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ORIGINAL ARTICLE

Tree-in-bud Nodules in Asian Population

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ABSTRACT

Objective: *The tree-in-bud sign is a common finding on thin-section computed tomography of the lungs. However, the differential diagnosis of this common radiological finding is long and exhausting. Knowledge of its common causes together with the patient's clinical history are essential to formulating an appropriate list of possibilities. This study aimed to evaluate the common causes of tree-in-bud opacities detected on computed tomographic thorax in Asians.*

Methods: *Records of 189 consecutive patients from two regional hospitals in Hong Kong underwent computed tomographic thorax and found to have tree-in-bud opacities during the period of January 2007 to June 2008 were retrospectively reviewed. This included a follow-up of their clinical progress, microbiological and histological findings.*

Results: *Mycobacterial infection was the commonest cause of such opacities, accounting for 68 (36%) of the cases. Other bacterial infection accounted for 54 (29%) cases. Whilst 31 (16%) were in patients with bronchiectasis and bronchiolectasis not associated with any bacterial infection, 12 (6%) of them had carcinoma of the lung, and 9 (5%) had other conditions.*

Conclusion: *This study suggests a list of differential diagnosis for commonly encountered tree-in-bud nodules on computed tomographic scans among Asians; the commonest being infection, particularly tuberculosis (which is much more prevalent than in the western populations). Non-bacterial bronchiectasis and bronchiolectasis are the next most common cause. Neoplasia, especially carcinoma of the lung, accounts for a small proportion. In contrast to western studies, cystic fibrosis, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, and pneumocystic carinii were not encountered in our sample.*

Key Words: *Bronchial diseases; Bronchioles; Lung diseases; Radiography, thoracic; Tomography, X-ray computed*

中文摘要

亞洲人群中的樹芽狀結節影像表現

尹宇瀚、岑承輝、關永豪、鄭志成

目的：肺部薄層CT經常見樹芽狀徵象，可是這種情況的鑑別診斷很難。要了解患者的病史，加上對於這種樹芽徵病因的認識，才可以歸納出病人發病可能的原因。本研究評估亞洲人中胸部CT呈樹芽狀陰影的普遍病因。

方法：回顧研究2007年1月至2008年6月期間於香港兩所分區醫院內連續189名作胸部CT掃描並發現有樹芽狀陰影的病人紀錄，包括臨床表現、微生物學及組織學的發現。

結果：結核菌感染為導致胸部CT呈樹芽狀陰影的最普遍原因，佔病例的36%（68例）；其他細菌感染佔29%（54例）。31例（16%）為沒有細菌感染的支氣管擴張症以及細支氣管擴張症；12例（6%）為肺癌，另9例（5%）屬其他疾病。

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結論：本研究歸納出亞洲人胸部CT呈樹芽狀陰影的普遍鑑別診斷，其中最常見的是感染，尤其是肺結核（結核比在西方國家更普遍）。其次是沒有細菌感染的支氣管擴張症以及細支氣管擴張症。腫瘤（尤其是肺癌）佔病例的較少數。外國文獻中有關於囊腫性纖維化、過敏性支氣管肺曲霉病、過敏性肺炎及肺囊蟲的記載，可是並未在本研究的病例中發現。

INTRODUCTION

The tree-in-bud sign is a common finding on thin-section computed tomography (CT) of the lungs. However, the differential diagnosis of this common radiological finding is long and exhausting. When formulating a differential diagnosis, knowledge of the common causes in the community together with the patient's clinical history, physical finding, and investigation results are essential. This study aimed to evaluate the common causes of tree-in-bud opacities detected on CT of the thorax in Asians.

METHODS

A total of 189 consecutive patients underwent CT thorax with the finding of tree-in-bud opacities from two regional hospitals in Hong Kong (Pamela Youde Nethersole Eastern Hospital and Ruttonjee & Tang Shiu Kin Hospitals) during the period of January 2007 to June 2008 were retrospectively reviewed. CT scans were performed using 1-to-5–mm collimation on Toshiba Aquilion 16 CT scanners (Toshiba, Japan). Images were obtained in supine or supine and prone positions at maximum inspiration. Iopamiro 370 (60 ml) were given intravenously for contrast scans with the delayed acquisition time at 55 seconds. Case selection was performed by searching for "tree-in-bud" as key words in the radiological report using the radiology information system. Two radiologists subsequently reviewed the CT images using the maximum intensity projection technique. Scans from 32 patients were excluded due to: absence of tree-in-bud opacities as determined in the retrospective CT review, the subject had defaulted or not yet been followed up, or had died without a definitive diagnosis. Follow-up on the clinical progress of the patients, as well as microbiological

Table 1. Causes of tree-in-bud patterns detected on computed tomographic thorax.

Cause	No. (%)
Infection	
Mycobacterial (43%)	
Mycobacteria tuberculosis (smear/culture +ve)	57 (30%)
Mycobacteria tuberculosis (empirical treatment)	11 (6%)
Non-tuberculous mycobacteria	14 (7%)
Bacterial (29%)	
Bacteria (culture +ve)	22 (12%)
Bacteria (empirical treatment)	32 (17%)
Viral (1%)	
Viral	1 (1%)
Bronchiectasis	
Negative results for mycobacilli or other bacteria	31 (16%)
Carcinoma of lung	12 (6%)
Others	9 (5%)
Total	189

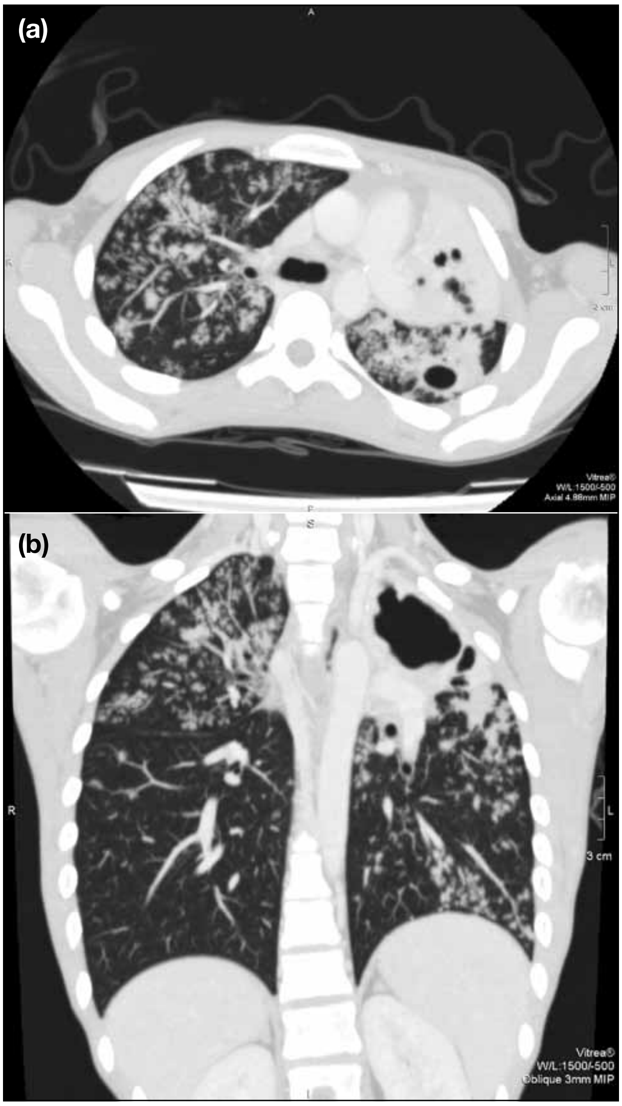

Figure 1. A male adult with confirmed mycobacterial tuberculosis infection: (a) Axial and (b) coronal post-contrast computed tomographic scans of the thorax in lung window and maximal intensity projection showing tree-in-bud opacities in both lungs, associated with a cavitating lesion and consolidation in the left upper lobe.

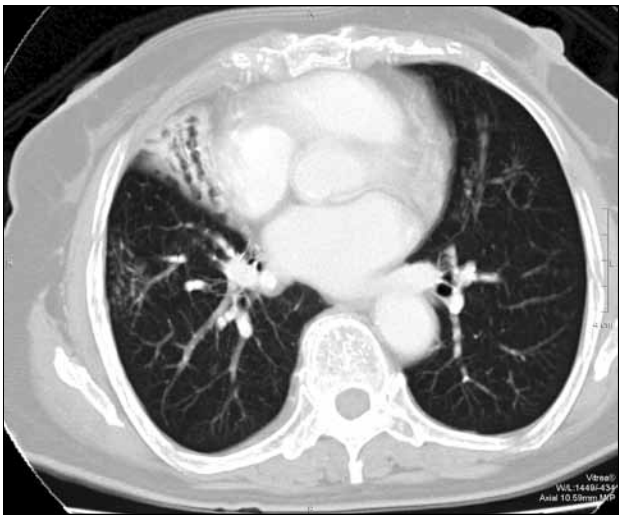

Figure 2. An adult male with confirmed non-tuberculous mycobacteria infection (*Mycobacterium chelonae*): an axial post-contrast computed tomographic scan of thorax in a lung window and maximal intensity projection showing tree-in-bud opacities in the right lower lobe, with consolidation in the right middle lobe.

Figure 3. An adult female with a confirmed bacterial infection (*Pseudomonas aeruginosa*): an axial post-contrast computed tomographic scan of thorax in a lung window with maximal intensity projection showing tree-in-bud opacities in both lungs.

and histological findings were also conducted via the electronic patient record.

RESULTS

The 189 patients included 99 males (52%) and 90 females (48%), with a mean age of 65 (range, 14-93) years.

Mycobacterial infection was the commonest cause of tree-in-bud opacities on CT thorax, accounting for 68 (36%) of the patients, of whom 57 had microbiological-proven mycobacterium tuberculosis infection (Table 1). Most of these patients had a sputum smear or culture-positive for acid fast bacilli (AFB), whilst in others, bronchial brush smear / bronchial washings or pleural fluid samples were AFB-positive. Empirical anti-tuberculosis treatment was given to 11 other patients on clinical and radiological grounds with improvement noted on follow-up (Figure 1). Non-tuberculous mycobacteria (NTM) including *Mycobacterium chelonae* (n = 7), *M. avium* complex (n = 3), *M. kansasii* (n = 2) and *M. fortuitum* (n = 2) were identified in 14 patients (Figure 2). The diagnosis of definitive NTM lung disease was determined based on the 2007 American Thoracic

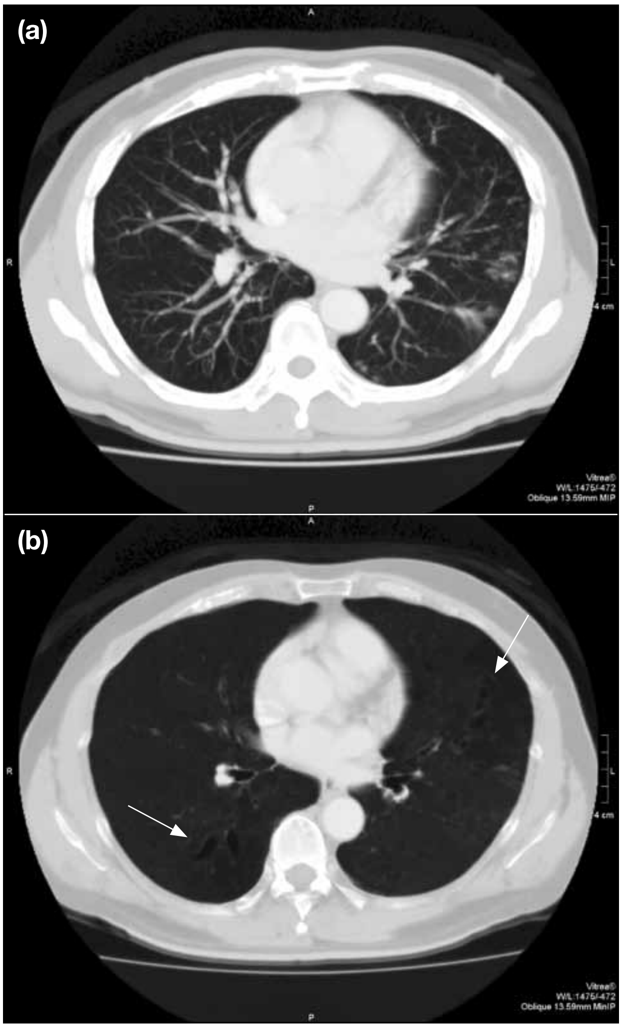

Figure 4. A male adult with bronchiectasis and negative results for mycobacterial or other bacterial infection: axial post-contrast computed tomographic scans of thorax (a) in a lung window with maximal intensity projection showing tree-in-bud opacities in the left lung, and (b) in a lung window with minimal intensity projection showing bronchiectasis (arrows) in the right lower lobe and left upper lobe.

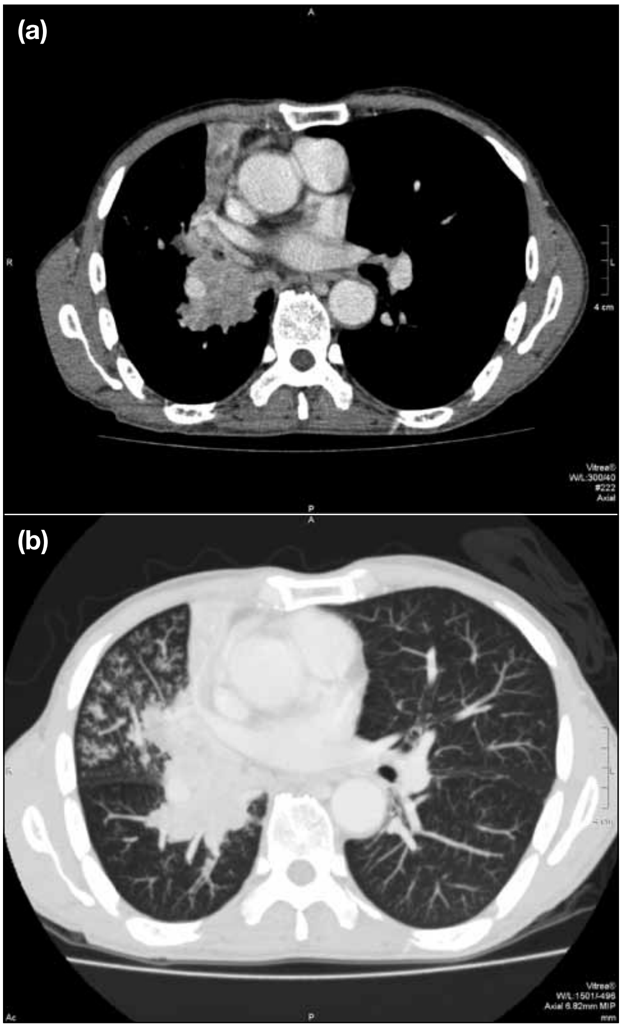

Figure 5. A male adult with lung carcinoma: axial post-contrast computed tomographic scans of thorax (a) in a soft tissue window showing a right-sided abnormal soft tissue mass compatible with lung carcinoma, and (b) in a lung window with maximal intensity projection showing tree-in-bud opacities in the right middle lobe.

Society diagnostic guideline,[1] which include clinical, radiological, and microbiological criteria.

Infection due to other bacteria was the second most common cause (54 cases, 29%; Figure 3). The relevant bacteria included: *Pseudomonas* species (n = 8), *Haemophilus influenzae* (n = 6), *Staphylococcus aureus* (n = 3), *Moraxella catarrhalis* (n = 3), *Actinomyces* (n = 1) and *Streptococcus* (n = 1). Whilst 32 other patients had empirical treatment for bacterial infection with clinical and radiological improvement after antibiotic treatment. One patient had influenza B viral infection.

In all, 31 (16%) of the patients had bronchiectasis and bronchiolectasis with negative results for mycobacilli and other bacteria (Figure 4).

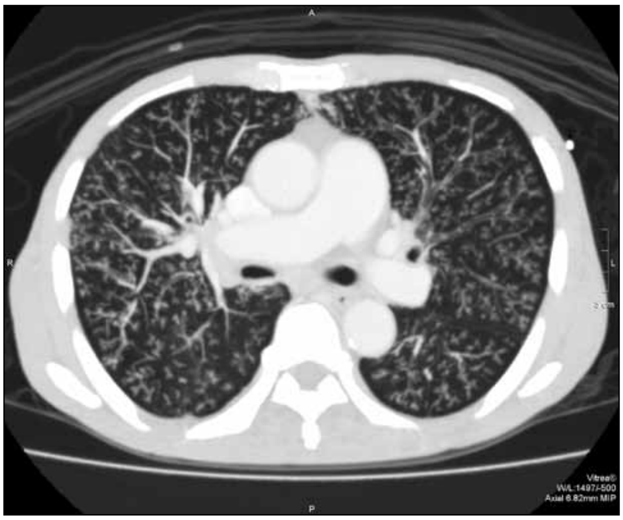

Figure 6. An adult male patient with panbronchiolitis: an axial post-contrast computed tomographic scan of thorax in a lung window and maximal intensity projection showing diffuse tree-in-bud opacities involving all lobes in both lungs.

In 12 (6%) of the patients, carcinoma of the lung was responsible. In each case, a 2-to-5–cm lung mass was also detected (Figure 5).

Other causes comprised nine (5%) cases as follows: three in asymptomatic smokers with CT features of respiratory bronchiolitis, one with Asian panbronchiolitis (Figure 6), and three with blood clots blocking bronchi diagnosed by bronchoscopy. Subsequently one patient had positron emission tomography, which showed non-specific inflammatory change. One other patient received no definite treatment, but was well on follow-up.

The distribution of tree-in-bud opacities is different in different parts of the lungs; such distribution based on causes is shown in Table 2. Cases with bacterial infections and lung carcinoma tended to be more localised (57%) or focal (67%), involved only one lung. No definite lobar predominance was recognised in patients with mycobacterial infections and bronchiectasis, though a slight predilection for bilateral lung involvement was noted. In the patient with Asian panbronchiolitis, tree-in-bud opacities affected all lobes in both lungs.

DISCUSSION

The tree-in-bud sign is a commonly encountered radiological finding on thin-section CT thorax. It represents bronchiolar impaction with mucus, pus or fluid,[2] and is characterised by small well-defined

Table 2. Tree-in-bud opacity distribution based on cause.

Cause	No. of cases	No. (%)												
		Frequency of involvement					No. of lobes involved					Lung side involved		
		RUL	RML	RLL	LUL	LLL	1	2	3	4	5	Right	Left	Both
Mycobacteria TB	68	44 (65)	33 (49)	35 (51)	40 (59)	30 (44)	22 (32)	16 (24)	9 (13)	2 (3)	19 (28)	22 (32)	13 (19)	33 (49)
Non-tuberculous mycobacteria	14	11 (79)	9 (64)	10 (71)	9 (64)	12 (86)	5 (36)	3 (21)	1 (7)	1 (7)	4 (29)	4 (29)	2 (14)	8 (57)
Other bacteria	54	22 (41)	13 (24)	26 (48)	22 (41)	20 (37)	30 (56)	13 (24)	6 (11)	1 (2)	4 (7)	24 (44)	12 (22)	18 (33)
Viral	1	-	-	-	-	1 (100)	1 (100)	-	-	-	-	-	1 (100)	-
Bronchiectasis	31	19 (61)	14 (45)	15 (48)	18 (58)	18 (58)	8 (26)	7 (23)	4 (13)	3 (10)	9 (29)	8 (26)	5 (16)	18 (58)
Lung carcinoma	12	5 (42)	3 (25)	6 (50)	5 (42)	6 (50)	8 (67)	2 (17)	1 (8)	-	1 (8)	6 (50)	3 (25)	3 (25)
Asian panbronchiolitis	1	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	-	-	-	-	1 (100)	-	-	1 (100)

Abbreviations: RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe; TB = tuberculosis.

Table 3. Differential diagnoses for tree-in-bud sign.

- Small airway disease
  - Infection
    - Mycobacterial
    - Bacterial
    - Viral
    - Fungal
  - Non-bacterial bronchiectasis
    - Congenital disorders – cystic fibrosis, Kartagener syndrome
  - Idiopathic disorders
    - Diffuse panbronchiolitis
    - Obliterative bronchiolitis
  - Connective tissue disorders
    - Rheumatoid arthritis
    - Sjogren syndrome
  - Immunologic disorders
    - Allergic bronchopulmonary aspergillosis
  - Aspiration / inhalation
    - Toxic fumes and gases
- Vascular abnormalities
  - Neoplastic emboli
    - Lung cancer and other tumours

peripheral centrilobular nodules of soft-tissue attenuation connecting to linear, branching opacities that have more than one contiguous branching site.[2] When seen in profile, the pattern resembles finger-in-glove appearance of impacted bronchi. The tree-in-bud sign is not readily visible on chest radiographs. Its differential diagnosis is diverse (Table 3), and includes small airway disease caused by infection (mycobacterial, bacterial, viral, or fungal), congenital disorders (cystic fibrosis, Kartagener syndrome), idiopathic disorders (diffuse panbronchiolitis, obliterative bronchiolitis), connective tissue disorders (rheumatoid arthritis, Sjogren syndrome), immunologic disorders (allergic bronchopulmonary aspergillosis) and aspiration / inhalation of toxic fumes and gases. It can also be associated with neoplasm as peripheral pulmonary vascular disease (neoplastic pulmonary emboli) due to lung cancer and lymphoma.[3,4] Knowledge of the common causes in our locality can be useful when formulating the differential diagnosis.

Infection was the commonest cause of tree-in-bud opacities (73%) in our sample, particularly tuberculosis. In mycobacterium tuberculosis infection, the tree-in-bud sign is related to the caseation necrosis and granulomatous inflammation within and surrounding the terminal and respiratory bronchioles and alveolar ducts, which results from endobronchial spread of tuberculosis. CT features of active tuberculosis such as consolidation, cavitation lymphadenopathy with central necrosis, pleural effusion and empyema necessitatis[3] should also be sought.

NTM infection is also common in our locality. Diagnosis of definite NTM lung disease was based on the 2007 American Thoracic Society diagnostic guideline,[1] which entailed clinical, radiological, and microbiological criteria. Clinically, the patient had to have presented with pulmonary symptoms, and have compatible chest radiograph or high-resolution CT findings. Microbiologically, positive culture should be obtained either from (a) at least two separate expectorated sputum samples, or (b) at least one bronchial wash or lavage. Alternatively, histopathologic support and one or more sputum, tissue samples or bronchial washings should be culture-positive for NTM. Expert opinions should be sought when NTM is detected on sputum culture, as such a finding is usually due to environmental contamination. On CT, bronchiectasis, small and large nodules are more common in NTM than in tuberculosis. Right middle lobe and lingular segments are commonly involved in *Mycobacterium avium*–intracellulare infection.

In infections associated with bronchiolitis due to bacterial, viral or fungal causes, the tree-in-bud opacities are usually less extensive. Air space consolidation is a dominant feature in pneumonia. After infection, bronchiectasis and bronchiolectasis were the second commonest cause in our series. When the terminal bronchioles and respiratory bronchioles are fluid-filled, tree-in-bud or centrilobular nodules may be visible.

The tree-in-bud pattern may rarely be related to carcinoma. In these cases, it may be related to obstructed bronchioles distal to the tumour, and can also be produced by dilatation or filling of the pulmonary arteries (running parallel to bronchi by tumour cells).[5] The common origins of tumour emboli in the pulmonary arteries include renal cell carcinoma, hepatoma, carcinoma of breast, stomach, prostate and ovary. They are encountered in about 3% of autopsies in patients with extrathoracic malignancies. Another mechanism is termed pulmonary tumour thrombotic microangiopathy (PTTM), which involves fibrocellular intimal proliferation of small pulmonary arteries induced by the tumour cells that result in luminal stenosis.[6] Most cases of PTTM are due to adenocarcinomas.

Asian panbronchiolitis or diffuse panbronchiolitis is a progressive inflammatory disease characterised by chronic inflammation of the paranasal sinuses and respiratory bronchioles, which is reported mostly in Asians. We only had one such case. Radiologically, stage 1 disease is characterised by the presence of small centrilobular nodules smaller than 5 mm in diameter on CT thorax. In stage 2, the centrilobular nodules are connected to distal bronchovascular structures in a Y-shaped configuration, giving a tree-in-bud configuration. Early bronchiectasis is recognised in stage 3 disease. In stage 4 disease, large cysts can be seen connected to dilated proximal bronchi.[7]

Congenital causes include cystic fibrosis and Kartagener syndrome and are not common in the studied local population as compared to the West.[8] Immunological disorders including allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis are also not common, as are AIDS (acquired immunodeficiency syndrome) patients. Collagen vascular disease, which was uncommon in our study, was also not common in western data, and was usually associated with follicular bronchiolitis. Bronchiolitis obliterans is usually presented as air trapping, whilst the tree-in-bud opacity is not common.

Limitations of our study include potential sampling errors, as case selection was based on issued reports, so that genuine tree-in-bud opacities may not have been reported by the radiologist. Moreover, as in all retrospective studies, some of the clinical data may not be available at the time of review causing cases to be excluded.

CONCLUSION

This study suggests a differential diagnosis list of commonly encountered tree-in-bud nodules on CT scans of Asians. The commonest cause was infection, particularly tuberculosis which is much more prevalent than in the West. Bronchiectasis and bronchiolectasis was the next common cause. Neoplasia, in particular carcinoma of the lung, forms a small subgroup with this radiological finding. In contrast to series described in the West, cystic fibrosis, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis and pneumocystic carinii were not encountered in our sample.

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