"Breaking Bud": a new twist to Tree-in-Bud pattern in bronchiolitis

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Learning objectives

- Revisit the normal anatomy of the secondary pulmonary lobule
- Define the term bronchiolitis and recognize the imaging appearance at chest radiography and high resolution CT (HRCT)
- Describe the classification into either cellular or constrictive types and discuss the wide spectrum of causes
- Make an appropriate differential diagnosis and depict the mimics of small airways diseases
Background

Small airways diseases, bronchiolitis, are very often found by radiologists and represent a true diagnostic challenge. It refers to bronchiolar inflammation and/or fibrosis. These bronchioles resemble branching linear structures that are connected to small centrilobular nodules, which results in the tree-in-bud pattern.

HRCT plays an important role in detecting small airways diseases and is used in conjunction with clinical data and pathologic findings to solidify a diagnosis. It is able to detect both direct and indirect signs of bronchiolitis and therefore it will help the radiologist to make a proper differential diagnosis between cellular and constrictive forms.
Findings and procedure details

NORMAL ANATOMY

The small airways, or bronchioles, are less than 2 mm internal diameter and lack cartilage. They are located at the center of the secondary pulmonary lobule which is the functional anatomic unit of the lungs, bounded by interlobular septa (Fig. 1 on page 12).

Terminal bronchiole is the last purely air conducting structure of the human respiratory system, eventually terminating in respiratory bronchioles, which are the longest bronchioles and supply alveoli and provide gas exchange.

BRONCHIOLITIS AS A RADIOLOGIST CHALLENGE

• There are many diseases that cause bronchiolar inflammation or fibrosis.
• There is not a good correlation between pathologic findings and the specific entities of bronchiolitis.
• Bronchiolitis often exhibits nonspecific clinical manifestation.
• Diverse types of bronchiolitis show the same constellation of radiologic findings.
• There is no consensus classification system for small airways disease.

PATHOLOGIC CLASSIFICATION OF BRONCHIOLITIS

Bronchiolitis is divided into two broad categories:

1. Cellular bronchiolitis: inflammatory cells infiltrates that affect the lumen and wall of the bronchioles causing different degrees of fibrosis.
2. Constrictive bronchiolitis: stenosis of bronchiolar lumen due to concentric fibrosis in the submucosa and in the adventitia (between the bronchiolar epithelium and the muscularis mucosae) resulting in extrinsic compression and obliteration of the airway. There is mural thickening by submucosal collagenous fibrosis with progressive concentric narrowing associated with luminal distortion, mucous stasis and chronic inflammation.

SEMIOLOGY OF SMALL AIRWAY DISEASE

There are two groups of CT signs of small airway disease:
1. **Direct signs**: they are the consequence of intraluminal filling (secretions, pus) and thickening of the bronchiolar wall by inflammatory cells and usually represent a **cellular/inflammatory bronchiolitis**.

   a. **Centrilobular nodules**: result from inflammation in the peribronchiolar alveoli and may be from 1-2-mm to 1 cm wide when coalesce into nodular foci of consolidation or ground-glass opacities that occupy nearly the entire secondary pulmonary lobule. Centrilobular micronodules are best characterized as not extending to the pleura (including the fissures), which differentiate them to perilymphatic and random (miliary) micronodules (Fig. 2 on page 12).

   b. **Tree-in-bud opacities**: Y-shaped branching linear opacities, which result from mucus plugging or pus filling of centrilobular bronchioles, that are connected to small centrilobular nodules that represent tree-in-bud pattern (Fig. 3 on page 13).

   c. **Bronchiolectasis**: result from dilated bronchioles and are identifiable close of the pleural surface. It is a less common direct sign of bronchiolitis and is found most commonly in chronic forms of bronchiolitis (Fig. 4 on page 14).

2. **Indirect signs**: they are the consequence of bronchiolar obstruction due to fibrosis and usually represent a **constrictive/obliterative bronchiolitis**.

   a. **Mosaic attenuation**: is the description given to the appearance at CT where there is a patchwork of regions of differing attenuation. They are geometric areas of abnormal decreased attenuation and reflect decreased perfusion of the poorly ventilated regions (Fig. 5 on page 15).

   b. **Air trapping**: areas of mosaic attenuation during inspiration that persist on expiration. On expiratory images, the lucent areas represent abnormally hypoaerated and hypoperfused portions of lung, whereas the high-attenuation areas are normal (Fig. 6 on page 16).

**IMAGING TECHNIQUE CONSIDERATIONS**

HRCT is the primary imaging tool for evaluation of small airways disease. HRCT uses **thin sections** (0.625-1.5 mm slice thickness) with a high spatial frequency reconstruction algorithm to enhance evaluation of pulmonary parenchyma and small airways. Basic HRCT protocols include supine **inspiratory and expiratory images** (Table 1 on page 17).

**BRONCHIOLITIS CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS**
There are 2 groups (Table 2 on page 30):

1. **Cellular bronchiolitis**: it is also known as inflammatory or proliferative bronchiolitis. In general, the different causes of cellular bronchiolitis have overlapping appearances at HRCT, but some findings may help narrow the differential diagnosis (in addition to using clinical information).

   a. The presence of *tree-in-bud* can help narrow the differential diagnosis further because it is most frequently encountered in patients with infectious or aspiration bronchiolitis.

   b. The presence of *ill-defined ground-glass centrilobular nodules* are frequently seen in either hypersensitivity pneumonitis, respiratory bronchiolitis (RB) or respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), especially when they are bilateral and symmetric.

1.1 Aspiration bronchiolitis (Fig. 7 on page 18).

   - Aspiration is a common cause of cellular bronchiolitis and may be acute, tends to be more focal, chronic, tends to be more diffuse, or acute on chronic.
   - Clinically, it may present as bronchorrhea, wheezing, or dyspnea associated with oral food ingestion. Histologically, it is characterized by chronic bronchiolar inflammation and foreign body reaction.
   - At HRCT, acute and chronic aspiration manifests with tree-in-bud opacities with or without bronchocentric consolidation.
   - **Diffuse aspiration bronchiolitis** is a specific entity characterized by chronic bronchiolar inflammation resulting from recurrent aspiration. Commonly, patients with diffuse aspiration bronchiolitis are elderly or bedridden with neurologic conditions or dementia predisposing to oropharyngeal dysphagia.

1.2 Infectious bronchiolitis:

   - Clinical manifestations are *nonspecific* and may include dyspnea, productive cough, and wheezing.
   - At HRCT, infectious bronchiolitis shows tree-in-bud opacities and centrilobular nodules corresponding to bronchiolar mural inflammation and associated cellular bronchiolitis.
   - **Acute** infectious bronchiolitis (Fig. 8 on page 19).

     o **Viral** (parainfluenza, respiratory syncytial virus, adenovirus, or mycoplasma).

     o **Infants**.
In adult patients are often immunocompromised so fungal infections, such as airway invasive aspergillosis, may occur, in addition to more common viral and bacterial etiologies.

- Chronic infectious bronchiolitis:

- Bacterial (Mycobacterium tuberculosis and nontuberculous mycobacteria).

- Adults

- Tuberculosis should be considered when both tree-in-bud and cavitation are present in the upper lobes or superior segments of lower lobes (Fig. 9 on page 20)

- Nontuberculous mycobacterial infection often involves the middle lobe and lingua with tree-in-bud, bronchiectasis, and volume loss (Fig. 10 on page 21).

1.3 Hypersensitivity pneumonitis:

- Hypersensitivity pneumonitis is an allergic lung disease caused by inhalational exposure to numerous offending agents, including organic dust, chemical compounds, and household mold.
- Clinically, hypersensitivity pneumonitis is more common in nonsmokers and include inspiratory crackles, weight loss, fatigue, recurring cough and dyspnea after antigen exposure.
- At HRCT, the characteristic finding is diffuse, symmetric, poorly defined centrilobular nodules or larger ground-glass opacities in case of wide alveolitis (Fig. 11 on page 22).
- The presence of air trapping confined to secondary pulmonary lobule and pulmonary cysts are also helpful features that can distinguish hypersensitivity pneumonitis from other entities with diffuse ground-glass centrilobular nodules, and may indicate a component of constrictive bronchiolitis (Fig. 12 on page 23 and Fig. 13 on page 24).

1.4 Respiratory bronchiolitis:

- RB and RB-associated interstitial lung disease almost always occur in smokers and are part of a spectrum with desquamative interstitial pneumonia.
- Clinically is asymptomatic.
- At HRCT, RB usually presents with upper lobe-predominant ground-glass nodules, but may overlap with findings of other smoking-related lung diseases, such as emphysema or desquamative interstitial pneumonia (Fig. 14 on page 25).
- The imaging findings may improve or completely resolve with smoking cessation.
1.5 Folicular bronchiolitis.

- Follicular bronchiolitis (FB) represents peribronchiolar lymphoid hyperplasia and reactive germinal centers along the small airways.
- FB is on the mild end of a spectrum of **lymphoproliferative disorders of the lung**.
- Clinically it is most common in middle-aged adults with progressive cough and dyspnea with underlying **immunodeficiency** (HIV, selective IgA deficiency, Evans syndrome, Wiscott-Aldrich syndrome) or **CTD** (rheumatoid arthritis, Sjögren syndrome)
- At HRCT, FB manifests as centrilobular nodules, which correspond to obstructed bronchioles and inflammatory cells infiltrating the adjacent alveolar interstitium. These nodules range in size and attenuation and can be ground-glass or some- times tree-in-bud, which includes lymphoid interstitial pneumonia.

1.6 Diffuse panbronchiolitis.

- Diffuse panbronchiolitis is a rare, but progressive inflammatory disease involving the upper and lower respiratory systems.
- Clinically, it usually affects middle-aged men of **Asian** descent, namely from Japan, who report **chronic sinusitis**, cough, and dyspnea with a subacute course. There is no known relationship with smoking.
- Histologically, diffuse panbronchiolitis shows peribronchial inflammatory cell infiltrates and foamy macrophages in the interstitium and alveolar spaces.
- At HRCT, findings include diffuse or lower-lobe-predominant centrilobular nodules and tree-in-bud opacities, followed in later stages by **bronchiolectasis and bronchiectasis**, **mosaic attenuation**, and cystic spaces indicative of evolution towards a constrictive bronchiolitis as the airways become further injured.
- Recurrence following lung transplantation has been reported.

2. Constrictive bronchiolitis: it is also known as fibrotic or obliterative bronchiolitis and is characterized by **irreversible**, concentric submucosal fibrosis resulting in **bronchiolar narrowing or occlusion**.

a. Causes of **cellular bronchiolitis** may also have a component of constrictive bronchiolitis (eg, FB, diffuse panbronchiolitis).

b. At HRCT, constrictive bronchiolitis manifests with **air trapping**, which is an indirect sign of small airways disease. Air trapping refers to heterogeneous parenchyma on inspiratory images, termed **mosaic attenuation**, and accentuated geometric areas of decreased attenuation on expiratory images.

2.1 Childhood infection
• Childhood airway infection, primarily viral etiologies, such as adenovirus, influenza A and M pneumoniae. Alveoli mature by age 8, so bronchiolitis before this time can disrupt alveoli and associated pulmonary vessel development, leading to an obliterative bronchiolitis with mosaic attenuation and air trapping.

• **Swyer-James (or Swyer-James-MacLeod)** syndrome is the most advanced, long-term complication of postinfectious bronchiolitis with involvement of an entire lobe, entire lung, and sometimes even both lungs (Fig. 15 on page 26).

• Imaging findings include regions of hyperlucent lung (and often decreased volume) with diminished vascularity, bronchiectasis, and air trapping. **Bilateral and asymmetric.**

• In **adults** it is usually an incidental finding and they are **asymptomatic**.

### 2.2 Bronchiolitis obliterans syndrome

• Bronchiolitis obliterans syndrome, a form of constrictive bronchiolitis, is a known complication of **lung transplantation** occurring in up to 50% of patients.

• It is considered a manifestation of chronic allograft rejection, developing at least 3 months after transplantation, and is associated with irreversible decreased pulmonary function (VEF1).

• Air trapping on expiratory HRCT images is the most sensitive and specific imaging feature of bronchiolitis obliterans syndrome in patients post-lung transplant, although the degree of air trapping does not necessarily correlate with severity of rejection.

• It has poor prognosis in lung transplant recipients with 5-year survival about 30% to 40% after onset of disease.

### 2.3 Graft-Versus-Host disease

• Constrictive bronchiolitis is also a common manifestation of graft-versus-host disease associated with **hematopoietic stem cell transplantation**, occurring in approximately 10% of recipients.

• Air trapping is the predominant imaging finding, and is similar in appearance to other causes of constrictive bronchiolitis (Fig. 16 on page 27).

• The clinical history of graft-versus-host disease, often affecting other organs, such as **skin** and **gastrointestinal tract**, helps confirm the diagnosis.

### 2.4 Inhalational lung disease

• Toxics implicated in constrictive bronchiolitis: **nitrous acid and nitrous oxide chemical compounds**, **popcorn flavoring agents** and **fire smoke**.

• These exposures cause epithelial injury leading to granulation tissue accumulation that ultimately results in airway obliteration.

• At HRCT, air trapping on expiratory phase and bronchiectasis may also be seen.
2.5 Connective tissue disease (CTD):

- Most commonly women with advanced **rheumatoid arthritis**.
- Clinically, such patients may present with dyspnea or cough
- Typically with a severe and progressive course that is **refractory to treatment**.
- Imaging findings are similar to other causes of constrictive bronchiolitis, and are usually seen independent of CTD-related interstitial lung disease (Fig. 17 on page 28).

2.6 Others: hypersensitivity pneumonitis, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, Sjögren syndrome, inflammatory bowel disease, paraneoplastic pemphigus.

**MIMICS**

Several entities may present with imaging findings similar to small airways disease and it is important for radiologists to be aware of these mimics.

1. Aerogenous spread of adenocarcinoma and vascular and lymphatic causes (malignancy, excipient lung disease) of centrilobular nodules may mimic cellular bronchiolitis.

1.1 Aerogenous spread of adenocarcinoma

- Aerogenous spread of lung adenocarcinoma is thought to represent a mechanism whereby the **tumor metastasizes to other parts of the lungs via the airways**
- Typical imaging findings of aerogenous spread of adenocarcinoma include **persistent centrilobular or tree-in-bud nodules** that slowly enlarge over serial examinations, especially in the context of a known lung adenocarcinoma.

1.2 Intravascular metastasis

- **Vascular tree-in-bud**: along pulmonary arterioles that course alongside bronchioles at the center of the secondary pulmonary lobule.
- Any tumors that result in hematogenous spread to the lung can cause this pattern and the visible abnormality usually represents filling of peripheral vessels with tumor cells (Fig. 18 on page 29).
- **Tumor thrombotic angiopathy** is a rare and serious complication of tumor emboli where diffuse centrilobular or tree-in-bud nodules are the result of widespread fibro-cellular intimal hyperplasia of arterioles.
- Patients with intravascular metastases may present with worsening dyspnea, hypoxia, **pulmonary hypertension, arrhythmia and sudden death**.
• More frequent in breast, liver, kidney, stomach, prostate and ovarian neoplasms.

1.3 Excipient lung disease

• Also known as drug abuser's lung, is a foreign body reaction within pulmonary arterioles caused by intravenous injection of crushed oral tablets.
• Excipients are the various insoluble, inert fillers that are added to a pill during production and, when injected, become lodged in the pulmonary arterioles and capillaries. These particles can incite an angiogranulomatous reaction that causes pulmonary hypertension and potentially death.
• Imaging findings in excipient lung disease include diffuse centrilobular nodules (nodules may favor the mid lower lung zones presumably caused by increased blood flow) and signs of pulmonary hypertension.
• Patients often have a history of drug use, chronic pain, and/or an indwelling catheter, and the radiologist may be the first to suggest the diagnosis because excipient lung disease is clinically underrecognized.

2. Small vessel disease (chronic pulmonary embolism, pulmonary arterial hypertension) or ground-glass opacity (Pneumocystis pneumonia)

may cause a mosaic attenuation pattern and mimic obliterative bronchiolitis.
**Fig. 1:** Secondary pulmonary lobule. The small airways, or bronchioles, are less than 2 mm internal diameter and lack cartilage. They are located at the center of the secondary pulmonary lobule which is the functional anatomic unit of the lungs, bounded by interlobular septa.

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Fig. 2: Various distributions of pulmonary nodules. Drawing shows the differences among centrilobular nodules (arrowhead); perilymphatic nodules (curved arrow) with involvement of the subpleural regions, right major fissure and peribronchovascular interstitium; and random nodules (straight arrow).

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**Fig. 3:** Axial CT images: (a) centrilobular micronodules are best characterized as not extending to the pleura. (b) Tree-in-bud opacities: nodular and branched "Y" opacities that resemble a budding tree, usually visible in the pulmonary periphery, reflecting the presence of dilated centrilobular bronchioles filled with mucus or pus.

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Fig. 4: Severe asthma and bronchiectasis. (a) Drawing of bronchial wall thickening and bronchiectasis shows normal thin smooth bronchial walls (straight arrow), thickened bronchial walls (arrowhead), and bronchiectasis with absence of normal bronchial tapering (curved arrow). (b) Axial CT slices: bronchiectasis in the right upper lobe and marked thickening of the wall of the bronchi of the upper lobes in another patient.

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Fig. 5: Mosaic attenuation. Drawing shows air trapping, which may manifest as mosaic attenuation on inspiratory images but is optimally depicted on expiratory images. The distribution may be lobular (straight arrow), subsegmental (arrowhead), or segmental (curved arrow). The dark grey areas represent air trapping.

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**Fig. 6**: Axial inspiratory (left) and expiratory (right) CT images of a 59-year-old man with hypersensitivity pneumonitis show lobular and subsegmental areas of mosaic attenuation in the expiratory image that are due to air trapping.

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<table>
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<tr>
<th>Patient position</th>
<th>Respiration</th>
<th>Slice thickness (mm)</th>
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<td>Supine</td>
<td>Inspiratory</td>
<td>0.625-1.5</td>
<td>Noncontiguous (every 10-20 mm) or Volumetric</td>
<td>High spatial frequency, +/- MIP, minIP</td>
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<td>Forced Expiratory</td>
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<td>Entire lungs at 10 to 20 mm intervals or 6-8 dynamic images obtained at three levels</td>
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<td>+/- Prono (interstitial disease valuation)</td>
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<td>0.625-1.5</td>
<td>Noncontiguous (every 10-20 mm) or Volumetric</td>
<td>High spatial frequency</td>
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**Table 1:** HRCT protocol

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Fig. 7: Aspiration bronchiolitis in a patient with carcinoma of the tongue. (a) Axial slices of CT and (b) Coronal MIP reconstruction: numerous «tree in bud» opacities predominant in the LID and some centrilobular nodules.

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**Fig. 8:** Acute viral bronchiolitis. (a) Anteroposterior chest radiograph shows ill-defined micronodules. (b) Coronal MIP image shows clustered centrilobular nodules and tree-in-bud opacities in the periphery of both lungs.

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**Fig. 9:** Progressive TB with endobronchial dissemination. Axial CT images: cavity in the LSI (*), extensive pulmonary consolidations and tree-in-bud opacities (yellow circle).

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**Fig. 10:** Mycobacterium avium-intracellulare infection. Axial CT images: varicose bronchiectasis with characteristic distribution in the middle lobe and lingula (arrows) and peripheral centrilobular opacities and tree-in-bud opacities (circles).

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Fig. 11: Hypersensitivity pneumonitis by inhalational exposure to pigeons (group I). (a) Axial section of CT and (b) Coronal MIP image: poorly defined centrilobular nodules and ground-glass opacities of patchy, multifocal distribution.

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Fig. 12: Hypersensitivity pneumonitis (group II). (a) Scattered lobular areas of lucency representing associated mosaic attenuation. (b) Axial expiratory CT image shows the coexistence of normal areas of lung with areas of both lobular air trapping and ground-glass opacities, the so-called headcheese pattern.

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**Fig. 13:** Hypersensitivity pneumonitis. (a) Axial inspiratory CT image shows mosaic attenuation. (b) Axial expiratory CT image shows scattered areas of air trapping. Air trapping is typically diagnosed at expiratory imaging but can be severe enough to manifest as mosaic attenuation on inspiratory CT.

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**Fig. 14:** Respiratory bronchiolitis associated with interstitial lung disease (RB-ILD). Axial CT images: poorly defined centrilobular nodules predominantly in the upper lobes.

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Fig. 15: Sywer-James syndrome. Axial CT slices showing a "mosaic" pattern in relation to patches areas of constrictive bronchiolitis. Note the small size of the pulmonary vessels within the areas of hypoattenuation.

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Fig. 16: Obliterative bronchiolitis due to Graft-Versus-Host disease. (a) Axial inspiratory CT: mosaic pattern and ground glass opacities (*). (b) Axial expiratory CT, pulmonary areas persist that do not increase the attenuation corresponding to air trapping.

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**Fig. 17:** Constrictive bronchiolitis in a woman with rheumatoid arthritis with a poor clinical course. (a) Hyperlucent lung due to air trapping demonstrated in the forced expiration study (b) predominantly in the upper lobes and lingula.

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**Fig. 18:** Vascular Tree-in bud in a patient with lung adenocarcinoma. Thickening of interlobular septa due to carcinomatous lymphangitis (red circle) and dilatation and nodularity of the centrilobular arteries due to tumor embolism (yellow circles).

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### BRONCHIOLITIS CLASSIFICATION

<table>
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<td>CELULAR B</td>
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**Table 2:** Bronchiolitis classification and differential diagnosis.

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Conclusion

Bronchiolitis is a very common finding at chest X-Ray and CT. That is why recognition of classic and additional imaging signs, along with clinical and history key elements, may be very useful to enable a focused diagnosis to guide the clinical management of patients.
Personal information

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