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Comparative analysis of airway invasive aspergillosis and endobronchial spread of tuberculosis on high resolution computed tomography

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Informed consent: written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in the future, at the time of data acquisition. The manuscript does not contain any individual person's data in any form.

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Abstract

The presence of tree-in-bud (T-I-B) pulmonary opacities on high-resolution computed tomography (HRCT) in tuberculosis endemic areas is frequently regarded as a *sine qua non* for endobronchial tuberculosis (TB). That is not always the case, however. They can also be found in immunocompromised non-neutropenic patients with airway-invasive aspergillosis (IA). Understanding the differences between the two conditions is thus critical for making an accurate diagnosis. This research aims to pinpoint those distinguishing characteristics. The study defines the distribution and morphology of T-I-B opacities and other ancillary pulmonary findings in the two conditions by performing a retrospective analysis of HRCT features in 53 immunocompromised patients with lower respiratory tract symptoms, 38 of whom were positive for TB on BAL fluid analysis and 15 confirmed IA by Galactomannan method. While the global distribution of T-I-B opacities affecting all lobes favoured TB ($p=0.002$), the basal distribution overwhelmingly favoured IA ($p<0.0001$). Morphologically, dense nodules with discrete margins were associated with TB, whereas nodules with ground-glass density and fuzzy margins were associated with IA. Clustering of nodules was observed in 18 TB patients ($p=0.0008$). Cavitation was found in 14 (36.84%) TB patients but not in any of the IA patients. Peribronchial consolidation was found in seven (46.67%) of the IA cases and four (10.53%) of the TB cases ($p=0.005$, 0.007). The presence of ground-glass opacity and bronchiectasis did not differ significantly between the two groups. Not all T-I-B opacities on HRCT chest in immunocompromised patients in endemic TB areas should be reported as tubercular. Immunocompromised non-neutropenic patients with airway IA can be identified earlier with tree-in-bud opacities on HRCT chest, even in the absence of a nodule with halo, resulting in earlier and more effective management.

Introduction

Invasive aspergillosis (IA) is a common opportunistic infection in the immunosuppressed patients. The angioinvasive form of pulmonary aspergillosis commonly occurs in the neutropenic host, where organisms invade the blood vessels of the airways causing occlusion of large or medium-calibre arteries with plugs of hyphae that lead to the development of infected infarcts [1]. Less commonly, the organisms invade the airways rather than the vessels [2]. The incidence of IA is probably underestimated in non-neutropenic immunosuppressed patients as most studies focus only on neutropenic patients. Studies have shown the susceptibility of immunosuppressed non-neutropenic patients to IA, particularly the airway invasive form [3,4].

Airway IA presents with non-specific symptoms such as fever, cough and dyspnoea [5]. The severity of the infection can remain masked in glucocorticoid-immunosuppressed patients [3]. On high-resolution computed tomography (HRCT), angioinvasive IA shows typical findings of discrete macronodular lesions surrounded by ground-glass opacity [6,7], whereas, in the airway IA, early HRCT findings are non-specific and appear as centrilobular nodules in a tree-in-bud pattern or peribronchiolar consolidation. Tree-in-bud (T-I-B) nodules/opacities were first described by Eisenber *et al*. in the endobronchial spread of TB [8]. Since then, many studies have shown T-I-B opacities in various diseases [8,9] although, in our setup, the most common cause remains the endobronchial spread of tuberculosis. High dose or prolonged continuous use of steroids can cause generalized immunosuppression with increased incidence of TB due to reactivation of latent infection [10,11]. Airway invasive aspergillosis remains an often neglected cause of T-I-B opacities in immunosuppressed patients. With this background, we aimed to determine if airway IA could be differentiated from the endobronchial spread of TB on HRCT chest.

Materials and Methods

Study design

This retrospective study was carried out in the Department of Radiodiagnosis in collaboration with the Department of Respiratory Medicine, at our institution, a tertiary care centre.

All HRCT studies performed for suspicion of lower respiratory tract infection in our department in the last two years were listed, and their clinical records were retrieved and analysed. Our target population comprised of i) patients who had received high dose or continuous long-term glucocorticoids as stand-alone or with other immunosuppressive therapy, and ii) patients admitted in ICU with a history of high dose steroid use (≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days) preceding admission [12]. All such immunosuppressed patients with clinical symptoms of lower respiratory tract infection formed part of the study population (n=96).

Patients with this clinical profile, who had undergone bronchoscopy with broncho-alveolar-lavage (BAL) fluid examination were selected. Records were then further analysed for completeness, management and workup, which these patients received.

We excluded cases where i) detailed clinical history and records of basic laboratory investigations including complete blood count, blood sugar, ESR and KFT, and ii) results of microbiological investigations including sputum examination, BAL fluid examination, blood cultures, and viral markers were not available.

Further, patients with the following conditions were also excluded from the final analysis to prevent confounding.

- Patients with a history or source of aspiration pneumonia as it can present as T-I-B on HRCT chest.
- Patients with neutropenia (defined as ≤500 cells/µL).
- Patients with diabetes and HIV-positive status as being immunocompromised can have other/mixed pulmonary infections with T-I-B on HRCT chest.
- Patients with known malignancy as tumour infiltration in the centrilobular peri-broncho-vascular interstitium and thrombus in pulmonary vasculature may also mimic T-I-B opacities.

All HRCT Chest examinations were performed in our department on either Siemens Somatom Definition Flash 256 slice CT or Philips Brilliance 40 slice CT scanner, using a standardised protocol. After taking informed written consent, HRCT had been performed in full inspiration and breath hold with the patient lying supine CECT chest imaging was carried out after injecting weight appropriate dose of intravenous contrast agent (non-ionic, iso-osmolar) using standard CECT protocol.

Post HRCT chest examination, all patients had undergone fibreoptic bronchoscopy in the Department of Respiratory Medicine using the standard protocol.

After taking informed written consent fibreoptic bronchoscopy had been performed by a trained endoscopist and the sampling area was selected based on the area with maximum T-I-B opacities on HRCT scan. BAL fluid samples were obtained by wedging the tip of the bronchoscope against the bronchus leading to the maximal affected bronchopulmonary segment. Those cases for whom both Gene-Xpert [13] for TB and Galactomannan (GM) detection by the sandwich ELISA (enzyme-linked immunosorbent assay method) had been carried out were selected. An optical density (OD) ratio ≥1.0 for GM in BAL fluid was considered positive [12]. The final diagnosis of TB was made on positive Gene-Xpert and the diagnosis of IA was made by positive GM in BAL fluid. Finally, our study participants included 53 cases of tuberculosis (n=38) and invasive aspergillosis (n=15).

Two experienced radiologists (RJ and CP), unaware of the clinical profile, diagnosis and course of the patients reviewed and assessed the HRCT chest images. The images were viewed on both lung window (window width of -1000 to -1500 HU and a level of -600 to -700 HU) and mediastinal window (width 450 HU; level 50 HU). Maximum-intensity projection (MIP) images were used to display the highest attenuation values within a dataset. CT findings were described on the basis of the recommendations of the Nomenclature Committee of the Fleischner Society [14].

Centrilobular nodules were defined as small nodular lesions located in the centre of the secondary pulmonary lobules separated by more than 2 mm from the pleural surface or interlobular septa. The tree-in-bud pattern of centrilobular nodules/T-I-B opacities represented branching structures that resembled a budding tree with the bronchiole depicting the branch and the alveolar ducts demonstrating the bud. The presence, location, distribution and morphology of T-I-B opacities were recorded. The morphology of T-I-B opacities was analysed for density, margins and presence of clustering. The T-I-B opacities were divided into three groups based on density of nodules: either less than (ground glass), equal to (Soft) or more than (dense) that of the corresponding vessels [15]. Ground-glass opacity (GGO), air space and peribronchial consolidation, cavitation, bronchiectasis, nodules with halo were recorded as additional findings on HRCT chest. The presence of lymph nodes and pleural effusion was assessed on CECT chest images.

Due to our study's retrospective nature, our Institute Review Board waived the ethical clearance.

Statistical analysis

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0. The presentation of the categorical variables was done in the form of number and percentage. Quantitative data with normal distribution were presented as mean ± SD. The following statistical tests were applied to the results:

1. The comparison of the variables which were quantitative in nature was analysed using Independent *t*-test.
2. The comparison of the variables which were qualitative in nature was analysed using Fisher's exact and Chi-square test. The differences were considered statistically significant if p-value <0.05.

Results

Our study comprised of 53 patients. 15 of these had IA and 38 had TB. All cases of IA were diagnosed with positive GM (optical density ≥1) in BAL fluid. Gene-Xpert for TB was negative in BAL samples of all these cases. All cases of TB were positive for Gene-Xpert in BAL samples. BAL GM was negative in all these cases.

Clinico-demographic characteristics

The average age of patients with IA was 60.73 ± 7.28 years and with TB was 53.45 ± 9.55 years. Male to female ratio in patients with IA was 4:1 and in patients with TB was 1:2 (p=0.005). All patients with both TB and IA had presented with cough. Eight (21.05%) cases with TB and five (33.33%) cases with IA presented with dyspnoea. Fever was present in seven (46.67%) cases with IA and 19 (50%) cases with TB. Four (10.53%) cases with TB presented with haemoptysis. These differences in clinical symptoms were not statistically significant.

Distribution of T-I-B opacities

Laterality

T-I-B opacities were present in only right lung in 8 (53.33%) cases with IA and 17 (44.74%) cases with TB. Only left lung was involved in one (6.67%) case with IA and three (7.89%) cases with TB. Laterality of involvement was, however, not statistically significant. (0.572 Chi-square, 1.00 Fisher's Exact test).

Lobar involvement

Lung involvement in TB cases was found to be more widespread than IA. T-I-B opacities were present in all lobes in 23 (60.53%) cases with TB and two (13.33%) cases with IA. This was statistically significant (p<0.002, Fisher's Exact test). IA was found to have a predilection for basal segments in most of the cases. Basal segments of lower lobe were involved in all 15 (100%) cases with IA and only four (10.52%) cases with TB. In eight (53.33%) cases with IA, T-I-B opacities were present only in the basal segments of lower lobes. In no case with TB, T-I-B opacities were restricted to basal segments. This difference was statistically significant (p<0.0001, Fisher's Exact test). The distribution of T-I-B opacities in IA and TB is shown in Table 1.

Morphology of T-I-B opacities

TIB opacities were seen as centrilobular nodules with few nodules showing a branching pattern were seen on thin section axial images (Figures 1a and 2a). On MPR and MIP reformation, TIB morphology was better appreciated (Figure 1c).

Density

Dense nodules with discrete, well-defined margins (Figure 2 c,d) were present in 34 (89.47 %) cases with TB and in no case with IA (p<0.0001, Fisher's Exact test). Ground glass density nodules with density less than the vascular channel running alongside were seen in 12 (80.00 %) cases with IA and in no case with TB (p<0.0001, Fisher's Exact test).

Margins

Fuzzy margins of nodules (Figure 1b) were present in 13 (86.66 %) cases with IA (p<0.0001, Fisher's Exact test). T-I-B nodules with ill-defined margins were seen in eight (21.05 %) cases with TB and two (13.33%) cases with IA (p=0.705) Nodules in cases with TB showed clubbed tips with diameter more than that of the proximal respiratory bronchioles (Figure 2d). Triangular shaped tips with branching nodules resembling a fern leaf were seen in cases with IA (Figure 1d).

Clustering of nodules

Clustered nodules were seen in 18 (47.37%) cases with TB and none of the cases with IA (p=0.0008, Fisher's Exact test) (Figure 2 b,c). The morphology of T-I-B opacities in IA and TB is shown in Table 2.

Table 1. Distribution of tree-in-bud opacities in invasive aspergillosis and tuberculosis

	TIB nodules	Invasive aspergillosis (n=15)	Tuberculosis (n=38)	p-value
Lung	Bilateral lung	8 (53.33%)	17 (44.74%)	0.572*
	Left lung	1 (6.67%)	3 (7.89%)	1#
	Right lung	6 (40%)	18 (47.37%)	0.627*
Lobes	All lobes	2 (13.33%)	23 (60.53%)	0.002#
	Upper lobe (only)	0 (0%)	8 (21.05%)	0.088#
	Upper and middle lobe only	0 (0%)	8 (21.05%)	0.088#
	Lower lobe	15 (100%)	4 (10.52%)	<0.0001#

*Chi Square test; #Fisher's exact test.

Table 2. Morphology of tree-in-bud opacities in invasive aspergillosis and tuberculosis.

	TIB nodules	Invasive aspergillosis (n=15)	Tuberculosis (n=38)	p-value (Fisher's exact test)
Density	Dense	0 (0%)	34 (89.47%)	<0.0001
	Soft	3 (20.00%)	4 (10.5%)	1
	Ground glass	12 (80%)	0 (0%)	<0.0001
Margin	Discrete	0 (0 %)	30 (78.94%)	<0.0001
	Ill defined	2 (13.33%)	8 (21.05%)	0.705
	Fuzzy	13 (86.66%)	0 (0%)	<0.0001
Clusters	Present	0 (0%)	18 (38%)	0.0008

Additional pulmonary findings on CT

The presence of a cavity in upper lobe was noted in 14 (36.84%) cases with TB and no case, with IA. Peribronchial consolidation was present in seven (46.67%) cases with IA and four (10.53%) cases with TB. Both findings were statistically significant (p=0.005, 0.007, Fisher's exact test). GGO was seen in five (33.33%) cases with IA and eight (21.05%) cases with TB, bronchiectasis was seen in five cases with TB (13.16%) and no case with IA, pleural effusion was seen in four (26.67%) cases with IA and five (13.16%) cases with TB. These findings were not statistically significant (p=0.349 Chi square, 0.305, 0.252 Fisher's exact test). However, pleural effusion was bilateral in all four (26.66 %) cases with IA and no case with TB, and this was statistically significant (p=0.0047, Fisher's exact test). Additional findings on CT chest are enlisted in Table 3.

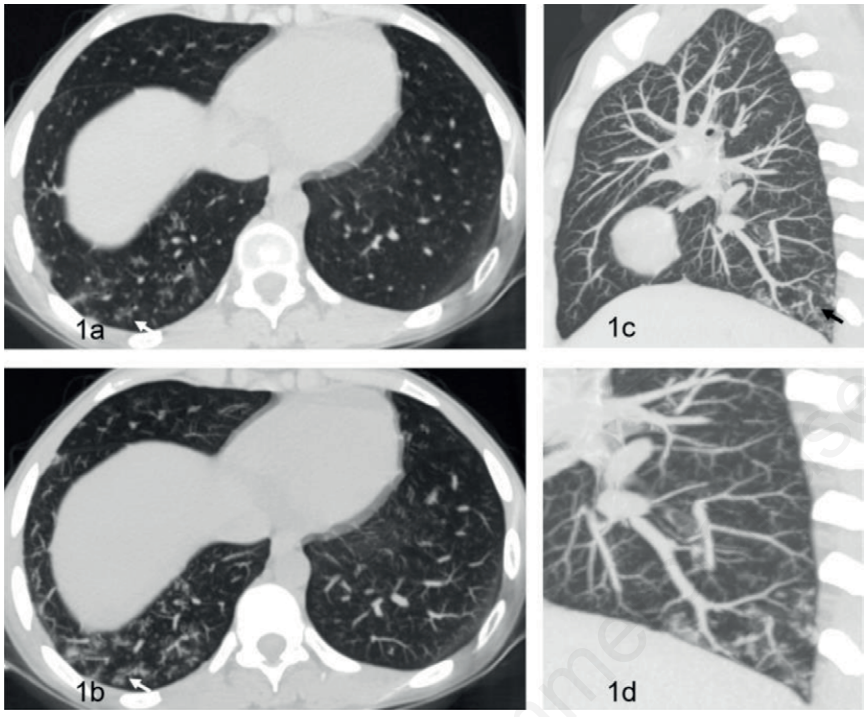

Figure 1. A 54-year-old male with dermatomyositis disease on high dose long-term corticosteroids presented with cough. High-resolution CT chest showed. a) On axial thin section CT image, ground glass density centrilobular nodules with fuzzy margins (white arrow) are noted in the right lower lobe basal segments. b) Axial MIP image at the same level further accentuates the tree-in-bud opacities with triangular-shaped tips (white arrow). Note the density of the nodules is less than the adjacent vessels. c) Sagittal reformatted MIP image shows tree-in-bud opacities with feathery fern leaf-like branching nodules in the posterior basal segment (black arrow). d) Magnified MIP sagittal image clearly demonstrates the feathery fern leaf-like pattern. BAL Galactomannan was positive suggestive of invasive aspergillosis.

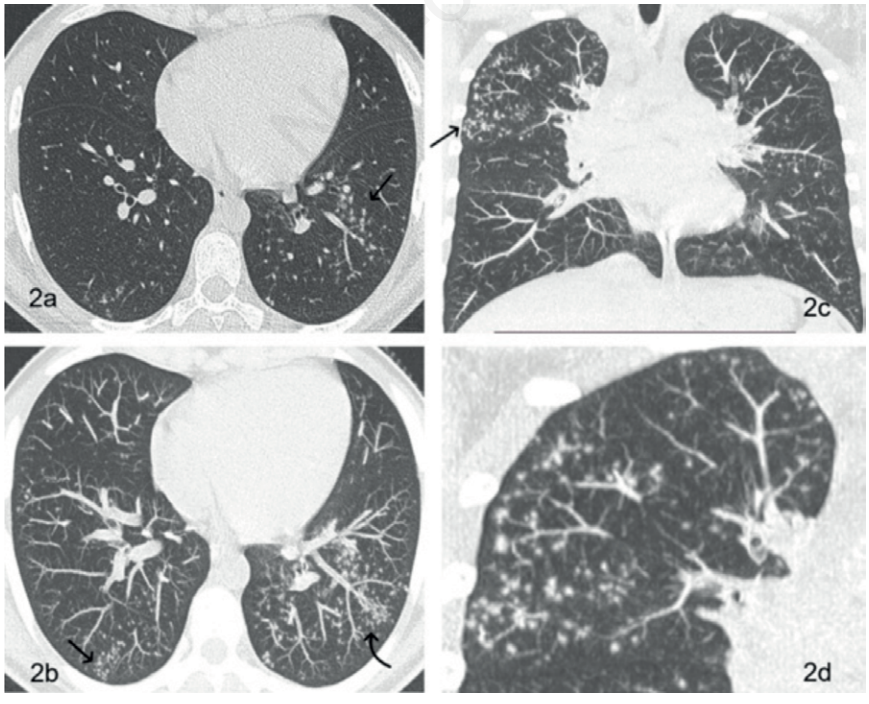

Figure 2. A 54-year-old female with SLE on long-term steroids and other immunosuppressants presented with cough and dyspnoea. a) Thin section axial image shows centrilobular nodules in bilateral lower lobes (arrow). b) MIP axial image at the same level shows clustered micronodules (curved arrow) in the left lower lobe with dense and discrete nodules arranged in a tree-in-bud pattern in the right lower lobe (straight arrow). c) Coronal reformatted MIP image shows tree-in-bud opacities (arrow) that appear like clusters of grapes (buds) hanging on stalks (respiratory bronchiole). d) Magnified coronal image clearly demonstrates the clubbed distal tips or buds of the tree-in-bud opacities with a diameter more than the stalk or respiratory bronchiole. Note the density of the nodules is more than the adjacent vessel. BAL GeneXpert was positive suggestive of pulmonary tuberculosis.

Table 3. Additional findings on CT in cases with invasive aspergillosis and tuberculosis.

	Invasive aspergillosis (n=15)	Tuberculosis (n=38)	p-value
Peri-bronchial consolidation	7 (46.67%)	4 (10.53%)	0.007*
GGO 5 (33.33%)	8 (21.05%)	0.349#	
Air space consolidation	2 (13.33%)	13 (34.21%)	0.182*
Bronchiectasis	0 (0%)	5 (13.16%)	0.305*
Cavity 0 (0%)	14 (36.84%)	0.005*	
Nodule with halo	2 (13.33%)	2 (5.26%)	0.568*
Lymph nodes	2 (13.33%)	10 (26.32%)	0.472*
Pleural effusion	4 (26.67%)	5 (13.16%)	0.252*
Bilateral pleural effusion	26.67%	0	0.0047*

*Fisher's exact test; #Chi square test.

Discussion

Although the outcome of invasive pulmonary aspergillosis has improved in neutropenic patients, the prognosis is still poor in other immunosuppressed patients as there is a low index of suspicion and late diagnosis in these cases [16]. We retrospectively analysed and compared HRCT lung features in immunosuppressed adult patients with tree-in-bud opacities in cases of pulmonary tuberculosis with endobronchial spread and airway invasive aspergillosis.

Lungs are the primary site of entry and germination of conidia of IA leading to hyphae formation. Galactomannan, a polysaccharide component of the cell wall of *Aspergillus*, is released into the body fluids by growing hyphae and to some extent by conidia. To discriminate between colonizing conidia and invasion of hyphae, the cut-off optical density of GM in BAL fluid was kept as ≥1.0, which also fulfils the criteria for mycological evidence for probable IA [12]. The high cut-off also took care of false positives or inflated GM in cases where antibiotic piperacillin-tazobactum may have been administered [17]. Immunosuppressed cases with high dose or continuous long-term intake of corticosteroids included in our study satisfied the host criteria for probable IA [3,11,12].

The bronchoalveolar phase of airway invasion that occurs before aspergillus hyphae invade the blood vessels is seen as T-I-B opacities on HRCT chest. In non-neutropenic cases of IA, the bronchoalveolar phase remains for a longer duration and angioinvasion remains delayed or absent [16].

In regions where tuberculosis is endemic, most of the T-I-B opacities in immunocompromised patients in the setting of infection are largely labelled as TB. In our study, we found differences in the pattern of distribution and morphology between T-I-B opacities seen in cases of TB and IA. 'Dependence predominance' [9], was seen with basal segments of the lower lobes involved in all cases with IA with 53.3% of cases showing only basal segment involvement. No restriction to basal segments was seen in any case with TB. Endobronchial spread is mostly seen in cases with reactivation of latent TB where initial acute necrotizing pneumonia with cavitation in the upper lung, spreads via the endobronchial route to other parts of the lung.

We also found clusters of micronodules representing aggregated T-I-B nodules only in cases with TB [15,18].

In cases with TB, dense and discrete nodules were seen with marginal clarity, even in small pin-head-sized nodules. The branching nodules comprising of the respiratory bronchiole and alveolar ducts were denser than the corresponding vessel in cases with TB due to bronchiolar and alveolar duct impaction with caseous material causing clubbed tips of alveolar ducts [15].

In cases with IA, the density of the centrilobular branching nodules was less than the corresponding vessel and the terminal portion of branching nodules lacked the clubbing or bud portion as seen in cases with TB. These terminal ends of the nodules showed triangular tips that had ground glass density with fuzzy margins. The branching stalk with nodules had a feathery, fern leaf-like appearance. Nodule with halo seen in three cases with IA, could be due to progress to the angioinvasive phase of IA disease. The presence of nodules with halo in two cases with IA and TB could suggest a low neutrophil count or some other cause at the time of HRCT. GGO present in IA cases was most likely due to haemorrhage caused by angioinvasion. GGO in TB cases could be due to haemoptysis.

Peri-bronchiolar consolidation seen in cases with IA was due to invasion of the basement membrane with peri-bronchiolar spread of exudate [5,6]. Peri-bronchiolar consolidation in cases with TB had well-defined, discrete margins due to organized exudate [15]. Although imaging patterns in IA and TB overlapped, overall blending of T-I-B with other lesions was more common in cases with TB [18,19]. Evenly distributed T-I-B s were common in IA.

A detailed analysis of TIB nodules in TB and IA has not been carried out before which makes for a major strength of our study. The cases were selected using a strict exclusion criterion (Box 1). Our results support that T-I-B nodules in cases with IA can be differentiated from those in TB and the presence of T-I-B nodules should be included in the radiological criteria for IA as airway IA can be missed in regions with endemic tuberculosis.

Our study had certain limitations. Due to the retrospective nature of our study, serial follow-up images of patients were not available to analyse the evolution of the T-I-B nodules after antifungal treatment. Bronchoscopic biopsy, fungal smear or culture on BAL samples required for proven IA were not available for every case. Finally, our sample size was small, which was a major constraint of our study. In future, more prospective follow-up studies with a higher number of cases will allow for better discrimination and comparison of the T-I-B opacities and other imaging features. In clinical practice, definitions of invasive fungal disease (IFD) cannot be strictly followed and antifungals are generally administered to any patient at risk, when fungi are detected by biomarkers in body fluids even without sufficient evidence to satisfy the consensus definitions of IFD [12].

Box 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients who had undergone HRCT chest examination in our department	Patients without TIB opacities on HRCT chest
Patients with T-I-B opacities on HRCT chest	Patients in whom detailed clinical history and records of basic laboratory investigations including complete blood count, blood sugar, ESR and KFT were not available
Immunosuppressed patients with clinical symptoms of lower respiratory tract infection and T-I-B opacities on HRCT	Patients in whom results of microbiological investigations including sputum examination, broncho-alveolar-lavage (BAL) fluid examination, blood cultures, and viral markers were not available
Patients who had received high dose or continuous long term glucocorticoids as stand alone or with other immunosuppressive therapy	Patients with history or source of aspiration pneumonia; as it can present as T-I-B on HRCT chest
Patients admitted in ICU with history of high dose steroid use (≥ 0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days) preceding admission	Patients with neutropenia (defined as ≤500 cells/µl)
Patients who had undergone bronchoscopy with bronchoalveolar lavage (BAL) fluid examination	Patients with diabetes and HIV positive status; as being immunocompromised can have other/mixed pulmonary infections with T-I-B on HRCT chest
Patients with complete records with respect to management and workup	Patients with known malignancy; as tumour infiltration in the centrilobular peri-broncho-vascular interstitium and thrombus in pulmonary vasculature may also mimic T-I-B opacities

Conclusions

In the clinical setting of lower respiratory tract infection, all T-I-B opacities on HRCT chest in immunosuppressed patients in regions with endemic TB should not be reported as tubercular in nature. Atypical T-I-B opacities on HRCT can point towards invasive aspergillosis. Immuno-suppressed non-neutropenic patients are less closely monitored for IA leading to sub-optimal management and late antifungal therapy. Such patients, with prolonged airway invasive aspergillosis, can be identified earlier with atypical tree-in-bud pattern of nodules on HRCT chest even in the absence of nodules with a halo sign leading to early and appropriate therapeutic management with a better outcome. Although not included currently, Tree-in-Bud opacities can be included in the consensus clinico-radiological criteria for diagnosis of Invasive Aspergillosis, especially in the immunosuppressed, so that early treatment can be expedited and crucial time is not lost by delaying treatment in clinical practice.

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