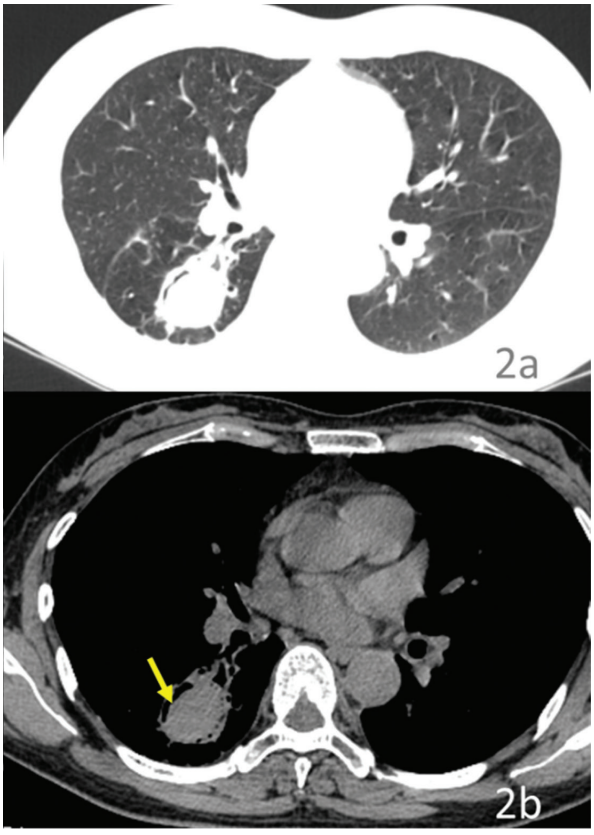

Figure 2 | Aspergilloma in a 56-year-old man with a history of TB.
2a, 2b CT scan showing a thin-walled mass with soft-tissue opacity and an air-crescent sign (arrow) located in "the golden area" (superior segment of the right lower lobe).

4. DISCUSSION

In human history, TB has been a disease of critical importance. Mycobacterium tuberculosis is the causative agent of pulmonary TB; the pathologic form of the pulmonary infection depends on the susceptibility of the infected host, and is divided into primary and postprimary categories [11-14]. At the apex of the lungs, nodular and linear areas with increased opacity or attenuation are the most common manifestations of postprimary TB [12-15]. At the microscopic level, the initial tissue reaction to a primary encounter with Mycobacterium tuberculosis involves local mobilization of neutrophil polymorphs at the site of implantation and subsequent infection. Rapidly following the onset of caseation necrosis, a variable lymphocytic, histiocytic, and giant cell reaction occurs, which is typically followed by mural fibrosis [14]. The postprimary form of the disease tends to progress, and foci of inflammation and necrosis enlarge and occupy greater portions of the lung parenchyma. This pattern of progression is typical of the disease. Communication with the airways is common during this process. After penetrating the airway, the infection may spread toward the lung's periphery and then rupture into the pleural space [15]. The mode of disease progression is determined by the interaction between the response of the host and the virulence of the organism. If host factors are successful, gradual healing occurs and is followed by the formation of parenchymal scars. The progression of the disease occurs either locally or in other parts of the lungs or body after bacteria spread via the airways, lymphatic vessels, or bloodstream when the bacterium can overcome the host's defenses [15-17]. Therefore, pulmonary TB in the pulmonary or extrapulmonary portions of the thorax may result in a variety of forms of sequelae and complications in the thorax. Approximately 25%–55% of patients diagnosed with aspergilloma have a previous medical history of chronic cavitary TB [5]. Hemoptysis is the most common clinical complication of aspergilloma, and its prevalence ranges from 50% to 90% [18], although aspergilloma can exist for years asymptomatically. Our findings indicated a prevalence of hemoptysis of 76.6%, in agreement with prior

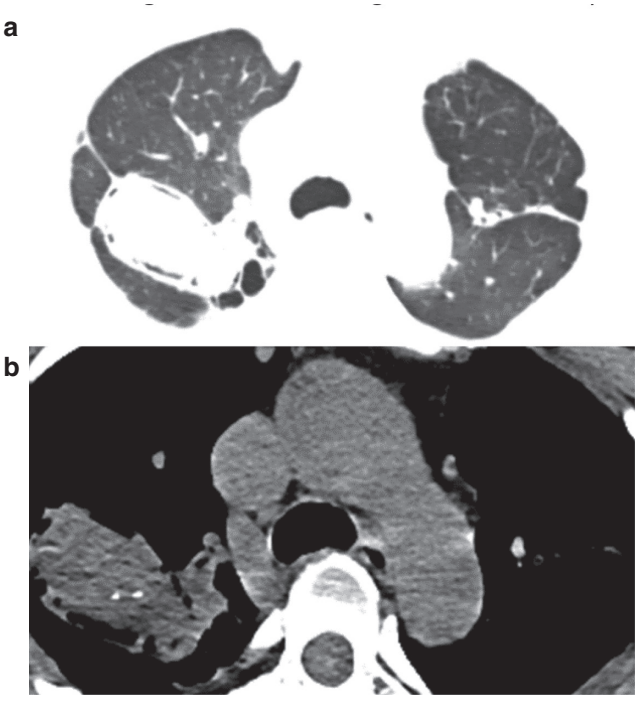

Figure 3 | A mass in a 43-year-old man without prior TB who had a complaint of cough for 2 years.
3a, 3b CT images showing perilesional bronchiectasis around the aspergilloma associated fibrosis and pleural thickening. Dot calcifications within the aspergilloma can also been seen.

findings [18]. In addition, cough is a symptom in 42.5% of patients with aspergilloma.

In the TB group, in contrast to the non-TB group, all aspergillomas were located in "the golden area," which is consistent with the postprimary tuberculous region. In TB, the nidus can be explained as being located in areas with high oxygen tension and impaired lymphatic drainage. In patients with a previous history of TB, the presence of aspergilloma was highly suggestive of a tuberculous origin. However, among patients without a previous history of TB, 77.8% of aspergillomas were found in "the golden area". In the TB group, in contrast to the non-TB group, all aspergillomas were located in "the golden area," which was consistent with the post-primary tuberculous region. In TB, the nidus location can be explained by high oxygen tension and impaired lymphatic drainage. Thus, for patients with a history of TB, aspergilloma was highly suggestive of a tuberculous origin. Aspergillus is a mold that is often found in dirt, dust, and hospitals [19]; nevertheless, pulmonary aspergillosis typically manifests only in people whose immune systems are compromised or who have an underlying lung disease [19]. Understanding of the mechanism predisposing people with a history of TB to pulmonary aspergillosis remains lacking. We hypothesized that the TB-induced degradation of lung parenchyma or airways may create favorable conditions for Aspergillus, and that the surrounding injured lung tissue is consequently unable to perform its normal role of effectively eliminating fungus. When the body's immunity is compromised, the lungs become susceptible to fungal infection.

Perilesional GGO in patients with hemoptysis has been supported by previous studies [20, 21] indicating that radiological signs on CT are highly suggestive of hemorrhage in the lung tissue. Destruction of the lung parenchyma is an important mechanism leading to the development of hemoptysis [21-23].

Calcification of the mycelial ball occurs in some cases [6, 18, 24], which are in agreement with our findings. In contrast, we observed no distinctions between the TB group and the non-TB group. Some studies [24, 25] have reported thick-walled tuberculous cavities or the adjacent pleura; however, our findings did not indicate particular distinctions between groups. Pleural infection is usually caused by the rupture of a subpleural caseous focus into the pleural space. In our research, we observed no difference in pleural thickening between groups. The involvement of TB in the bronchial wall and subsequent fibrosis can sometimes lead to the development

Table 3 | Radiological manifestations of hemoptysis.

Imaging manifestations, n (%)	Hemoptysis group (n-36)	Non-hemoptysis group (n=11)	P-value
Number of aspergillomas			0.29
Single	30(83.3)	8(72.8)	
Double	4(11.1)	3(27.3)	
Multiple	2(5.6)	0	
Located in "the golden area"	32(88.9)	9(81.9)	0.921
Calcification	12(33.3)	2(18.2)	0.559
Perilesional GGO	28(77.8)	4(36.4)	0.027
Perilesional bronchiectasis	9(25.0)	5(45.5)	0.194
Pleural thickening	16(44.4)	6(54.5)	0.557

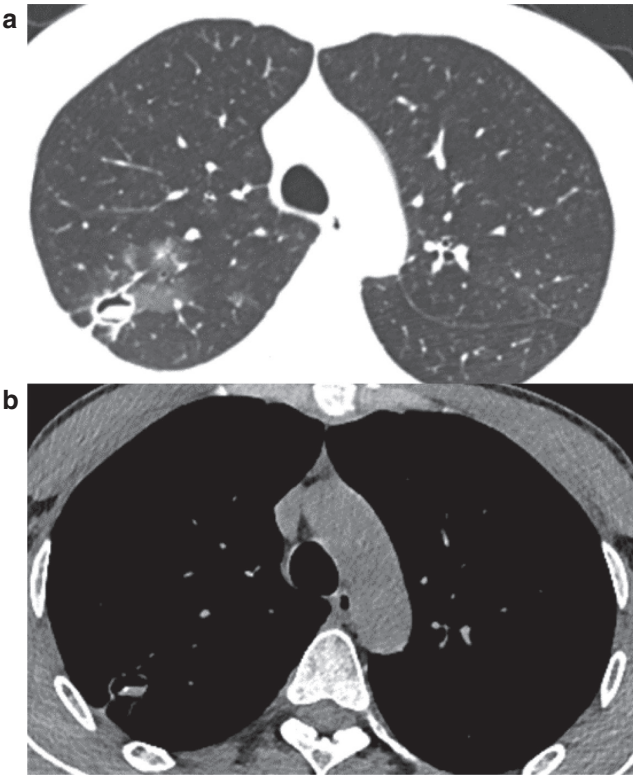

Figure 4 | Perilesional GGO of an aspergilloma in a 38-year-old woman with prior TB with a complaint of hemoptysis for 3 months.

4a, 4b Patchy ground-glass opacity surrounding a fungus ball within a thin-walled cavity. Dot calcification can be seen within the aspergilloma.

of bronchiectasis. On high-resolution CT, bronchiectasis is seen in 71%–86% of patients with inactive disease and 30%–60% of patients with active postprimary TB [26, 27]. Although bronchiectasis in postprimary TB can result from cicatricial bronchostenosis following a local infection, the condition more commonly develops as a result of the destruction and fibrosis of the lung parenchyma with traction bronchiectasis [5]. However, the group with TB did not have more favorable findings than the non-TB group in perilesional bronchiectasis.

Clinical diagnosis of aspergilloma is based on a combination of respiratory symptoms; mycological, histopathological, or cytopathological evidence of aspergillosis; and CT manifestations. Aspergillus is histopathologically difficult to distinguish from other filamentous fungi such as Mucorales; however, micromorphology may provide information on the fungal class [28]. Aspergillus typically has dichotomous and septate hyphae, whereas Mucorales has pauci-septate and 90° branching hyphae [28]. Fungus-specific stains, such as Gomori's methenamine silver stain, periodic acid-Schiff stain, and fluorescent dyes are critical for diagnosing Aspergillus infections [29, 30]. The mycological criteria for aspergillosis include positive culture and/or microscopy results for sputum, BALF, or bronchial brush samples; positive Aspergillus specific IgG in the serum; or positive ELISA-based commercial assays or BALF GM tests [19, 31].

The first-line therapy for fungal infections often consists of antifungal drugs, such as voriconazole and itraconazole [19]. According to the particular category of pulmonary aspergillosis, the duration of antifungal treatment may range from 6 weeks to 6 months, depending on the immunological condition of the patient as well as the structural lung disorders present. No standards have been established for the treatment of individuals with aspergilloma who have already been diagnosed with TB. Surgical excision of the fungus ball is useful in treating recurring hemoptysis [32-34]. In addition, BAE can provide an instant response in patients with severe hemoptysis [32, 34].

TB co-infections are common in clinical practice and are associated with more severe thoracic symptoms and a lower chance of recovery than those in the absence of co-infections; therefore, medical professionals must pay special attention to patients with co-infections. Patients previously diagnosed with TB are at elevated risk of non-tuberculous mycobacterial infection lung disease [31]. Non-tuberculous mycobacterial infection together with pulmonary TB may affect 7%–11% of individuals [31]. The severity of the illness, likelihood of progression, existence of comorbidities, tolerance to therapy, and aims of treatment all influence the choice of whether to begin treatment for individuals who meet the diagnostic criteria. In addition, in HIV-positive patients, who are several times more likely to develop pulmonary TB than those without HIV, physicians must exercise caution, because the use of highly active antiretroviral therapy in patients who are already infected with TB may result in paradoxical worsening of pulmonary disease [9]. During the multiple waves of the coronavirus disease 2019 (COVID-19) pandemic, numerous studies in adults revealed that patients with COVID-19 and TB have a two times greater risk of death than those without TB and are less likely to recover than patients with COVID-19 without TB [35]. Comorbidity with TB is strongly associated with moderate–severe COVID-19 illness in children at admission [35]. Concomitant mucormycosis and TB infection is uncommon [36, 37], and the outcomes of the ten cases documented in the literature have been poor [37]. The death rate for invasive pulmonary mucormycosis may be as high as 70% [37], although medical and surgical therapies are available. These findings underscore the need for early diagnosis and treatment of simultaneous pulmonary mucormycosis and TB in immunocompromised individuals.

5. CONCLUSIONS

Hemoptysis caused by aspergilloma is a common complaint in clinical practice, and perilesional GGO is highly suggestive of hemoptysis. For patients infected with TB,

the location of aspergilloma tends to be in "the golden area." Images obtained from CT scans may provide information to guide future therapy.

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