'Tree-in-Bud': Thinking beyond Infectious Causes

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Established Facts

- The two most common pulmonary complications in patients with leukemia are hemorrhage and infectious infiltrates.
- The entities showing a 'tree-in-bud' sign on high-resolution computed tomography are most frequently associated with infectious causes, but immunological, congenital, and idiopathic disorders as well as aspiration, inhalation of toxic agents, and pulmonary vascular diseases may also cause it.

Novel Insights

- On CT scans, pulmonary infiltrations of chronic lymphatic leukemia (CLL) are nonspecific, mainly showing interstitial thickening. However, in patients with the 'tree-in-bud' sign, pulmonary infiltrations of CLL should also be considered.
- Bronchoalveolar lavage can be used to exclude differential diagnoses, but the diagnosis of pulmonary infiltration of CLL may be missed. Transbronchial biopsies can lead to the diagnosis.

Key Words

Leukemia · Chronic lymphatic leukemia · Pulmonary infiltrations · Tree-in-bud sign

Abstract

High-resolution computed tomography is an important diagnostic instrument in pneumology. The 'tree-in-bud' sign is a common finding in HRCT scans. The list of the most frequent differential diagnoses for 'tree-in-bud' sign includes infections with *Mycobacterium tuberculosis*, nontuberculous mycobacteria, and other bacterial, fungal, or viral pathogens. Other causes could be immunological, congenital, and idiopathic

disorders as well as aspiration or inhalation of toxic agents. Rare differential diagnoses are malignant conditions. We present a case with 'tree-in-bud' pulmonary infiltrates of chronic lymphatic leukemia which was only diagnosed by transbronchial biopsies, and discuss other differential diagnoses.

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Introduction

The 'tree-in-bud' sign is visible in high-resolution computed tomography (HRCT) and it is characterized by small centrilobular nodules of soft-tissue attenuation,

connected to multiple branching linear structures of a similar caliber, originating from a single stalk [1, 2]. It was first described as an endobronchial spread of *Mycobacterium tuberculosis* [3] although it is not specific for only one entity. Other causes are infections, congenital, idiopathic, and immunological disorders, and aspiration [4]. Pulmonary complications of chronic lymphatic leukemia (CLL) are most commonly caused by hemorrhage and infection [5]. About one third of patients with leukemia show pulmonary infiltrates in the autopsy [6] but rarely on chest radiographs [5]. On HRCT scans, pulmonary infiltrations of leukemia are mostly described as nonspecific [7]. Clinical and radiological signs often prompt empiric antibiotic treatment, as infection seems the most likely cause. Here we describe the presentation of a 'tree-in-bud' sign in HRCT as a rare pulmonary infiltration of CLL and discuss the differential diagnoses.

Case Report

A 65-year-old male with known CLL presented with cough, purulent sputum, and progressive dyspnea. In the past he had received chemotherapy with fludarabine, cyclophosphamide, and rituximab. Saturation was 90% with 6 liters O₂/min. Blood gas analysis revealed a pO₂ of 69 mm Hg and a pCO₂ of 36 mm Hg with a pH of 7.45 on 6 liters O₂/min via nasal cannulas. C-reactive protein (5.9 mg/dl) and leukocytes ($36.5 \times 10^3/\mu\text{l}$) were elevated. The chest X-ray showed prominent hila and interstitial infiltrations, increasing from the upper to the lower lobes (fig. 1). The HRCT scan suggested infectious bronchiolitis predominantly in the mid and lower lung fields with 'tree-in-bud' signs and mediastinal lymphadenopathy (fig. 2). Fiberbronchoscopy showed signs of chronic bronchitis. Bronchoalveolar lavage (BAL) revealed normal cell counts, with 14% neutrophils, 85% macrophages, and only 1% lymphocytes. Considering the known immunosuppression, infections with *M. tuberculosis*, nontuberculous mycobacteria, *Legionella pneumophila*, *Mycoplasma pneumoniae*, cytomegalovirus, *Aspergillus* spp., and *Pneumocystis jirovecii* were excluded. Bacterial cultures remained negative. Empiric antibiotic treatment with meropenem yielded no radiological or clinical improvement. Eventually, transbronchial biopsies showed peribronchial and alveolar infiltrations with monomorphic lymphocytes (CD20 and CD79a positive) (fig. 3) while immunohistochemical analysis confirmed the rare (noninfectious) presentation of 'tree-in-bud' infiltrates of the known CLL.

Differential Diagnosis of the 'Tree-in-Bud' Sign

The 'tree-in-bud' sign is a common radiological finding on HRCT. It was first described as an endobronchial spread on *M. tuberculosis* [3]. In HRCT, *M. tuberculosis* infection is often associated with consolidation, cavitation, pleural effusion, lymphadenopathy, and bronchial

Fig. 1. Chest X-ray suggesting bilateral, lower-zone-dominant nodular infiltrations and mediastinal lymphadenopathy.

Fig. 2. HRCT scan (1 mm) with centrilobular noduli and a typical 'tree-in-bud' pattern.

wall thickening with or without bronchiectasis [2]. Infection with nontuberculous mycobacteria and other bacteria like *Staphylococcus aureus* and *Haemophilus influenzae* present with a 'tree-in-bud' sign [2], while this sign is less frequently found in fungal and viral infections [1].

Fig. 3. Pulmonary infiltration of CLL in transbronchial biopsies.

Respiratory syncytial virus as a cause of the ‘tree-in-bud’ sign is commonly seen in infants [2], while cytomegalovirus infection of the lung can also present with the same radiological pattern [2]. In the presented case, infectious causes were widely excluded, as shown above.

Congenital disorders can cause the ‘tree-in-bud’ sign [1]. The ‘tree-in-bud’ pattern can be an early sign of cystic fibrosis [8]. In advanced disease, HRCT scans show mosaic perfusion, mucus plugging, and bronchiectasis [8]. The HRCT findings for Kartagener syndrome, primary ciliary dyskinesia, are, besides the ‘tree-in-bud’ pattern, bronchial wall thickening, bronchiectasis, and bronchiolectasis [9]. In the presented case, we regarded cystic fibrosis and Kartagener syndrome as implausible diagnoses. The patient was too old for early signs of cystic fibrosis, which usually occurs in children. In Kartagener syndrome, the immotility of sperm can lead to infertility; however, the patient had a healthy son.

Diffuse panbronchiolitis is a chronic obstructive lung disease of idiopathic cause reported almost exclusively in Asians [10], accompanied by chronic sinusitis and bronchiolitis [10]. HRCT scans show centrilobular nodules, thick wall bronchioles filled with mucus, and hence often a ‘tree-in-bud’ pattern [9]. HRCT of obliterative bronchiolitis – an often idiopathic condition but one which is also associated with transplantation, toxic inhalation, collagen vascular disorders, and viral infections, which can cause the ‘tree-in-bud’ pattern – reveals central and peripheral bronchiectasis and bronchial wall thickening [11]. Air trapping on expiratory HRCT is a sensitive sign of diagnosis of a possible obliterative bronchiolitis [2].

Connective tissue disease, like rheumatoid arthritis and Sjögren syndrome, can present with bronchiectasis, poorly defined centrilobular nodules, and branching linear opacities. Ground glass, air trapping, and ‘tree-in-bud’ patterns may also occur [2].

An additional differential diagnosis for the ‘tree-in-bud’ sign is allergic bronchopulmonary aspergillosis, which describes an immune response to the endobronchial proliferation of *Aspergillus* species [12]. The main diagnostic criteria of allergic bronchopulmonary aspergillosis are a history of asthma, central bronchiectasis, a positive skin prick test to *Aspergillus*, elevated serum total IgE levels, and elevated specific IgE or IgG to *Aspergillus* [12]. Bronchiectases with a predilection for the upper and middle lobes are often associated with centrilobular nodules and mucus impaction. If mucus impaction extends to the bronchiole, it appears as a ‘tree-in-bud’ sign on HRCT [2, 12].

Our patient did not present with a history or clinical symptoms and signs that might have pointed to an idiopathic, immunological, or connective tissue disease.

Aspiration and inhalation of toxic agents should be considered as differential diagnoses of a ‘tree-in-bud’ sign in HRCT [2]. Repeated aspiration results in diffuse aspiration bronchiolitis [2]. The ‘tree-in-bud’ sign has been described in cases of acute aspiration [13]. Aspiration and inhalation of toxic agents were potential differential diagnoses in the presented case.

Malignancy can be associated with the ‘tree-in-bud’ sign. Intravascular pulmonary tumor embolism often occurs in cancers of the breast, liver, kidney, stomach, prostate, and ovaries and can lead to the tree-in-bud sign in HRCT [2, 14]. Bronchiolar involvement of neoplasms resulting in a ‘tree-in-bud’ sign has been described in cases of juvenile laryngotracheobronchial papillomatosis [9]. ‘Tree-in-bud’ has only been described in a single case in the literature as a feature of CLL, where the diagnosis was based on transbronchial biopsy [15].

Generally, pulmonary involvement of leukemia is described very infrequently in imaging studies. A review of 10 cases with pulmonary leukemic infiltrates demonstrated thickening of the interlobular septae and parenchymal nodules, while 9 cases showed thickened bronchovascular bundles, resembling the perilymphatic distribution of leukemic infiltrates, and 7 showed ground glass attenuation [7]. A case study of CLL with pulmonary infiltrates showed centrilobular nodules, air trapping, and mosaic perfusion. As BAL revealed leukemic B lymphocytes, the authors recommended BAL for the diagnosis of pulmonary involvement of CLL [16].

In the case presented, BAL and radiological signs did not raise suspicions of a malignant cause. Only histopathological and immunological analyses demonstrated the pulmonary involvement of CLL with a centrilobular nodules and 'tree-in-bud' pattern on HRCT.

Conclusion

The 'tree-in-bud' sign is an unspecific sign of bronchiolar and alveolar pathology. Many of the more common differential diagnoses, particularly infectious

causes, can be determined by analyzing the features of HRCT in conjunction with the patient history, the clinical presentation, and a microbiological analysis of the BAL.

This case, which presented a pulmonary infiltration of CLL and resembled a 'tree-in-bud' pattern on HRCT, was only diagnosed by histopathological evaluation of a trans-bronchial biopsy. Hence, we recommend that, if there are no contraindications and noninfectious causes of 'tree-in-bud' are within the differential diagnosis, a biopsy for histopathological and microbiological analysis should be performed.

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