CHEST

Original Research

IMAGING

Causes and Imaging Patterns of Tree-in-Bud Opacities

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Background: **Multiple causes for tree-in-bud (TIB) opacities have been reported. However, to our knowledge the relative frequencies of the causes have not been evaluated. The purpose of this study was to determine the relative frequency of causes of TIB opacities and identify patterns of disease associated with TIB opacities.**

Methods: **Cases with TIB opacities in the radiology report in 2010 were identified by searching the Radiology Information System. Medical records and CT scan examinations were reviewed for the causes of TIB opacities. Patterns of disease associated with TIB opacities were evaluated.**

Results: **Causes for TIB opacities were established in 166 of 406 (40.9%) cases. Respiratory infections (119 of 166, 72%) with mycobacteria (65 of 166, 39%), bacteria (44 of 166, 27%), viruses (four of 166, 3%), or multiple organisms (six of 166, 4%) were most common. Aspiration was the cause in 42 of 166 (25%). Alternating areas of normal lung with regions of small airways disease (TIB opacities, bronchiectasis) (random small airways pattern) was specific (0.92) for *Mycobacterium avium* complex infection. Nearly uniform distribution of bronchiectasis (widespread bronchiectasis pattern) was specific for "diseases predisposing to airway infection" (specificity 0.92), such as cystic fibrosis, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis, and immunodeficiency states. Consolidation and TIB opacities (bronchopneumonia pattern) were usually due to bacterial infection or aspiration. Dependent distribution (specificity 0.79) and esophageal abnormality (specificity 0.86) with TIB opacities were associated with aspiration. Chronicity of findings was associated with mycobacterial infection ($P < .0001$, sensitivity 0.96). Acuteness of findings was associated with bacterial infection ($P < .001$, specificity 0.87).**

Conclusions: **TIB opacities are most often a manifestation of infections or aspiration. Patterns of disease can provide clues to the most likely diagnosis.** ***CHEST 2013; 144(6):1883–1892***

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; DPAI = diseases predisposing to airway infection; GGO = ground-glass opacity; MAC = *Mycobacterium avium* complex; TIB = tree-in-bud

Tree-in-bud (TIB) opacities are a common imaging finding on thoracic CT scan. These small, clustered, branching, and nodular opacities represent terminal airway mucous impaction with adjacent peribronchiolar inflammation.[1-4] Reported causes include infections, aspiration, and a variety of inflammatory conditions.[1,5-16]

TIB opacities can be seen in isolation, bronchiolitis,[13,14] or with other inflammatory imaging findings, including bronchial wall thickening, consolidation, and/or ground-glass opacities (GGOs). The combination of TIB opacities and consolidation, in the setting of infection, indicates the presence of a "bronchopneumonia."[11] TIB opacities are also associated with bronchiectasis and small airways obliteration (resulting in mosaic air trapping).[11] TIB opacities represent a central imaging finding in the range of airway-associated inflammatory conditions. The purpose of our study was to (1) determine the relative frequencies of causes of TIB opacities, (2) identify the imaging patterns associated with TIB opacities, and (3) determine any imaging clues that can predict the underlying cause of TIB opacities.

Materials and Methods

Study Design

The study was approved by the center's institutional review board (IRB #7, protocol #813882) and is Health Insurance Portability and Accountability Act compliant. Given the retrospective nature of the project, informed consent was waived. The study population was an unselected mixture of inpatients and outpatients

undergoing imaging at two northeastern US hospitals: a 725-bed tertiary care center and a 324-bed community hospital.

Our Radiology Information System was searched for the term "tree-in-bud" from January 1, 2010, to December 31, 2010, identifying 599 examinations. Of these, 182 cases were excluded for the following reasons: 78 indicating the absence/resolution of TIB opacities, 26 incomplete thoracic CT scan studies, 75 duplicate individuals, two insufficient quality examinations, and one missing medical record. Eleven examinations were excluded because of superimposed pulmonary diseases (five primary or metastatic cancer, two interstitial pulmonary edema, one invasive aspergillosis, one large bilateral pleural effusions, one interstitial lung disease, and one fibrothorax) that might obscure the airway-related disease under review. Our study group consisted of the remaining 406 cases. The electronic medical records were reviewed for the causes of TIB opacities, including the clinical symptoms (cough, chest pain, wheezing, fever) associated with the disease at the time of performance of the CT scan examination.

Proof of Diagnosis

A diagnosis of bacterial infection was made if there were respiratory symptoms of bronchopulmonary infection and any of three laboratory indicators of pulmonary infection within 7 days of the CT scan examination: (1) positive respiratory culture with a bacterial lung pathogen, (2) blood cultures growing *Streptococcus pneumoniae*, or (3) positive *Legionella* or pneumococcal urinary antigen. Cultures with normal oral flora were not considered to be evidence of infection.

A diagnosis of viral infection was made if there were respiratory symptoms of bronchopulmonary infection and a positive polymerase chain reaction assay of respiratory secretions for influenza, respiratory syncytial virus, adenovirus, or parainfluenza within 7 days of the CT scan examination.

A diagnosis of nontuberculous mycobacterial infection was made if the patient met American Thoracic Society criteria.[17] Since mycobacteria are chronic illnesses, we accepted positive clinical and microbiologic data at the time of the index CT scan or at the time of any previous CT scan in which the imaging findings had remained unchanged from the index examination. This included cultures up to 2 years prior to the index examination. We assumed a diagnosis of TB if cultures of respiratory secretions were positive for *Mycobacterium tuberculosis*.

Aspiration was diagnosed if the patient had either (1) a barium swallow examination indicating laryngeal penetration or tracheobronchial aspiration or (2) predisposing conditions for aspiration (oropharyngeal or laryngeal malignancies, oropharyngeal or laryngeal surgery or radiation therapy, or altered mental status) and no other cause identified. The electronic medical record was also reviewed for indications of other diseases to which TIB opacities were attributed.

We recorded history of predisposing conditions for recurrent pulmonary infection: cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA), primary ciliary dyskinesia, immunodeficiency states, panbronchiolitis, and tracheobronchomegaly. In this publication, we call these conditions diseases predisposing to airway infection (DPAI).

Table 1—*Imaging Protocols*

Name	Viewing Slice Thickness, mm	Contrast Rate	Expiratory Series[a]
Unenhanced (n = 171)	5	None	No
Spiral HRCT scan (n = 83)	1	None	Yes
Contrast enhanced (n = 101)	5	1-2 mL/s[b]	No
PE protocol (n = 35)	1	3-5 mL/s[c]	No
CT angiography (n = 16)	1	4-5 mL/s[b]	No

All examinations are acquired at 1-mm collimation taken at deep inspiration through the thorax. HRCT = high-resolution CT; PE = pulmonary embolism.
[a]Additional expiratory series performed.
[b]Timed to aortic opacification.
[c]Timed to pulmonary artery opacification.

CT Scan Protocols and Analysis

Thoracic CT scan protocols were moderately heterogeneous and are listed in Table 1. A thoracic radiologist with 20 years of experience in thoracic imaging (W. T. M.) performed a review, blinded to clinical information, of CT scan examinations for the distribution of several airway-related imaging findings: TIB opacities, bronchiectasis, GGOs, pulmonary consolidation, and mosaic air trapping (83 studies with expiratory series) as defined by the Fleischner Society.[18] Imaging findings were categorized as "focal" if they involved a single contiguous region of the lung, "multifocal" if they were found in multiple regions of the lung separated by intervening normal lung, or "diffuse" if they were found relatively uniformly distributed across both lungs.

"Dependent predominance" was defined as disease most severe in the lower lobes with less disease in the right middle lobe, lingula, or posterior segments of the upper lobes with sparing of the remaining segments and anterior and apical lung. The esophagus was evaluated for the following abnormalities: dilatation, air-fluid levels, reflux of contrast, wall thickening > 5 mm, gastric pull through, or presence of a hiatal hernia.

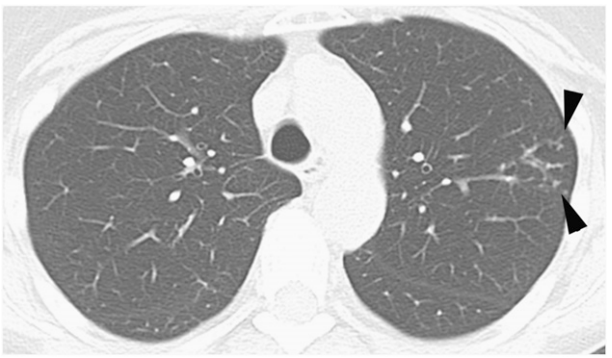

FIGURE 1. Focal bronchiolitis pattern. A 70-year-old woman with transitional cell carcinoma and no pulmonary symptoms. There is a cluster of small tree-in-bud (TIB) opacities (arrowheads) in the left upper lobe. No other findings were present, and no further evaluation was performed.

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Conceptually, inflammation of the airways follows a logical progression from bronchitis to bronchiolitis to bronchopneumonia, although in any individual case disease can follow this progression or only produce one of these morphologies. Following this logic, we subdivided diseases into (1) focal bronchiolitis (Fig 1), characterized by a single region of TIB opacities; (2) widespread bronchiolitis (Fig 2), characterized by diffuse or multifocal distribution of TIB opacities; and (3) bronchopneumonia (Fig 3), characterized by TIB opacities in association with multiple regions of GGOs or consolidation.

Bronchiectasis is a chronic manifestation of airway inflammation and might indicate other causes when seen in association with TIB opacities. Thus, we separated patients with bronchiectasis and TIB opacities into three other patterns: (4) focal bronchiectasis, characterized by a single region of bronchiectasis with associated TIB opacities; (5) random small airways disease (Fig 4), characterized by clusters of bronchiectasis, TIB opacities separated by regions of normal intervening lung parenchyma; and (6) widespread bronchiectasis (Fig 5), characterized by nearly uniform distribution of bronchiectasis across both lungs with associated TIB opacities. We included the random small airways pattern because one of the authors had anecdotally associated this pattern with nontuberculous mycobacterial infection, and we wanted to test this association.

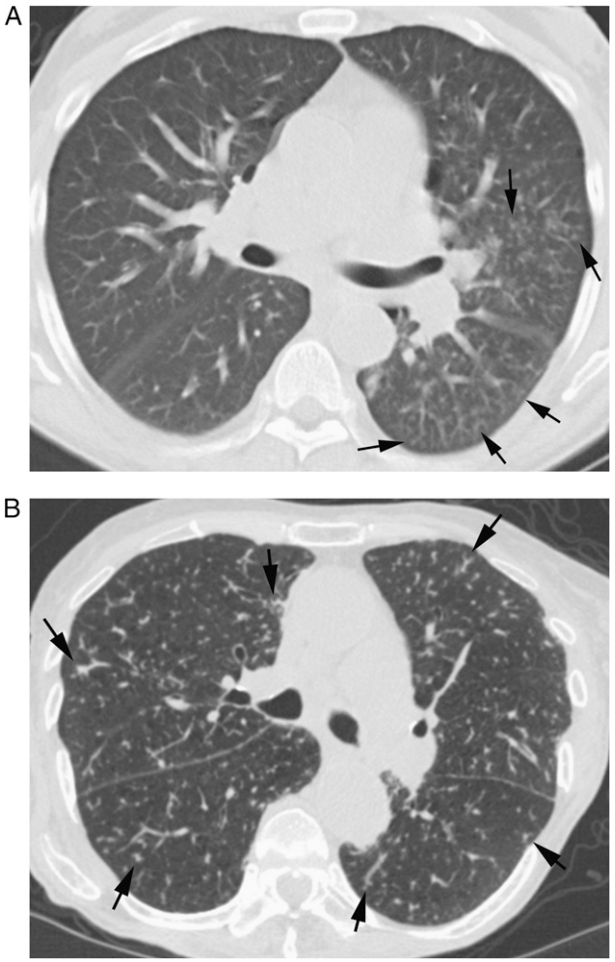

FIGURE 2. Widespread bronchiolitis pattern. A, A 54-year-old man with cough and fever. The examination shows widespread TIB opacities (arrows) in the left upper and left lower lobes. Throat swab was positive for parainfluenza. B, A 79-year-old woman with mantle cell lymphoma and fevers. The examination shows a nearly uniform distribution of TIB opacities (arrows) across the lungs bilaterally. Surgical lung biopsy was diagnostic of pulmonary lymphoma. See Figure 1 legend for expansion of abbreviation.

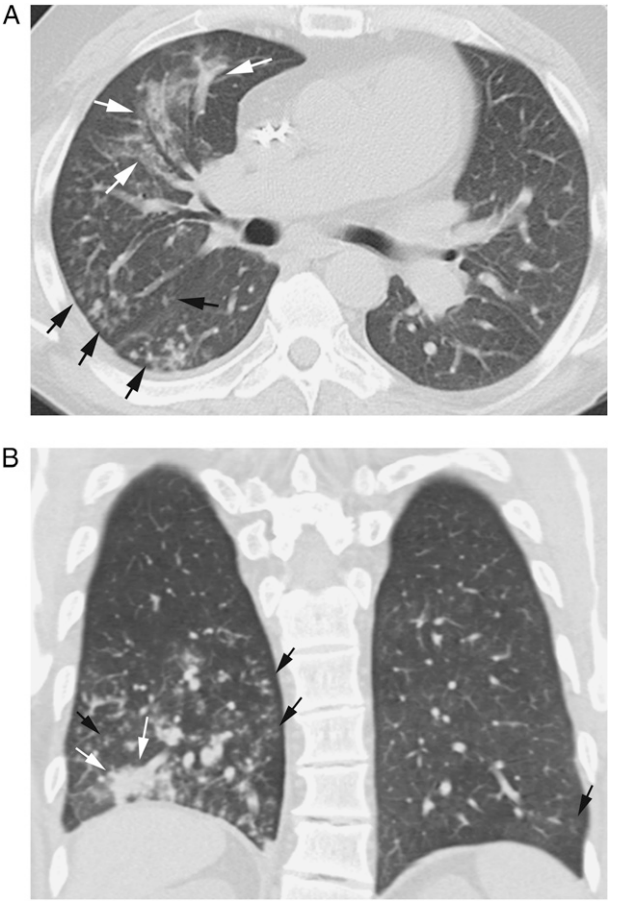

FIGURE 3. Bronchopneumonia pattern. A, A 52-year-old man with multiple myeloma and 2 weeks of cough and fever. The examination demonstrates small TIB opacities (black arrows) and a region of consolidation and ground-glass opacities (GGOs) (white arrows). Sputum cultures were positive for *Stenotrophomonas maltophilia*. B, A 46-year-old man with cough and dyspnea. Coronal CT scan shows a basilar predominance of small TIB opacities (black arrows) and consolidation (white arrows) in the right lower lobe. Sputum cultures were positive for *Pseudomonas aeruginosa* and *Escherichia coli*. Barium swallow showed the presence of aspiration. See Figure 1 legend for expansion of other abbreviation.

Since tuberculous and nontuberculous mycobacterial infections can frequently involve the lung apices and are known causes of TIB opacities, we identified an additional pattern: (7) apical/cavitary disease, characterized by apical predominance of bronchiectasis with or without cavitation associated with TIB opacities.

We recorded any additional patterns in patients that did not meet one of these seven anticipated patterns. When available, chest CT scan examinations before and after the index examination were reviewed for presence of airway-related findings. Appearance/resolution of findings within 3 months was defined as "acute." Stability of findings for > 3 months was defined as "chronic." Partial progression or resolution of findings was defined as "acute on chronic," and waxing and waning findings were defined as "relapsing."

Statistical Analysis

χ^2 Analysis or Fisher exact test were performed to compare categorical data. All *P* values reported are two sided, with a *P* value < .05 considered significant.

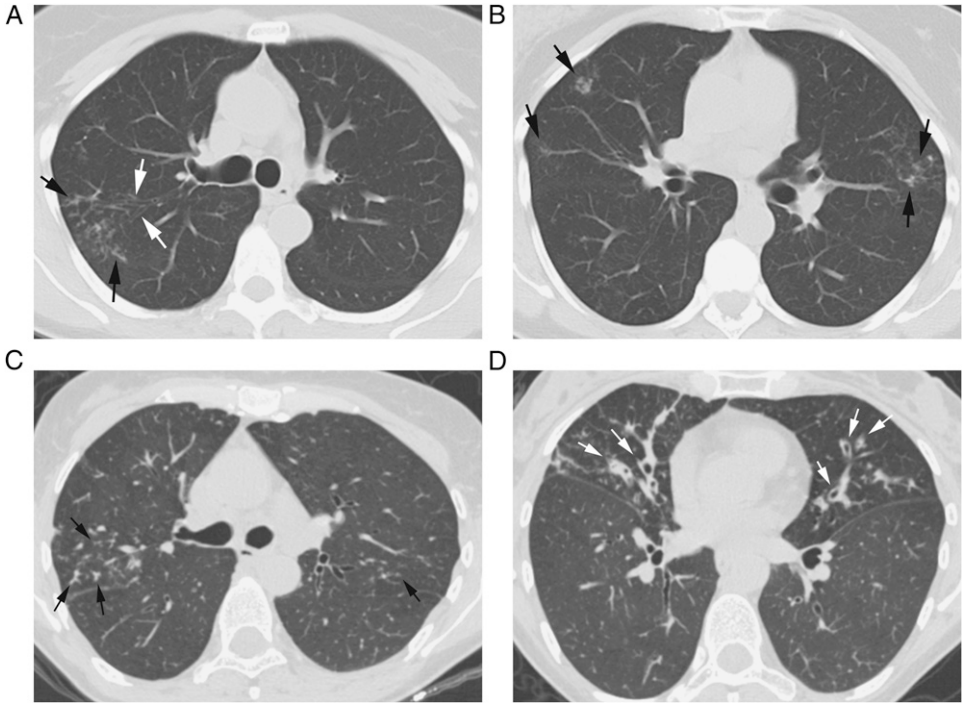

FIGURE 4. Random small airways pattern. A and B, A 60-year-old woman with chronic cough. There are small clusters of TIB opacities (black arrows) in the right upper lobe, right middle lobe, and lingula; mild bronchiolectasis (white arrows) in the right upper lobe; and normal intervening lung. C and D, A 57-year-old woman with chronic cough, fever and dyspnea. There are mixtures of TIB opacities (black arrows), bronchiectasis (white arrows), and bronchial wall thickening in the right upper lobe, right middle lobe, and lingula, with regions of normal intervening lung. These are examples of mild and severe random small airways pattern, in both cases due to chronic infection with *Mycobacterium avium* complex. See Figure 1 legend for expansion of abbreviation.

RESULTS

Causes of TIB Opacities

Our 406 examinations accounted for 3.0% (406 of 13,540) of all thoracic CT scans performed at our institutions in 2010. A cause of disease was established in only 166 of 406 (40.9%). Diseases associated with TIB opacities are listed in Table 2.

Some individuals had multiple underlying causes for TIB opacities, with 24 of 166 cases (14%) having two and six of 166 cases (4%) having three superimposed causes of TIB opacities. Multiple underlying causes were most often combinations of DPAI with a superimposed bacterial and/or mycobacterial infection (15 of 30, 50%), combinations of bacterial infection and aspiration (nine of 30, 30%), or combinations of bacterial and mycobacterial infections (five of 30, 17%).

In 119 of 166 patients (72%), infection was the cause of TIB opacities, by mycobacteria (65 of 166, 39%), bacteria (44 of 166, 27%), viruses (five of 166, 3%), or multiple organisms (six of 166, 4%) (Figs 2-4). Organisms recovered from respiratory secretions are listed in Table 3.

Aspiration, with or without associated infection, was a cause of TIB opacities in 42 of 166 cases (25%) (Fig 6). Twenty-four cases (57%) had a predisposing condition to aspiration, including head and neck cancer and/or irradiation (15 of 42, 36%), altered mental status (four of 42, 10%) (seizure in two, syncope in one, stroke in one), esophagectomy (three of 42, 7%), achalasia (one of 42, 2%), esophagitis (one of 42, 2%), vocal cord paralysis (one of 42, 2%), and vomiting with witnessed aspiration (one of 42, 2%). In 18 of 42 (43%), no predisposing condition was identified, but a barium swallow indicated the presence of laryngeal penetration or aspiration.

Twenty-three patients (23 of 166, 14%) had a DPAI (Table 2). These disorders frequently cause bronchiectasis, and 18 of 23 patients with DPAI had bronchiectasis (Fig 5). However, five patients had TIB opacities without bronchiectasis (two ABPA, two primary ciliary dyskinesia, one IgG deficiency).

Bronchiectasis was a contributing cause of TIB opacities in 87 of 166 cases (52%), associated with infection (69 of 87, 79%), aspiration (11 of 87, 13%), and DPAI (23 of 87, 26%) (Figs 4, 5). We did not consider bronchiectasis alone as a sufficient cause of TIB opacities in our study. However, across the entire database, bronchiectasis was a contributor cause of TIB opacities in 35% (141 of 406). If bronchiectasis alone were considered a cause of TIB opacities, an

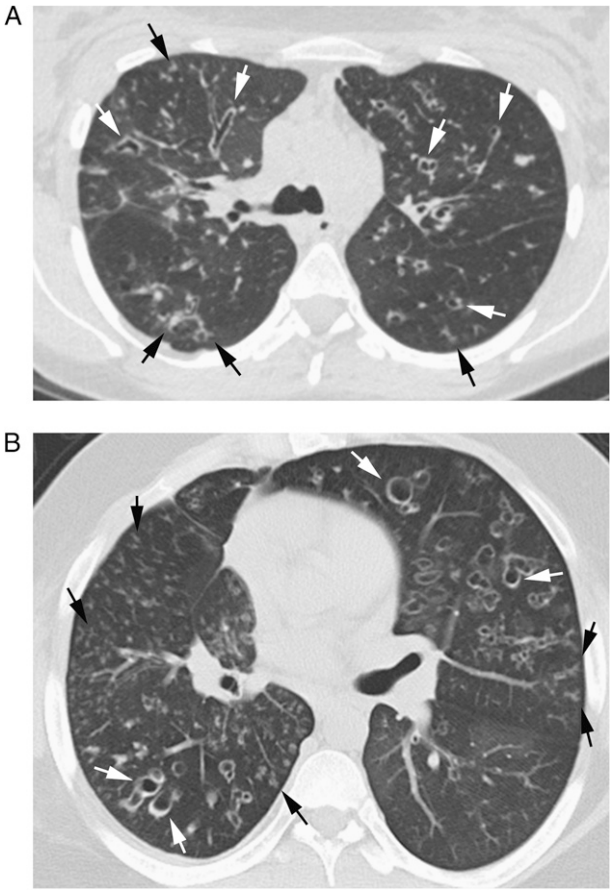

FIGURE 5. Widespread bronchiectasis pattern. A, A 22-year-old woman with cystic fibrosis and acute onset of cough, dyspnea, and fever. There are mildly dilated airways (white arrows) uniformly distributed across the lungs bilaterally, with associated bronchial wall thickening and a few TIB opacities (black arrows) in the superior segment of the left lower lobe. B, A 30-year-old man with primary ciliary dyskinesia and cough. There is widespread cystic bronchiectasis (white arrows) with scattered small TIB opacities (black arrows). No infectious organisms were recovered from either patient. These are examples of the range of appearance of the widespread bronchiectasis pattern. See Figure 1 legend for expansion of abbreviation.

additional 54 cases with a proven cause of TIB opacities are counted, leading to a total of 220 proven cases. Using this metric, there were 63 of 220 cases (29%) in which bronchiectasis alone, without accompanying infection or aspiration, was the cause of TIB opacities. Miscellaneous causes of TIB opacities were seen in 11 of 166 (6.6%) (Fig 2, Table 2).

Imaging Patterns Associated With TIB Opacities

Table 4 lists the frequencies of each imaging pattern and the frequency with which a cause was identified. TIB opacities were seen in association with bronchiectasis in 30% (123 of 406) of cases and with an apical-predominant disease in 2.5% (10 of 406) cases. In the remaining 67% (273 of 406) of cases, they were seen without permanent structural changes in the lung.

Table 2—*Patients With Proven Causes of TIB Opacities (N = 166)*

Cause of TIB Opacities	No.	%
Infectious causes	119	72
Mycobacteria only	65	39
With bronchiectasis[a]	51	31
Without bronchiectasis[b]	14	8
Mycobacteria and bacteria	5	3
With bronchiectasis[c]	4	2
Without bronchiectasis	1	0.6
Bacteria only	44	27
With bronchiectasis[d]	14	8
Without bronchiectasis[e]	30	18
Virus only[f]	4	2
Virus and bacteria[f]	1	0.6
Aspiration	42	25
Without infection	31	19
With infection	11	7
Bacteria	9	5
Mycobacteria	2	1
DPAI	23[g]	14
Cystic fibrosis	11[h]	7
ABPA	7[h]	4
Primary ciliary dyskinesia	3	2
Hyper IgE syndrome	1	0.6
Acquired IgG deficiency	1	0.6
Panbronchiolitis	1	0.6
Tracheobronchomegaly	1	0.6
Bronchiectasis	87	52
Miscellaneous	11	7
BO/BOS[i]	5	3
Graft-vs-host disease	3	2
Obstructing lesion	1	0.6
Pulmonary lymphoma	1	0.6
BOOP/pulmonary fibrosis	1	0.6

Sum of subheadings exceeds 166 because there were cases with multiple causes. ABPA = allergic bronchopulmonary aspergillosis; BO = bronchiolitis obliterans; BOOP = bronchiolitis obliterans with organizing pneumonia; BOS = bronchiolitis obliterans syndrome; DPAI = diseases predisposing to airway infection; TIB = tree-in-bud.

[a]Two with an underlying airway inflammatory syndrome.

[b]One associated with airway inflammatory syndrome.

[c]Four with an underlying airway inflammatory syndrome.

[d]Five with an underlying bronchiectasis syndrome and one associated with aspiration.

[e]Eight associated with aspiration and 1 with associated airway inflammatory syndrome.

[f]No bronchiectasis.

[g]Sixteen with superimposed infectious cause of TIB opacities. All had associated bronchiectasis except two patients with ABPA, two patients with primary ciliary dyskinesia, and one patient with IgG deficiency.

[h]One with associated bacterial infection.

[i]Two patients had both cystic fibrosis and ABPA.

The single most common pattern of TIB opacities was a small focal region of TIB opacities without other imaging findings (focal bronchiolitis) in 24.6% of cases (100 of 406) (Fig 1). This pattern was also the least likely pattern to have a cause identified, with only 9% of cases (nine of 100) having a proven cause. This was significantly less than the 51.3% (157 of 306) proven rate of the remainder of the study population

Table 3—*Infectious Causes of TIB Opacities*

Organism	No. of Cases
Mycobacteria	70
MAC	59 (84)
Mycobacterium abscessus complex	6 (9)
Mycobacterium chelonae	3 (4)
Mycobacterium fortuitum	4 (6)
Mycobacterium kansasii	2 (3)
Mycobacterium massiliense	1 (1)
Mycobacterium terrae	1 (1)
Mycobacterium tuberculosis	1 (1)
Bacteria	50
Pseudomonas aeruginosa	29 (58)
Staphylococcus aureus	19 (38)
Klebsiella pneumonia	3 (6)
Escherichia coli	2 (4)
Moraxella catarrhalis	2 (4)
Haemophilus influenza	2 (4)
Enterobacter cloacae	1 (2)
Acinetobacter baumannii complex	1 (2)
Achromobacter xylosoxidans	1 (2)
Streptococcus agalactiae	1 (2)
Stenotrophomonas maltophilia	1 (2)
Burkholderia cepacia complex	1 (2)
Bordetella bronchiseptica	1 (2)
Klebsiella oxytoca	1 (2)
Actinomyces israelii	1 (2)
Viruses	5
Respiratory syncytial virus	2 (40)
Parainfluenza	3 (60)

Data are presented as No. or No. (%). Sums of the organisms exceed the total number of cases because some individuals had multiple organisms recovered. MAC = *Mycobacterium avium* complex. See Table 2 legend for expansion of other abbreviation.

($P < .0001$). The low level of proven diagnosis may have been due to fewer symptoms. Of the 406 patients, 354 had sufficient data to evaluate for the presence or absence of symptoms. Cases of focal bronchiolitis were asymptomatic in 31 of 80 (39%), whereas all other imaging patterns were asymptomatic in 46 of 274 (13%) ($P < .0001$). Patients with permanent structural changes in the lung, such as cavities or bronchiectasis, were more likely to have an underlying cause diagnosed (90 of 133, 68%) than those without permanent structural changes (76 of 273, 28%) ($P < .0001$).

Associations Between Imaging Pattern and Underlying Cause of TIB opacities

Table 5 lists the patterns and underlying causes of TIB opacities in 166 patients for whom a cause could be established, and Table 6 lists the sensitivity, specificity, positive predictive value, and negative predictive value for patterns as predictive of particular causes. Each of the causes of TIB opacities had a wide variety of imaging manifestations, and, as a result, no imaging pattern was highly sensitive for a particular underlying cause of TIB opacities. However, some imaging patterns were specific for particular causes of TIB opacities. Table 7 lists the longevity of imaging findings as a function of cause of TIB opacities.

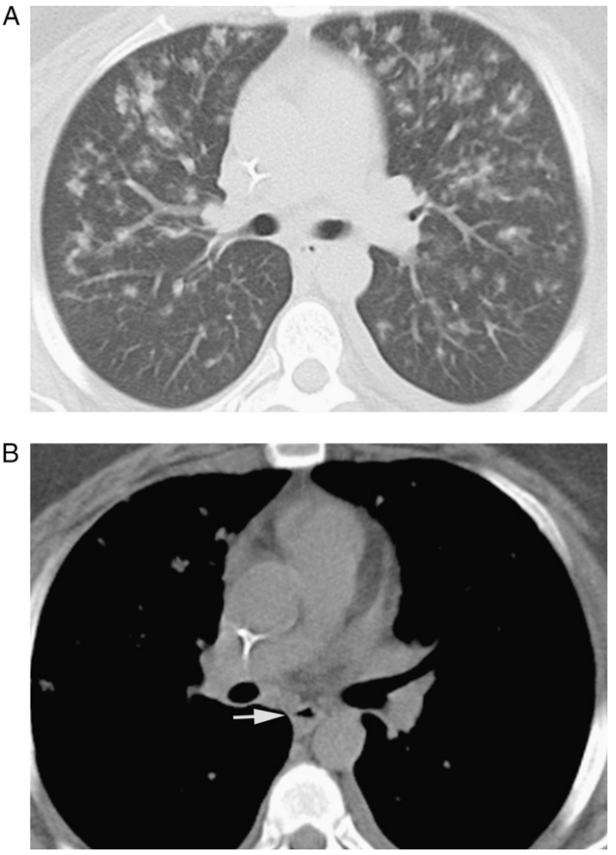

FIGURE 6. Bronchiolitis due to aspiration. This 30-year-old woman with promyelocytic leukemia was neutropenic and febrile. A, There are widespread TIB opacities throughout both lungs, with predominance in the anterior (nondependent) portions of the lungs, a finding that would normally suggest a diagnosis other than aspiration. However, in any individual case, all causes of TIB opacities should be considered. B, Soft tissue windows show a small air-fluid level in the esophagus (arrow). This is an abnormal finding, likely indicating the presence of gastroesophageal reflux. A variety of esophageal abnormalities can be a clue to aspiration as a cause of TIB opacities. Viral throat swab and bacterial cultures were negative. However, barium swallow demonstrated silent aspiration of barium. See Figure 1 legend for expansion of abbreviation.

DISCUSSION

Since their description by Im and colleagues[1] in 1993 as a manifestation of pulmonary TB, TIB opacities have increasingly become recognized as a common feature of airways inflammation. Prior reports indicate that TIB opacities can be a manifestation of a variety of conditions;[1-16] however, the relative frequency of the causes of TIB opacities has not been previously determined, to our knowledge. Our results indicate that TIB opacities are most often a manifestation of pulmonary infections (72%, 119 of 166) and aspiration (25%, 42 of 166). Our analysis indicates overlap between the causes of TIB opacities and their imaging manifestations. However, although insensitive for

Table 4—*Imaging Patterns in 406 Patients With TIB Opacities*

Pattern	Proven	Unproven	Total
Without bronchiectasis	76 (46)	197 (82)	273 (67)
Focal bronchiolitis	9 (5)	91 (38)	100 (25)
Widespread bronchiolitis	20 (12)	35 (15)	55 (14)
Bronchopneumonia	42 (25)	53 (22)	95 (23)
Other[a]	5 (3)	18 (8)	23 (6)
With bronchiectasis	81 (49)	42 (17)	123 (30)
Focal bronchiectasis	6 (4)	0	6 (1)
Random small airways	45 (27)	39 (16)	84 (21)
Widespread bronchiectasis	26 (16)	0	26 (6)
Bronchiectasis, nonspecified	4 (2)	3 (1)	7 (2)
Apical/cavitary disease	9 (5)	1 (0.4)	10 (2)
Apical cavity/bronchogenic spread	7 (4)	0	7 (2)
Upper lobe bronchiectasis	2 (1)	1 (0.4)	3 (1)
Total	166	240	406

Data are presented as No. (%). See Table 2 legend for expansion of abbreviation.

[a]Patients had TIB opacities that were not focal bronchiolitis, diffuse bronchiolitis, or bronchopneumonia, and there was no bronchiectasis.

individual diseases, several imaging patterns had moderate to high specificity for causes of TIB opacities (Fig 7).

Mycobacterial Infections and the Random Small Airways Pattern

Mycobacteria, primarily *Mycobacterium avium* complex (MAC), were the most common infectious cause of TIB opacities, accounting for 39% (70 of 166) of cases. TB was identified in only one instance in our urban US practice but would likely be a common cause of TIB opacities in developing countries.

The random small airways pattern is characterized by alternating regions of normal lung with regions of small airways abnormality (bronchiectasis and TIB opacities) (Fig 4). This pattern was nearly always caused by chronic infection with nontuberculous mycobacteria, especially MAC (specificity, 0.92).

Bacterial Infections and the Bronchopneumonia Pattern

Bacterial infections were a cause of TIB opacities in 30% (50 of 166) of cases. The causative organisms were usually common respiratory pathogens, such as *Pseudomonas aeruginosa* (58%, 29 of 50) and *Staphylococcus aureus* (38%, 19 of 50), but were also due to a wide variety of bacteria (Table 3). The bronchopneumonia pattern (Fig 3), characterized by TIB opacities with regions of consolidation and/or GGOs, was associated with bacterial infections (specificity, 0.84).

Viral Infections

Viral infections accounted for only 3% (five of 166) of cases. The frequency of immunization against influenza was very high during the year of our study, 2010, the second season after the 2009 influenza A(H1N1) pandemic. We previously published our experience with viral infections from 2006 to 2008.[12-14] Over that 3-year span, there were 11, 15, and 20 viral infections annually that showed TIB opacities on CT scans. Thus, if other causes of TIB opacities remain constant, the relative incidence of viral infections as a cause of TIB opacities could range from as low as 3% (five of 166) to as high as 11% (20 of 181) of causes of TIB opacities.

Aspiration and Associations With Dependent Disease and Esophageal Abnormalities

One-fourth (42 of 166) of our cases of TIB opacities were in part due to aspiration. Recognition of

Table 5—*Imaging Patterns in 166 Patients With TIB Opacities and Proven Underlying Cause*

Pattern	Total	Mycobacteria	Bacteria	Aspiration	DPAI	Other
Without bronchiectasis	76					
Bronchiolitis, focal	9	3	4	3	0	1 (BOS)
Bronchiolitis, widespread	20	6	3	7	3	2[a]
Bronchopneumonia	42	4	24	17	1	8[b]
Other pattern[c]	5	0	0	3	1	1 (GVHD)
With bronchiectasis	81					
Random small airways	45	39	0	5	2	1 (BO)
Widespread bronchiectasis	26	7	15	2	14	2 (GVHD, BOOP)
Bronchiectasis, focal	6	4	1	1	1	1 (BOS)
Bronchiectasis, nonspecified	4	2	0	2	0	0
Apical/cavitary disease	9					
Cavity/bronchogenic spread	7	4	2	2	1	0
Other—upper lobe bronchiectasis	2	1	1	0	0	0

Sums of individual categories can exceed totals because some cases had more than one cause of TIB opacities. GVHD = graft-vs-host disease. See Table 2 legend for expansion of other abbreviations.

[a]One viral, one pulmonary lymphoma.

[b]Four viral, two BOS, one GVHD, one post obstructive.

[c]Patients had TIB opacities that were not focal bronchiolitis, diffuse bronchiolitis, or bronchopneumonia, and there was no bronchiectasis.

Table 6—*Associations Between Imaging Pattern and Causes of TIB Opacities*

Pattern	Sensitivity	Specificity	PPV	NPV	*P* Value
Random small airways with mycobacterial infection	0.56	0.94	0.87	0.84	< .0001
Random small airways with MAC	0.65	0.92	0.80	0.84	< .0001
Widespread bronchiectasis with DPAI	0.61	0.92	0.54	0.94	< .0001
Widespread bronchiectasis with DPAI and bacterial infection	0.83	0.90	0.38	0.99	< .0001
Bronchopneumonia with bacterial infection	0.48	0.84	0.57	0.79	< .0001
Bronchopneumonia with aspiration	0.40	0.80	0.40	0.80	.02
Bronchopneumonia with bacterial infection and aspiration	0.41	0.90	0.81	0.60	< .0001
Dependent distribution with aspiration	0.42	0.79	0.42	0.80	.007
Esophageal abnormality with aspiration	0.45	0.86	0.53	0.82	< .0001
Dependent distribution and esophageal abnormality with aspiration	0.23	0.96	0.67	0.79	.0005
Acute findings with bacterial infection	0.79	0.87	0.54	0.96	< .0001
Chronic findings with mycobacterial infection	0.56	0.96	0.68	0.94	< .0001

NPV = negative predictive value; PPV = positive predictive value. See Table 2 and 3 legends for expansion of other abbreviations.

one of the predisposing conditions to aspiration should lead to a high index of suspicion that TIB opacities are a result of aspiration. However in 43% (18 of 42) of our cases, we identified no predisposing condition, and, therefore, the possibility of aspiration as an cause for TIB opacities should always be considered (Fig 6).

Aspiration is known to be a common cause for pneumonia, and 26% (11 of 42) of our cases had associated infections. Conventional techniques underestimate the incidence of pulmonary infection,[19-21] and so it is likely that the coexistence of infection with aspiration is underreported in this study. However, it is also likely that aspiration can lead to the development of TIB opacities in the absence of airway infection.

Bronchopneumonia, a pattern of TIB opacities with consolidation or GGOs, was moderately specific for aspiration (specificity, 0.80). Furthermore, a dependent distribution of disease (specificity, 0.79), the presence of esophageal abnormality (specificity, 0.86) and both (sensitivity, 0.96) were associated with aspiration as the cause of TIB opacities (Fig 6). Esophageal abnormalities included dilatation with air-fluid levels or debris (n = 6), air-fluid levels alone (n = 4), dilatation alone (n = 3), esophagogastrectomy (n = 3), hiatal hernia (n = 2), and esophageal thickening (n = 1).

Table 7—*Patients With Follow-up Examinations (N = 118)*

Cause of TIB Opacities	No.	Acute	Acute on Chronic	Chronic	Relapsing
Mycobacteria only	56	2 (4)	1 (2)	53 (95)	0
Mycobacteria and bacteria	6	1 (17)	1 (17)	4 (67)	0
Bacteria only	19	15 (79)	0	4 (21)	0
Virus only	3	3 (100)	0	0	0
Virus and bacteria	1	1 (100)	0	0	0
Aspiration without organisms	22	8 (36)	0	11 (50)	3 (14)
DPAI without organisms	5	0	1 (20)	4 (80)	0
Other[a]	6	1 (17)	1 (17)	3 (50)	1 (17)

Data are presented as No. or No. (%). See Table 2 legend for expansion of abbreviations.

[a]Bronchiolitis obliterans, bronchiolitis obliterans syndrome, post obstructive inflammation, graft-vs-host disease.

DPAI and the Widespread Bronchiectasis Pattern

Cystic fibrosis, primary ciliary dyskinesia, ABPA, immunodeficiency states, and some other conditions can predispose individuals to airway infection and inflammation. These disorders accounted for 14% (23 of 166) of causes of TIB opacities. A moderately uniform, bilateral distribution of bronchiectasis and TIB opacities, the widespread bronchiectasis pattern, was highly associated with DPAI (specificity, 0.90) (Fig 5). Although DPAI usually cause both bronchiectasis and TIB opacities, in 22% of cases (five of 23), DPAI caused TIB opacities without bronchiectasis. Thus, a bronchiolitis pattern without bronchiectasis can occasionally be an early indicator of underlying DPAI.

Bronchiectasis

Bronchiectasis is known to be associated with impaired mucociliary clearance,[22] which likely results in TIB opacities on CT scan examinations. Bronchiectasis was a contributing factor to the cause of TIB opacities in 35% of cases (141 of 406). This was often associated with accompanying infection or aspiration. However, bronchiectasis without other cause may have been the cause of TIB opacities in an additional 29% (63 of 220) of cases.

Uncommon Causes of TIB Opacities

As previously reported,[9,11] less common causes of TIB opacities include chronic rejection in lung transplants, graft-vs-host disease in bone marrow transplants, obstructive airway lesions, and bronchiolitis obliterans organizing pneumonia. The only noninflammatory

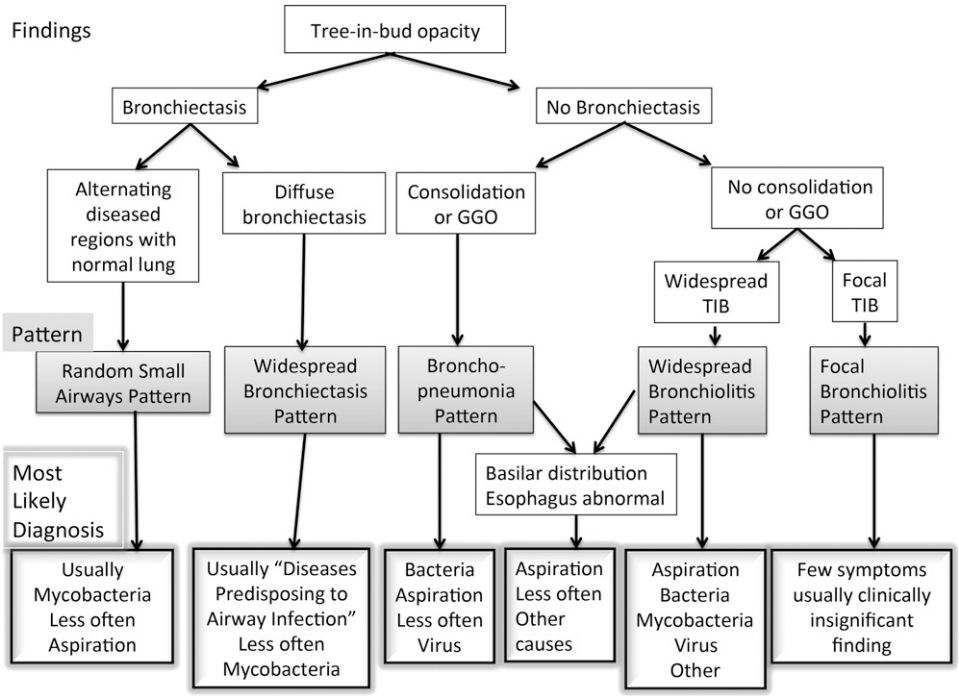

FIGURE 7. TIB opacity flowchart. The flowchart provides a simple method for identifying the most common causes of diseases associated with TIB opacities based on the patient's imaging features. See Figure 1 and 3 legends for expansion of abbreviations.

cause of TIB opacities in our study was lymphoma, which has previously been reported[16] (Fig 2).

Nonspecificity of the Bronchiolitis Pattern

Widespread bronchiolitis, characterized by TIB opacities without regions of alveolar filling (consolidation, GGO), was the least specific of the common TIB opacities patterns. Bronchiolitis was seen in all of the major causes of TIB opacities, including mycobacterial, bacterial, and viral infections; aspiration; and airway inflammatory syndromes; and was also one of the more common patterns seen in the rare causes of TIB opacities, such as bronchiolitis obliterans and graft-vs-host disease (Figs 2, 6).

Insignificance of Focal Bronchiolitis

Focal bronchiolitis was the most frequently encountered pattern (25%, 100 of 406), but a definitive diagnosis for the cause of the disease was rarely identified, because the clinicians caring for the patient chose to not perform further evaluations to diagnose the cause (Fig 1). Our study suggests that this type of disease is often asymptomatic. We believe that in most cases a pattern of focal TIB opacities will be clinically irrelevant.

Finding Longevity

Our study suggests that resolution of TIB opacities within 3 months is the typical response to infections with bacteria and viruses (Table 7), although persistence of TIB opacities for >3 months is typical of mycobacterial infections and TIB opacities associated with DPAI. Finally, aspiration is a common cause of both acute and chronic TIB opacities.

Imaging Algorithm for TIB Opacities

TIB opacities are a common finding on thoracic CT scan examinations and were seen in 3% of all chest CT scans performed at our institutions. Our study suggests that imaging features can provide an important starting point in the differential diagnosis of TIB opacities, as outlined in Figure 7. However, our study indicates that the imaging patterns of the diseases causing TIB opacities overlap with each other, and, in any individual situation, the entire spectrum of causes needs to be considered.

Limitations

The primary limitation to this study is the retrospective nature of the research. Only 40.9% of cases had an established diagnosis for the cause of TIB opacities. We have no way of proving that the undiagnosed cases have similar causes to those with diagnoses. Furthermore, the clinical evaluation of patients was very heterogeneous. Of individuals with proven causes, testing for all causes of TIB opacities was not performed. Therefore, it is possible that some individuals who had a single cause identified may have had additional

superimposed causes, such as coexistence of viral and bacterial causes. It is likely that this has resulted in underreporting of the incidence of some causes of TIB opacities, especially infectious causes. Furthermore, the association between imaging patterns and causes of disease could be skewed by differences between diagnosed and undiagnosed cases. Also, the imaging protocols were heterogenous, with 67% (272 of 406) of examinations having only thick section (5 mm) images. This may have reduced the sensitivity for some subtle findings. Because of these limitations, our results can only be considered provisional.

In conclusion, TIB opacities are a common finding on CT scan examinations of the thorax and are most frequently due to mycobacterial, bacterial, and viral infections; aspiration; and several congenital or acquired syndromes predisposing to airways inflammation. The imaging manifestations of these diseases overlap, and in any individual all causes of TIB opacities should be considered. However, imaging patterns can predict the most likely cause of TIB opacities. The random small airways pattern is highly associated with MAC infection. Widespread uniform bronchiectasis and TIB opacities are highly associated with the inflammatory airway syndromes. Bronchopneumonia will most often be a complication of bacterial infection or aspiration. The presence of dependent TIB opacities or an abnormality of the esophagus increases the likelihood of aspiration as the cause of the imaging abnormalities. A small focal region of TIB opacities is usually clinically irrelevant.

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Dr Miller: contributed to study design, data collection, data analysis, statistical analysis, and manuscript preparation.
Dr Panosian: contributed to data collection, data analysis, and manuscript preparation.
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