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Obliterative Bronchiolitis

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Summary

Obliterative bronchiolitis (OB) is a condition characterized by inflammation and fibrosis of the bronchiolar walls resulting in narrowing or obliteration of the bronchiolar lumen. The most common causes are childhood lower respiratory tract infection, hematopoietic stem cell or lung and heart-lung transplantation, and toxic fume inhalation. The most frequent clinical manifestations are progressive dyspnea and dry cough. Pulmonary function tests demonstrate airflow obstruction and air trapping. Radiographic manifestations include reduction of the peripheral vascular markings, increased lung lucency, and overinflation. The chest radiograph, however, is often normal. High-resolution CT is currently the imaging modality of choice in the assessment of patients with suspected or proven OB. The characteristic findings on high-resolution CT consist of areas of decreased attenuation and vascularity (mosaic perfusion pattern) on inspiratory scans and air trapping on expiratory scans. Other CT findings of OB include bronchiectasis and bronchiolectasis, bronchial wall thickening, small centrilobular nodules, and three-in-bud opacities. Recent studies suggest that hyperpolarized ^{3}He-enhanced magnetic resonance imaging may allow earlier recognition of obstructive airway disease and therefore may be useful in the diagnosis and follow-up of patients with OB.

Key Words: Bronchiolitis; bronchiolitis obliterans; bronchiolitis obliterans syndrome; constrictive bronchiolitis; computed tomography; obliterative bronchiolitis; small airways disease.

1. INTRODUCTION

Bronchiolitis is a generic term applied to various inflammatory and fibrosing diseases that affect the small airways, which by definition are airways that measure less than 2 mm in diameter (i.e., primarily membranous and respiratory bronchioles) (1,2). Bronchiolitis is common and occurs in various clinical settings (1–5). Several classification schemes have been proposed based on histologic features, etiology, or computed tomography (CT) findings (1–3,6,7). Although none of these classification schemes is widely accepted and there is controversy about the classification of some of the subtypes of bronchiolitis, there is overall agreement on the histologic, radiologic, and clinical features of obliterative bronchiolitis (OB).

2. DEFINITION AND TERMINOLOGY

Obliterative bronchiolitis, also known as *constrictive bronchiolitis*, *bronchiolitis obliterans*, or *cicatricial bronchiolitis*, is a condition characterized by inflammation and fibrosis of the bronchiolar walls and contiguous tissues resulting in narrowing and, in some cases, complete obliteration of the bronchiolar lumen (1,2,8). OB may result from a large number of acute and chronic processes and may occasionally be idiopathic (Table 1).

Table 1
Most Common Conditions Associated with Obliterative Bronchiolitis

Childhood respiratory infection, most commonly adenovirus, respiratory syncytial virus, and *Mycoplasma pneumoniae* bronchiolitis and bronchopneumonia

Chronic rejection following lung and heart-lung transplantation

Chronic graft-versus-host disease following allogeneic hematopoietic stem-cell transplantation

Postinhalational

   Nitrogen dioxide (Silo filler's disease), ammonia, chlorine, fire smoke, hydrogen bromide, hydrogen selenide, sulfur dioxide, thionyl chloride, and diacetyl (2,3-butanedione)

Ingested toxins

   Sauropus androgynus (vegetable alleged to help weight control)

Connective tissue disorders, most commonly rheumatoid arthritis. Occasionally, Sjögren's syndrome, systemic lupus erythematosus, and scleroderma

Drugs

   D-penicillamine, lamustine, and gold therapy

Inflammatory bowel diseases

   Ulcerative colitis and Crohn's disease

Cryptogenic (idiopathic)

Other conditions

   Diffuse idiopathic neuroendocrine cell hyperplasia with multiple carcinoid tumorlets

   Eosinophilic fasciitis

   Stevens–Johnson syndrome and paraneoplastic pemphigus

   Asthma

   Bronchiectasis

   Cystic fibrosis

   Hypersensitivity pneumonitis

   Sarcoidosis

There has been historical confusion between the term "bronchiolitis obliterans" as it refers to OB and the term "bronchiolitis obliterans organizing pneumonia" (BOOP) *(9–11)*. The histologic hallmark of BOOP is the presence of buds of loose granulation tissue, termed Masson bodies, within alveolar ducts and air spaces, that is, organizing pneumonia *(1,2,12)*. The patients may or may not have granulation polyps within terminal and respiratory bronchioles, but they rarely have fibrosis within the bronchiolar walls or peribronchiolar tissues, that is, they do not have OB. Because the predominant clinical, histologic, and radiologic manifestations of BOOP are those of organizing pneumonia, the American Thoracic Society and European Respiratory Society multidisciplinary consensus classification recommended that the term BOOP be replaced by the term organizing pneumonia and idiopathic BOOP by cryptogenic organizing pneumonia *(12)*. Organizing pneumonia may result from various causes or underlying pathologic processes including pulmonary infection, aspiration, collagen vascular disorders, drugs, radiation, inhalational injury, and hypersensitivity pneumonitis. Cryptogenic organizing pneumonia is currently classified as a form of idiopathic interstitial pneumonia *(12,13)* and is beyond the scope of this chapter. We will limit our discussion to the histologic, clinical, and radiologic findings of OB.

3. CLINICAL FEATURES

The most common clinical manifestations of OB consist of progressive dyspnea, nonproductive cough, and airflow obstruction, which usually progress over weeks to months. Associated symptoms may include chest pain, respiratory distress, and cyanosis *(14)*. Auscultation of the chest may reveal crackles and midinspiratory squeaks. Occasionally, patients may present with pneumothorax or pneumomediastinum *(15–17)*. In many cases, OB is first detected on CT in patients with no apparent symptoms or with symptoms secondary to associated conditions such as bronchiectasis or asthma.

A presumptive diagnosis of OB can often be made with a high degree of confidence based on a clinical history of persistent symptoms of obstructive pulmonary disease, demonstration of airflow obstruction on pulmonary function tests, and characteristic findings on high-resolution CT. However, the clinical diagnosis of OB requires exclusion of other causes of chronic airway obstruction, including emphysema, chronic bronchitis, and asthma *(18,19)*.

4. PULMONARY FUNCTION TESTS

The functional manifestations of OB are those of airflow obstruction, and air trapping with reduction in forced expiratory volume in 1 s (FEV_1), increased residual volume (RV) and RV to total lung capacity (TLC) ratio, and no significant response to bronchodilators *(8,18)*. The TLC is often normal until the late stages of the disease, which accounts for the usually normal lung volumes on the chest radiograph. Lung diffusion as measured by the carbon monoxide diffusing capacity (DLCO) is typically within normal limits, which allows distinction from emphysema.

5. HISTOLOGIC FINDINGS

Obliterative bronchiolitis is characterized histologically by concentric or, less commonly eccentric, thickening of terminal and respiratory bronchiolar walls by submucosal collagenous fibrosis resulting in progressive narrowing and distortion of the bronchiolar lumen. Associated features include epithelial metaplasia, smooth muscle hyperplasia, bronchiolectasis with mucous stasis, and patchy chronic inflammation (cellular bronchiolitis) (Fig. 1) *(1,2)*. Severe fibrosis may result in complete obliteration of the bronchiolar lumen, the bronchiole being replaced by scar tissue (Fig. 2). In such cases, the diagnosis may be difficult to make histologically, the obliterated bronchiole being misinterpreted as being a small scar.

The pathogenesis of OB is not well known. The initial event is believed to be bronchiolar inflammation, with resulting epithelial necrosis. The inflammation can involve the mucosa, submucosa, and peribronchiolar parenchyma and be followed by the development of fibrous connective tissue that compromises the bronchiolar lumen. Significant involvement of the interstitium is uncommon. OB may be classified as "active" when an inflammatory component is present or "inactive" when inflammation is absent *(20)* .

Definitive diagnosis of OB requires lung biopsy. The patchy distribution of the disease and inadequate tissue sampling result in a large percentage of false-negative diagnosis on transbronchial biopsy specimens *(21–26)*. It should be noted that even on surgical biopsy specimens, subtle changes or completely distorted and scarred bronchioles may be missed on routine hematoxylin-eosin stains. Optimal assessment requires the use of elastic tissue stains (Fig. 3) *(2,14)*. Because of the subtlety of the histologic findings, lung biopsies in patients with BO may occasionally be read as normal or near-normal. In such patients, the presence of typical imaging findings should prompt a request for review, re-staining, or re-sectioning of the biopsy specimen.
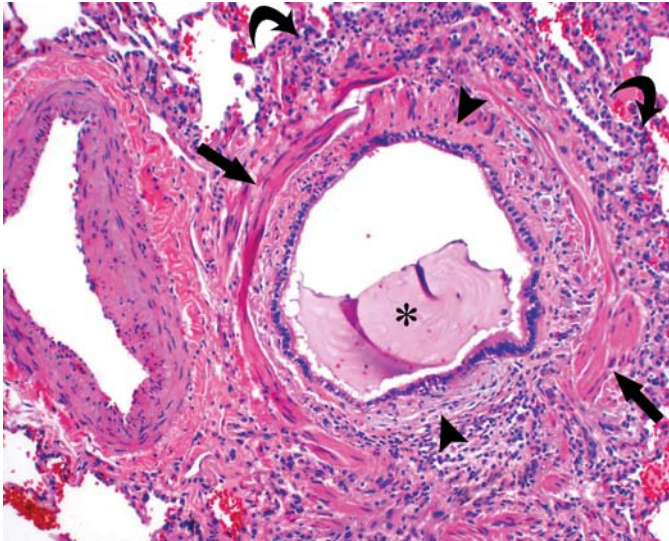
Fig. 1. Obliterative bronchiolitis. Surgical lung biopsy specimen shows small bronchiole with submucosal fibrosis (arrowheads), muscle hypertrophy (straight arrows), peribronchiolar inflammation (curved arrows), and associated mucostasis (asterix). The findings are characteristic of mild obliterative bronchiolitis (H and E, intermediate magnification) (Courtesy of Dr. Thomas Colby, Mayo Clinic, Scottsdale).
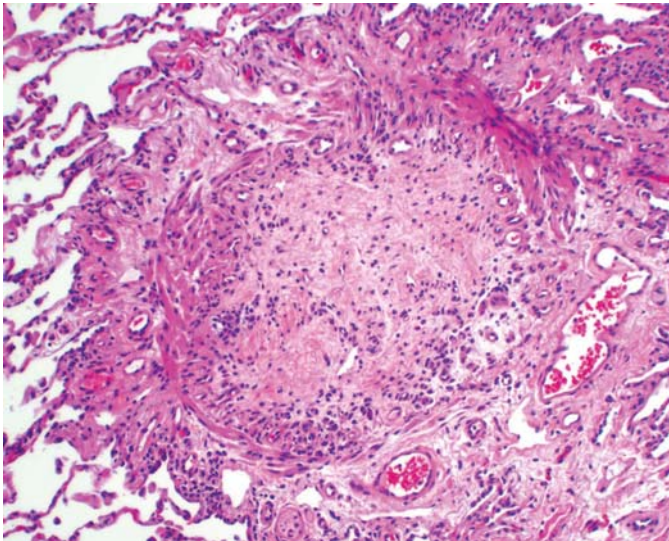

Fig. 2. Obliterative bronchiolitis. Surgical lung biopsy specimen demonstrates complete obliteration of bronchiolar lumen by fibrous tissue (H and E, intermediate magnification). (Courtesy of Dr. Thomas Colby, Mayo Clinic, Scottsdale).
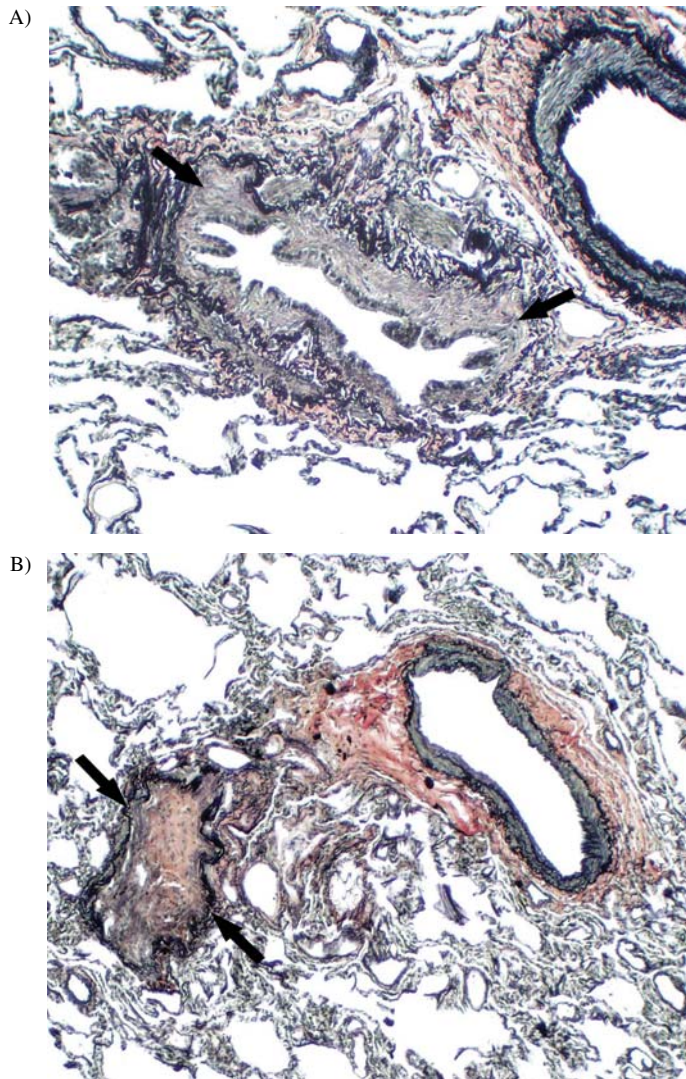
Fig. 3. Obliterative bronchiolitis. Surgical lung biopsy specimen shows bronchiole with concentric submucosal scarring (arrows, **A**), and completely obliterated bronchiole (**B**) in which the preexisting elastica is highlighted with elastic tissue stain (arrows) (elastic tissue stain, intermediate magnification) (Courtesy of Dr. Thomas Colby, Mayo Clinic, Scottsdale).

6. IMAGING FINDINGS

The most common imaging modalities used in the assessment of patients with suspected or proven OB are chest radiography and high-resolution CT. Scintigraphy plays a limited role. Ventilation/perfusion scans generally reveal diminished ventilation in the lung periphery; perfusion abnormalities may also be present, but these are usually much milder than the ventilation abnormalities *(27,28)*. Recently, it has been shown that magnetic resonance (MR) allows functional imaging of pulmonary ventilation and perfusion with the additional benefit of lack of radiation *(29)*. Hyperpolarized ³He-enhanced MR may allow earlier recognition of obstructive airway disease and therefore

be useful in the early recognition and follow-up of patients with OB *(30,31)*. Although potentially useful, functional MR imaging is only available at a very small number of centers and remains an investigational tool.

6.1. Chest Radiography

In patients with mild-to-moderate OB, the chest radiograph is often normal. The earliest manifestations, which are often quite subtle, consist of increased lung lucency and reduction of the peripheral vascular markings. Severe disease results in hyperinflation detected by the overall increase in lung volumes, flattening of the diaphragm, and increase in the retrosternal airspace (Fig. 4). Other findings include increased bronchial markings, bronchiectasis, and, occasionally, nodular or reticulonodular opacities *(9,32–36)* (Table 2).

There is poor correlation between the radiographic findings and the clinical and functional severity of disease *(37)* and considerable inter-observer and intra-observer variability in interpretation of findings *(38)*. The chest radiograph therefore plays a limited role in the diagnosis and follow-up of patients with OB.

6.2. Computed Tomography Findings

High-resolution CT is currently the imaging modality of choice in the assessment of patients with suspected or proven small airways disease, being superior to chest radiography in demonstrating the presence and extent of abnormalities *(39)*. Because the bronchiolar wall is too thin to be visualized on high-resolution CT, even in patients with OB, the analysis of the CT images is limited to assessment
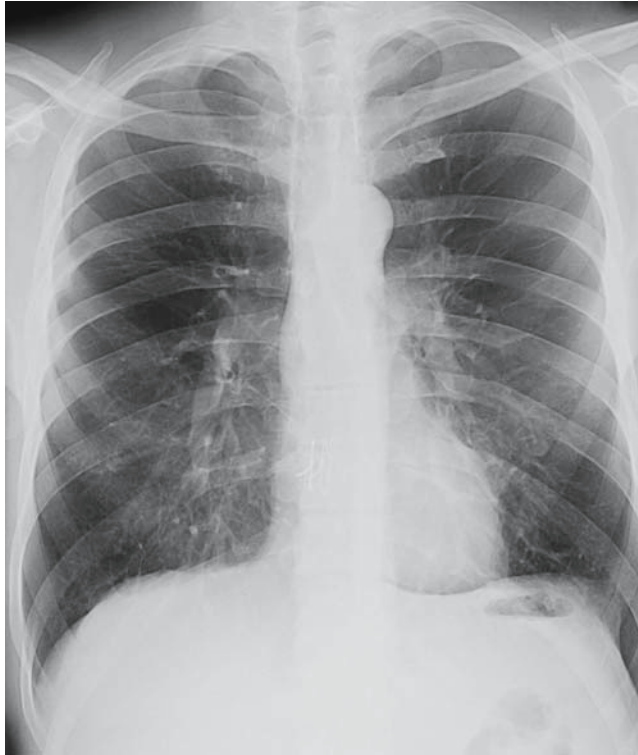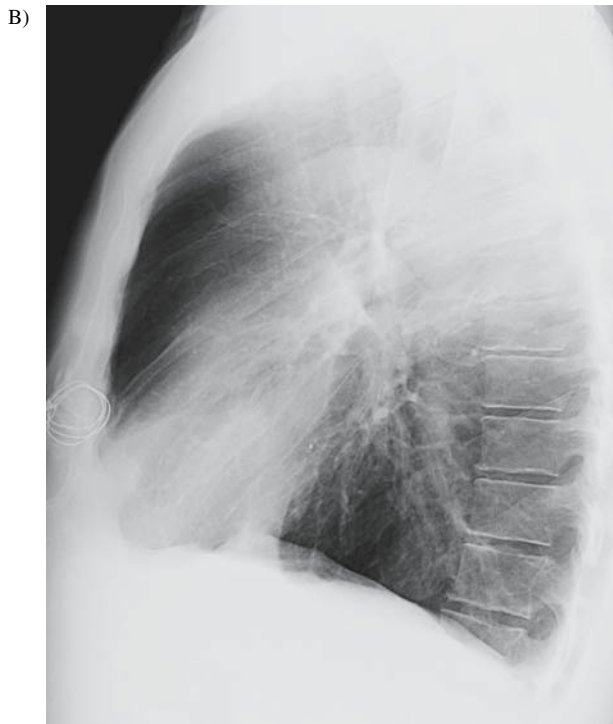
Fig. 4. *(Continued)*

Fig. 4. Obliterative bronchiolitis on chest radiography. (**A**) Posteroanterior chest radiograph show increased lung volumes and reduction of the peripheral vascular markings. (**B**) Lateral view shows increased retrosternal airspace and flattening of the diaphragm. The patient was a 44-year-old man with obliterative bronchiolitis following bilateral lung transplantation for cystic fibrosis.

of secondary signs related to the small airway obstruction. The main CT finding of OB on CT scans performed at end-inspiration is a geographic inhomogeneity of lung attenuation (mosaic attenuation pattern), seen in 40–80% of patients *(40–47)* (Table 3). This pattern consists of patchy lobular, segmental or, occasionally, lobar regions of decreased attenuation and vascularity and blood flow redistribution to relatively normal lung resulting in areas of normal or increased attenuation and

Table 2
Radiographic Findings of Obliterative Bronchiolitis

Chest radiograph may be normal in mild to moderate disease
Common findings

    Increased lung lucency
    Reduction of peripheral vascular markings

Late findings

    Hyperinflation
    Flattening of the diaphragm
    Increased retrosternal airspace

Ancillary findings

    Prominent bronchial markings, bronchiectasis, and nodular or reticulonodular opacities

Table 3
High-Resolution CT Findings of Obliterative
Bronchiolitis

Common findings

    Decreased attenuation and vascularity
    Mosaic perfusion pattern
    Air trapping at expiratory images

Ancillary findings

    Bronchiectasis and bronchiolectasis
    Bronchial wall thickening
    Centrilobular nodules
    Tree-in-bud opacities

increased vascularity (mosaic perfusion pattern) (Fig. 5) *(6,8,46)*. The areas of decreased attenuation result from decreased perfusion of hypoventilated alveoli distal to obstructed bronchioles. The abnormalities may be subtle on inspiratory images. The presence of airflow obstruction and air trapping is usually easier to detect on CT scans performed during maximal expiration or at end-expiration *(48–51)*. Regions with airflow obstruction because of OB show no decrease in volume or less decrease in volume than the adjacent uninvolved lung and therefore remain lucent while the remaining lung increases in attenuation. This results in increased contrast between areas with airflow obstruction and normal lung facilitating recognition of air trapping on high-resolution CT (Fig. 6). Expiratory CT images may demonstrate air trapping in patients with normal findings on inspiratory scans (Fig. 7) *(48,50,52–55)*. The extent of air trapping on expiratory CT in patients with OB correlates with severity of airflow obstruction and air trapping on pulmonary function tests *(18)*. CT performed during maximal expiratory maneuver or at end-expiration therefore plays an important role and is recommended in the initial evaluation and follow-up of patients with OB *(50,52)*.
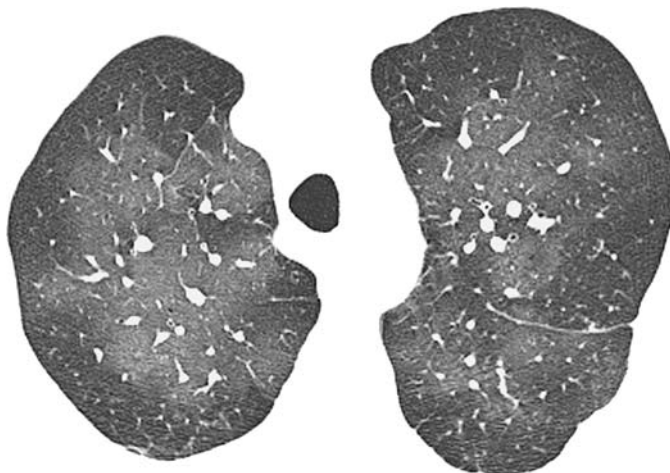

Fig. 5. Mosaic perfusion pattern. High-resolution CT image demonstrates geographic areas of decreased attenuation and vascularity interspersed with areas of increased attenuation that contain enlarged vessels, reflecting pulmonary blood flow redistribution. The patient was 48-year-old man with obliterative bronchiolitis.
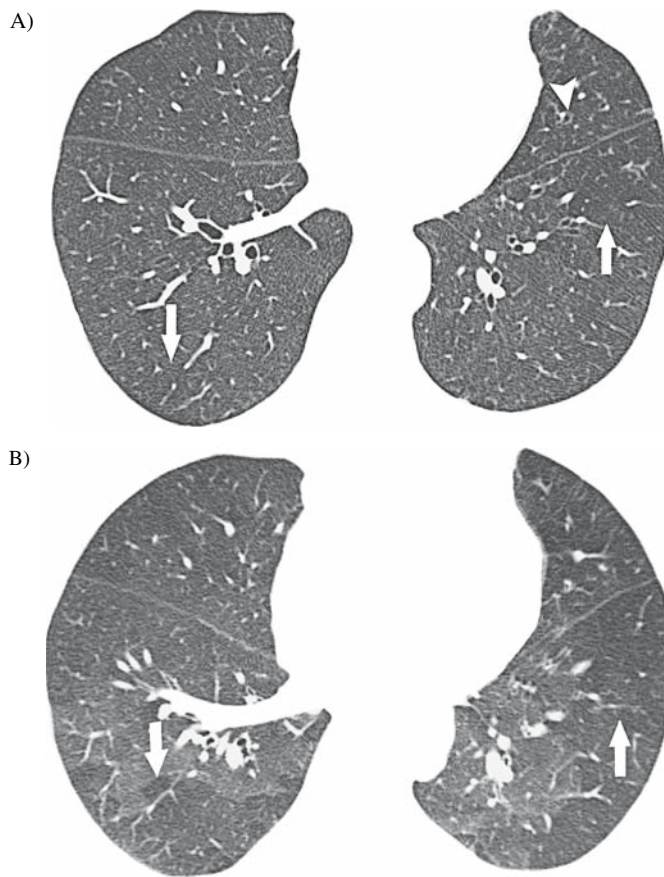
Fig. 6. Air trapping in obliterative bronchiolitis. (**A**) High-resolution CT scan obtained at end-inspiration shows subtle areas of decreased attenuation (straight arrows). Also noted is mild bronchiectasis in the lingula and anteromedial basal segment of the left lower lobe (arrowhead). (**B**) High-resolution CT scan performed at the end of maximal expiration demonstrates air trapping (arrows). The patient was a 66-year-old woman with cryptogenic obliterative bronchiolitis.

Several studies have suggested that post-processing of high-resolution CT images particularly with the use of minimum intensity projection (MinIP) reconstructions improves the detection of subtle areas of low attenuation encountered in patients with emphysema and small airways disease (Fig. 8). *(56–61)* These techniques may be particularly helpful in patients with high clinical suspicion for OB and otherwise apparently normal CT findings.

Ancillary high-resolution CT findings of OB include central and peripheral bronchial dilatation (bronchiectasis), bronchiolectasis, and bronchial wall thickening, findings that have been reported in 20–90% of patients (Fig. 9). *(18,40,43,46,47,62)* Less common CT findings of OB include small centrilobular nodules and tree-in-bud opacities representing thick-walled bronchioles with or without intraluminal debris, seen in up to 30% of patients (Fig. 10) (see Table 3) *(47).*

In the appropriate clinical setting, the presence of mosaic perfusion, air trapping, and ancillary CT findings can be diagnostic of OB. It should be emphasized, however, that mosaic perfusion is a nonspecific finding seen in a number of conditions, that mild air trapping is commonly seen in normal subjects, and that there is overlap between the high-resolution CT manifestations of OB and the findings seen in other causes of airway obstruction such as asthma and emphysema *(19).*

Fig. 7. Normal inspiratory CT in obliterative bronchiolitis. (**A**) High-resolution CT scan obtained at end-inspiration on a multidetector CT scanner is within normal limits. (**B**) Expiratory image at the same level as (**A**) demonstrates patchy lobular and segmental areas of air trapping. (**C**) Coronal reformatted image better demonstrates the extent of air trapping. The patient was a 54-year-old woman with postinfectious obliterative bronchiolitis.
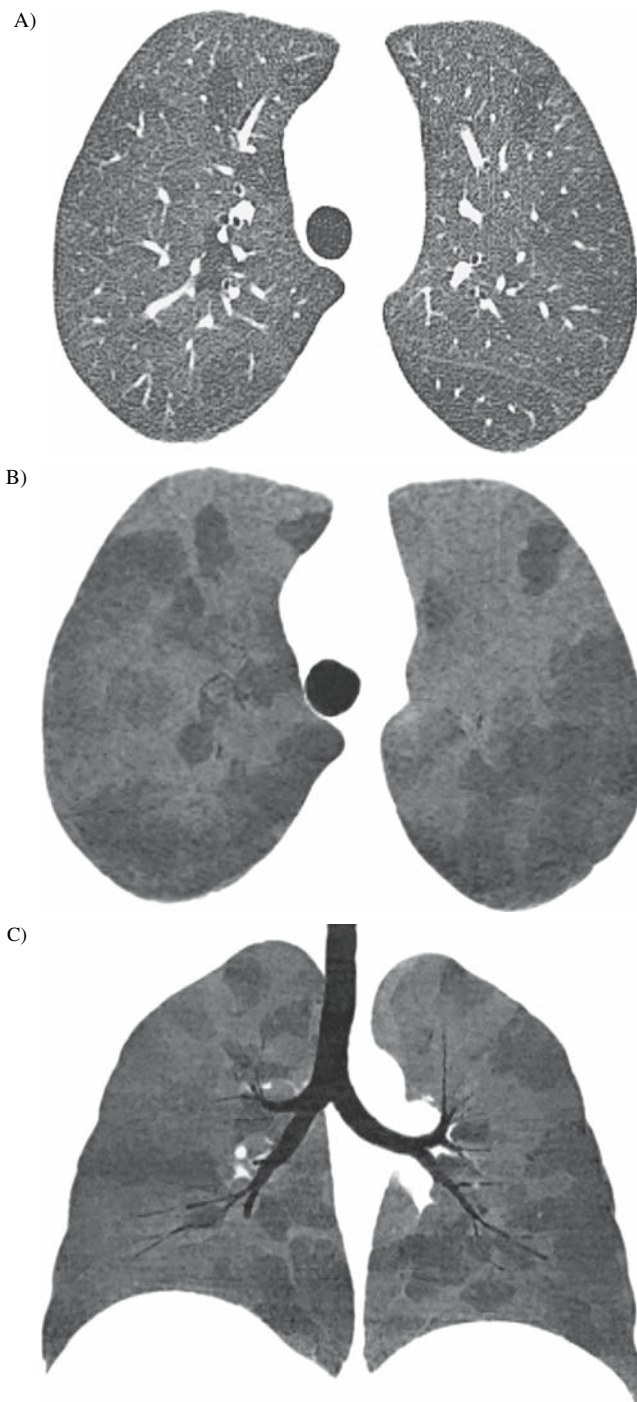
Fig. 8. Minimum intensity projection (MinIP) in the assessment of obliterative bronchiolitis. (**A**) High-resolution CT scan obtained in a multidetector CT scanner at the level of aortic arch shows subtle lobular areas of decreased attenuation and vascularity. (**B** and **C**) Cross-sectional and coronal minimum intensity projection (MinIP) reformation images improve the detection of lobular areas of decreased attenuation. The patient was a 29-year-old woman with chronic graft-versus-host disease and obliterative bronchiolitis 1 year after allogeneic hematopoietic stem-cell transplantation.

A)

B)
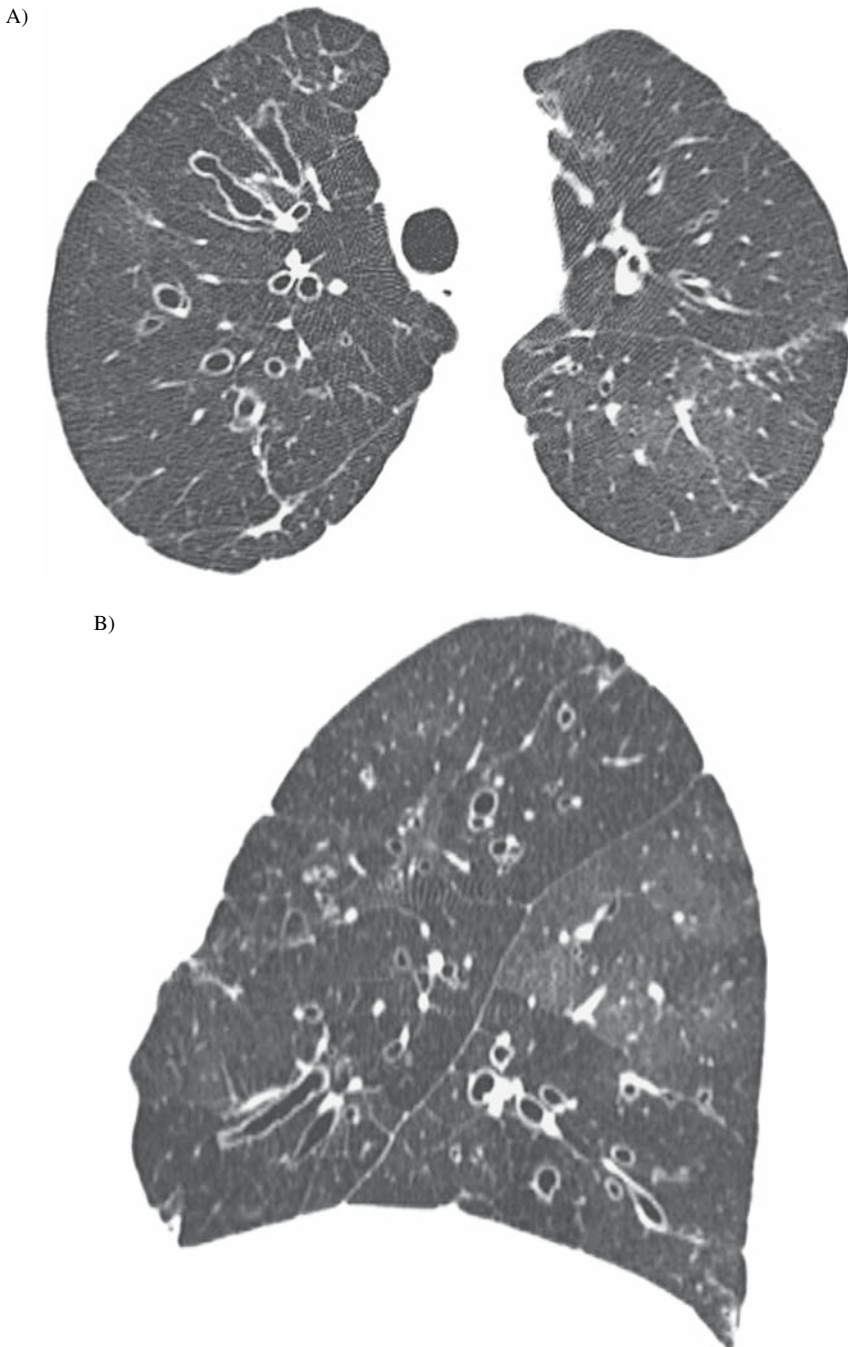
Fig. 9. Ancillary CT findings of obliterative bronchiolitis. Cross-sectional (**A**) and sagittal (**B**) reformatted high-resolution CT images obtained on multidetector CT scanner show diffuse areas of decreased attenuation and vascularity with associated cylindrical and varicose bronchiectasis and bronchial wall thickening. The patient was a 21-year-old woman with severe airflow obstruction and obliterative bronchiolitis 8 years after lung transplantation for cystic fibrosis.

Fig. 10. Obliterative bronchiolitis. High-resolution CT image shows mosaic perfusion pattern and centrilobular nodules and tree-in-bud opacities (arrows) representing thick-walled bronchioles with or without intraluminal debris (same patient as Fig. 5).
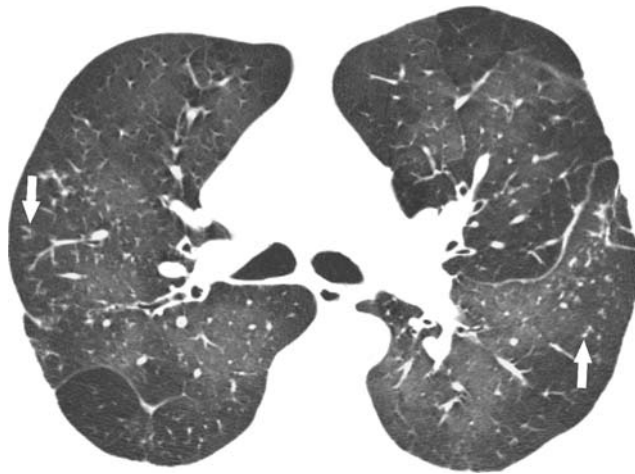
Mosaic perfusion can be seen in various airway diseases including OB, asthma, and bronchiectasis; in occlusive pulmonary vascular disease (particularly chronic pulmonary thromboembolism) (Fig. 11); and infiltrative lung disease, such as hypersensitivity pneumonitis *(45,52,63–66)*. The differential diagnosis requires careful analysis of associated findings such as bronchial dilatation and enlargement of the main pulmonary artery and interpretation of the CT images in the proper clinical context. Airway diseases that cause mosaic perfusion can usually be distinguished from vascular causes such as chronic pulmonary thromboembolism by the presence of bronchial dilatation, seen in more than 70% of patients with airway abnormalities, and the lack of enlargement of the main pulmonary artery, a finding seen in the majority of patients with chronic pulmonary thromboembolism associated with mosaic perfusion *(45)*. It should be noted however that bronchial dilatation may also occur
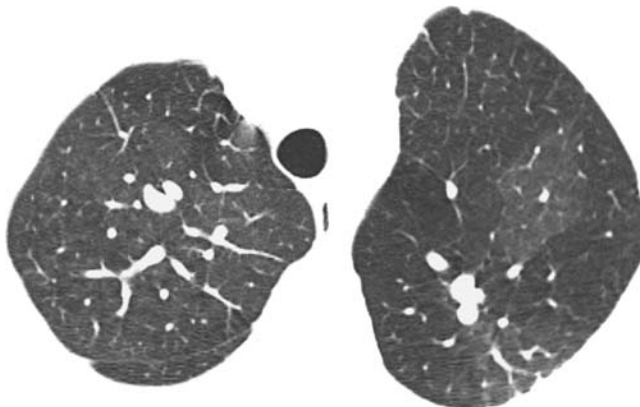

Fig. 11. Mosaic perfusion pattern in chronic pulmonary thromboembolism. High-resolution CT image shows mosaic perfusion in the upper lobes with enlargement of the segmental arteries in areas of increased attenuation. The patient was a 57-year-old woman with chronic thromboembolic pulmonary arterial hypertension.

in patients with chronic pulmonary thromboembolism *(67)*, and there are no reliable distinguishing features between mosaic perfusion resulting from OB and mosaic perfusion because of other airway diseases. Furthermore, air trapping can also be seen in patients with pulmonary embolism. In a study by Arakawa et al. *(68)*, air trapping at expiratory images was identified in 9 of 15 (60%) patients with pulmonary embolism, including four with acute pulmonary embolism, one with chronic pulmonary embolism, and four with acute and chronic pulmonary embolism.

Air trapping is frequently seen in asymptomatic subjects with normal pulmonary function *(48,69–73)* particularly in older subjects and smokers (Fig. 12) *(70,73,74)*. Lobular air trapping involving fewer than three adjacent secondary pulmonary lobules *(48)* can be seen in approximately 50% of asymptomatic subjects and in various clinical settings, including OB, cigarette smoking, asthma, bronchiolitis associated with hypersensitivity pneumonitis (Fig. 13), and sarcoidosis *(64–66,73,75–77)*. Extent of air trapping, not simply its presence, therefore needs to be taken into account in the interpretation of expiratory CT scans *(48,73)*. It has been shown that mosaic perfusion and air trapping can be considered abnormal when they affect an area of more than 25% of the total area of the lung *(48,73)* and are not limited to the superior segment of the lower lobe or the lingula tip *(48)*. The presence of additional CT features in areas of decreased attenuation is also valuable in differentiating between abnormal air trapping in patients with OB and normal subjects. In a review of the high-resolution CT findings of 15 patients with pathologically proven OB after lung transplantation and 18 control subjects, the combination of bronchial dilatation on the inspiratory CT scan and air trapping on the expiratory CT scan was seen only in patients with OB and were the two most sensitive and specific findings on high-resolution CT scans of patients with OB *(46)*.

Copley et al. *(19)* assessed the discriminatory value of high-resolution CT to distinguish between OB, asthma, centrilobular emphysema, panlobular emphysema, and normal controls. A correct first-choice diagnosis was made in 199 of 276 (72%) observations, and a correct first-choice diagnosis was made in 35 of 38 (92%) observations in patients with OB. The major sources of diagnostic inaccuracy were difficulty in differentiating between panlobular and centrilobular emphysema, asthma and normality, and asthma and OB. Distinguishing features between OB and panlobular emphysema because of α_1-antitrypsin deficiency were the presence of parenchymal destruction, vascular distortion,

Fig. 12. Normal air trapping on CT. High-resolution CT image at the level of aortic arch obtained at end of maximal expiration shows a few lobular areas of air trapping. The patient was a 56-year-old man with no pulmonary symptoms.
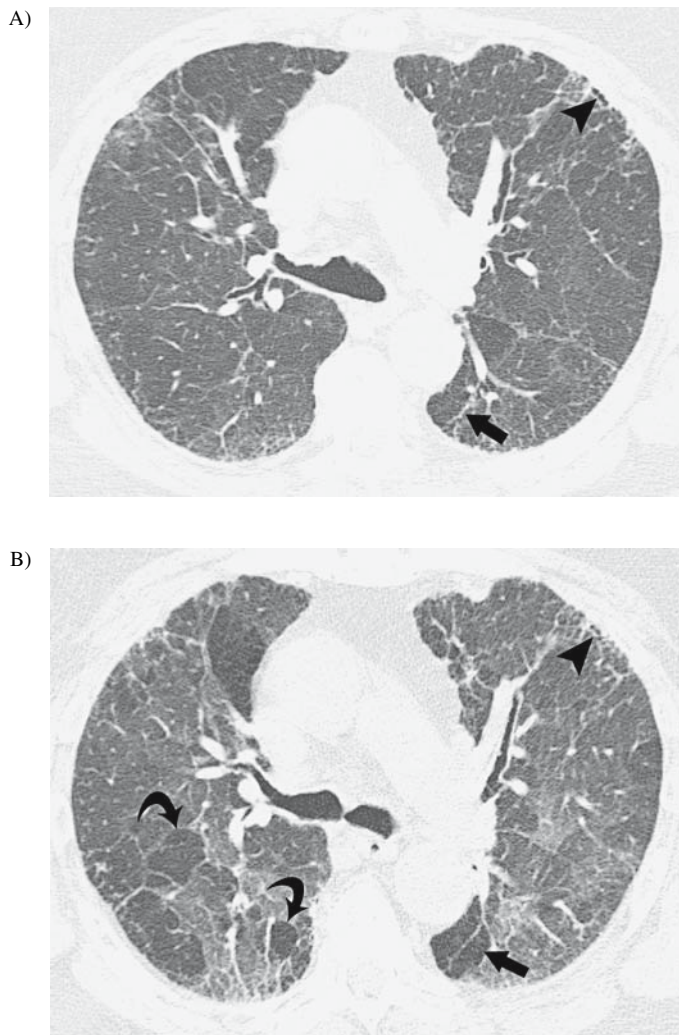
Fig. 13. Lobular air trapping in a 79-year-old man with subacute and chronic hypersensitivity pneumonitis. (**A**) High-resolution CT image shows bilateral patchy ground-glass opacities, fine reticulation, and mild subpleural honeycombing (arrowhead). Also noted are a few lobules with decreased attenuation and vascularity (straight arrow). (**B**) Expiratory high-resolution CT scan at the same level as (A) demonstrates air trapping in lobules that had decreased attenuation on the inspiratory CT (straight arrow) and in other lung regions (curved arrows). The lobular areas of air trapping are presumably related to obliterative bronchiolitis and the ground-glass opacities due to interstitial lymphocytic infiltration.

and linear scars or thickened septa at the lung bases in most patients with panlobular emphysema (Fig. 14). Patients with OB were more likely to have bronchial dilatation and decreased parenchymal attenuation and vascularity than asthmatics patients. The authors concluded that high-resolution CT is helpful to distinguish diseases that cause airflow obstruction, and it is particularly accurate in the identification of OB *(19)*. Jensen et al. *(47)* compared the CT findings in patients with refractory asthma with those of patients with idiopathic OB. A mosaic pattern of lung attenuation was seen in 50% of OB patients compared with only 3% of patients with refractory asthma.

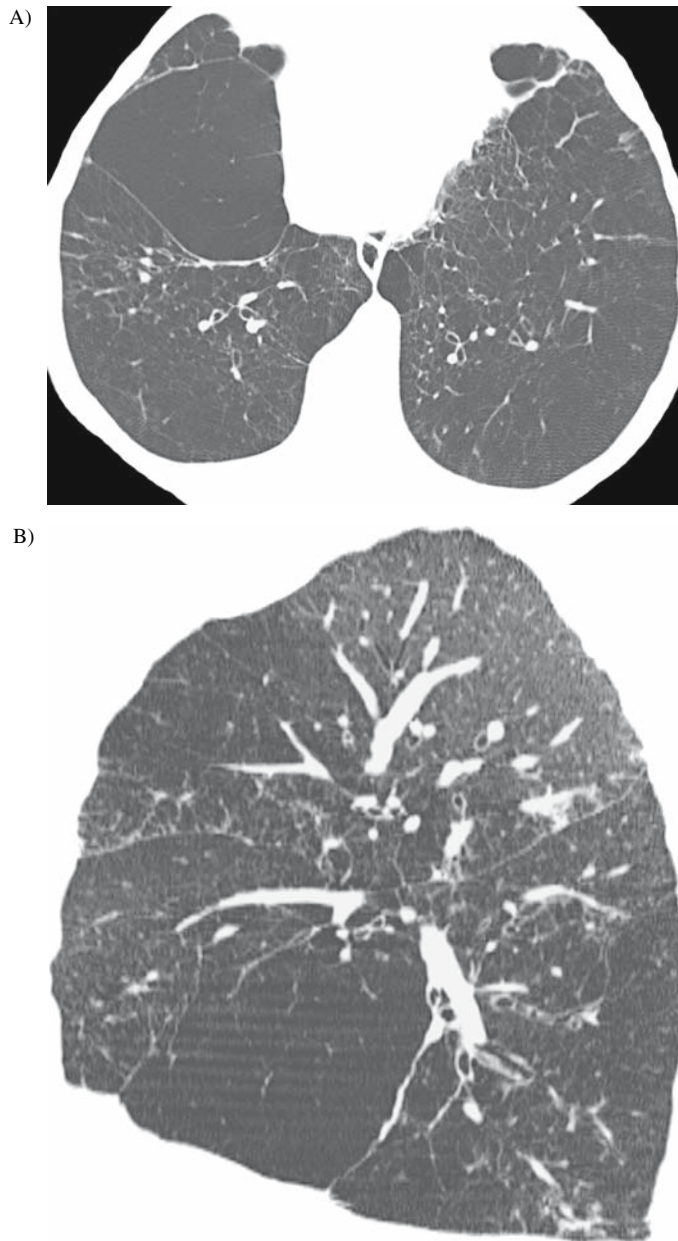**Fig. 14.** Severe panlobular emphysema in 53-year-old man with α_1-antitrypsin deficiency. (**A**) High-resolution CT image obtained in a multidetector CT scanner shows extensive areas of decreased attenuation with parenchymal destruction, vascular distortion, and linear scars. (**B**) Sagittal reformatted image shows the predominance of abnormalities in the lower lung regions typical of panlobular emphysema.

7. SPECIFIC CAUSES AND UNDERLYING DISEASES ASSOCIATED WITH OBLITERATIVE BRONCHIOLITIS

A large number of conditions may result in OB (see Table 1). The vast majority of cases, however, occur following childhood viral or mycoplasma infection *(3,40,78)*, hematopoietic stem cell or lung and heart-lung transplantation *(79–82)*, and toxic fume inhalation *(3,5,83)*. Less common causes include connective tissue disorders (especially rheumatoid arthritis) *(84–90)*, drug therapy including D-penicillamine, lamustine and gold *(5,91)*, ingestion of toxines such as Sauropous androgyn *(92–94)*, neuroendocrine cell hyperplasia with multiple carcinoid tumorlets *(95–97)*, inflammatory bowel disease *(98,99)*, eosinophilic fasciitis *(3,5)*, Stevens–Johnson syndrome and paraneoplastic pemphigus *(100,101)*. OB may be seen as a component of interstitial lung disease (hypersensitivity pneumonitis and sarcoidosis) *(64,75,76)* or large airway disease (asthma, bronchiectasis, and cystic fibrosis) *(102–105)*. Rarely OB may be idiopathic *(106)*.

7.1. Postinfectious Obliterative Bronchiolitis

Obliterative bronchiolitis may be a late sequela of lower respiratory tract infections occurring in infancy or childhood, particularly by adenovirus *(40,107,108)*. Other causes include respiratory syncytial virus, parainfluenza virus, influenza virus, measles, and *Mycoplasma pneumoniae (5,109)*. The true prevalence of OB due to infection is unknown; however, it has been estimated that approximately 1% of the patients with acute viral bronchiolitis develop postinfectious OB *(110)*. The diagnosis of postinfectious OB in the childhood is based on history of lower airway infection, usually acute viral bronchiolitis, followed by persistent chronic obstructive pulmonary disease. The time interval between the acute illness and the development of postinfectious OB is generally 6 months (range 1–42 months) *(111)*. In the majority of the cases, the condition does not become apparent until adulthood. Most patients with postinfectious OB are asymptomatic or present with mild-to-moderate clinical findings and have a good prognosis *(40,78,112)*. Occasionally, severe and sometimes fatal disease may occur *(112,113)*. In a prospective study performed to define the clinical course and the prognosis of 31 patients who had symptomatic postinfectious OB during a mean of 3.5 years of follow-up, clinical remission was identified in 23% of the patients, persistence of respiratory symptoms in 68%, and death in approximately 10% *(112)*. Lung transplantation or lung volume reduction surgery should be considered for patients who show persistent and severe obstructive symptoms and progressive impairment in lung function *(114)*. The chest radiograph may be normal or show various findings including unilateral hyperlucency of a lobe or lung; bilateral hyperlucent lungs; complete collapse of the affected lobe; a mixed pattern of hyperlucency and persistent collapse; and peribronchial thickening *(78)*. High-resolution CT usually demonstrates bronchial wall thickening, bronchiectasis, mosaic perfusion, and air trapping (see Figs 7 and 15) *(109,115)*.

Swyer–James (MacLeod) syndrome is an uncommon condition characterized radiographically by a hyperlucent lobe or lung and functionally by normal or reduced TLC and presence of expiratory air trapping. The hyperlucency of the lobe or lung results from decreased pulmonary blood flow secondary to OB. Swyer–James syndrome typically follows lower respiratory tract infection in a developing lung, most commonly adenovirus bronchiolitis or bronchopneumonia. The pulmonary tissue and pulmonary vasculature are hypoplastic. The chest radiograph performed at TLC shows hyperlucency and decreased vascularity of the involved lobe or lung, normal or decreased size of the involved lobe or lung, and decreased size of the ipsilateral hilum (Fig. 16). Expiratory chest radiograph shows air trapping in the involved lobe or lung.

High-resolution CT, similar to the radiograph, shows hyperlucency and decreased vascularity and normal or decreased size of the involved lung or lobe on inspiratory images and air trapping on expiratory images *(116–118)*. In the vast majority of cases, CT demonstrates bronchiectasis and areas of abnormally low attenuation and perfusion and air trapping in the contralateral lung (Fig. 17)

Fig. 15. Obliterative bronchiolitis in 41-year-old man with history of repeated childhood respiratory tract infections. High-resolution CT image shows areas of decreased attenuation and vascularity (straight arrows) interspersed with areas of increased attenuation because of blood flow redistribution (mosaic perfusion pattern), particularly in the left upper lobe. Also noted are bronchial wall thickening and a few centrilobular nodules and tree-in-bud opacities (arrowheads).

Fig. 16. Swyer–James (MacLeod) syndrome. Posteroanterior chest radiography shows hyperlucency, decreased vascularity, and decreased volume of the left lung with ipsilateral mediastinal shift. The patient was an asymptomatic 40-year-old man with obliterative bronchiolitis following childhood viral infection.

Fig. 17. Swyer–James (Macleod's) syndrome. High-resolution CT image demonstrates extensive areas of decreased attenuation and vascularity in the left upper lobe and to lesser extent in the right upper lobe (arrowheads). Also noted are decreased volume of the left lung and left upper lobe bronchiectasis.

(116,117). Air trapping is seen on CT performed at end-expiration and on dynamic expiratory CT *(119)*. The majority of patients with Swyer–James syndrome are asymptomatic adults. Occasionally, patients may present with a history of repeated lower respiratory tract infections or shortness of breath.

7.2. Obliterative Bronchiolitis Associated with Transplantation

Obliterative bronchiolitis is a common and important complication of lung and heart-lung transplantation and remains the single leading cause of morbidity and mortality in these patients. The prevalence of OB following lung transplantation is approximately 20% at 1 year and greater than 50% at 3–5 years *(79,120–123)*. OB is the primary cause of death in 30% of the affected individuals after the third postoperative year and more than half of affected individuals after 5 years *(120,121,123,124)*. Clinically, OB typically is first recognized 16–20 months after transplantation although it may manifest as early as the second or third month after transplantation *(80,125,126)*. OB is believed to be a manifestation of chronic rejection. Although by definition OB is a pathologic diagnosis, histologic confirmation is difficult to obtain. The reported sensitivity of transbronchial biopsy ranges from 15 to 87% and the specificity approximately 75% *(21–23,25,26)*. Surgical biopsy is seldom performed on these patients. Bronchoalveolar lavage is usually nonspecific and may show neutrophilic and/or lymphocytic inflammation *(127,128)*. However, transbronchial biopsy and bronchoalveolar lavage are important in excluding other possible diagnoses as contributing causes of deteriorating pulmonary function in patients with lung transplantation and heart-lung transplantation, such as acute rejection and infection *(129,130)*. Because of the low sensitivity of transbronchial biopsy in demonstrating OB, the International Society for Heart and Lung Transplantation has established the concept of bronchiolitis obliterans syndrome (BOS) and a staging system to quantify the severity of airflow obstruction *(131)*. According to the revised classification system, the staging is based on the reduction in the forced expiration volume in 1 s (FEV_1) and mid-expiratory flow rate (FEF_{25-75}), in comparison with baseline post-transplant values, with or without histologic documentation of OB, and the exclusion of other causes for the functional abnormality *(132)*. On the basis of the severity of functional

impairment, BOS can be subdivided into five different categories: BOS 0 (FEV_1 > 90% of baseline, and FEF_{25-75} > 75% of baseline), BOS 0-p (potential OB; FEV_1 81–90% of baseline, and/or FEF_{25-75} ≤ 75% of baseline), BOS 1 (mild OB; FEV_1 66–80% of baseline), BOS 2 (moderate OB; FEV_1 51–65% of baseline), and BOS 3 (severe OB; FEV_1 ≤ 50% of baseline).

Post-transplant OB has a variable course. Some patients experience a sudden onset with rapid decline of lung function and respiratory failure. Others experience insidious onset with a slow, progressive decline over time or, less commonly, an initial rapid decline in FEV_1 followed by a prolonged period of stability *(133,134)*. Clinical symptoms at onset are usually absent or nonspecific. Some patients present with an asymptomatic fall in FEV_1 and/or biopsy findings of OB. Clinical symptoms include malaise, dry cough, and shortness of breath on exertion. Sputum production at presentation is typically absent; however, repeated episodes of bacterial infection, followed by permanent airway colonization with pathogenic bacteria and fungi (e.g., *Pseudomonas* and *Staphylococcus* spp. and *Aspergillus fumigatus*), may result in productive cough later in the course of the disease *(134)*.

Obliterative bronchiolitis is also the most common noninfectious late pulmonary complication of allogeneic hematopoietic stem-cell transplantation (HSCT) *(127,135)*. OB in these patients typically occurs more than 3 months following transplantation and in the setting of underlying chronic graft-versus-host disease (GVHD) *(82,127)*. OB is estimated to affect approximately 20% of patients who receive allogeneic transplants *(81,82)* but is rare after autologous transplantation *(136)*. In a recent study, the 5-year survival rate of 47 HSCT recipients with OB was 10%, compared with 40% for those without OB *(137)*. Occasionally, air-leak syndromes including pneumomediastinum, pneumothorax, pneumopericardium, subcutaneous emphysema, and cervical emphysema may complicate severe OB in these patients *(17,138–140)*.

The pathogenesis of OB in lung transplantation and heart-lung transplantation is not well understood. The main risk factors for the development of BOS are acute rejection, particularly when recurrent or severe, lymphocytic bronchitis/bronchiolitis, and cytomegalovirus pneumonitis *(132,134,141–144)*. Gastroesophageal reflux with occult microaspiration that may promote chronic inflammation and bacterial infections in the lower airways may be a potential risk factor for BOS *(145,146)*. The etiology of post-transplant gastroesophageal reflux is probable multifactorial and includes intraoperative vagal injury, drug-induced prolonged gastric emptying, and impaired lower esophageal sphincter function *(145–148)*. Preliminary studies suggest that antireflux surgery, such as fundoplication, may improve lung function in some of these patients *(149)*. Risk factors for OB among allogeneic recipients are probably also multifactorial and include acute and chronic GVHD, older donor and recipient age, myeloablative conditioning, methotrexate use, antecedent respiratory infection, and serum immunoglobulin deficiency *(81,82,150)*.

Early diagnosis of OB in transplanted patients is important because prompt initiation of therapy may help to preserve lung function and improve long-term survival *(81,134)*. The treatment of OB usually consists of corticosteroids and augmented immunosuppression. However, only a minority improve. BOS does not appear to recur in an accelerated manner after retransplantation *(151–153)*. The risk of developing OB is similar to that of first-time lung transplant recipients.

Lung function is currently the gold standard for detecting chronic allograft dysfunction in transplanted patients. High-resolution CT is a valuable tool in the evaluation and follow-up of transplanted patients (Fig. 18). CT is a direct measure of the lung structure and allows the identification of structural abnormalities associated with chronic allograft dysfunction, including bronchiectasis, airway wall thickening, mucus in small and large airways, and air trapping because of small airway abnormalities (see Figs 8 and 9). The presence of air trapping on expiratory high-resolution CT scans is the most sensitive and accurate radiologic indicator of OB following transplantation *(46,154–158)*. High-resolution CT has been used to predict BOS in both adults and children; however, more recent studies have shown that the value of air trapping at expiratory high-resolution CT before the clinical
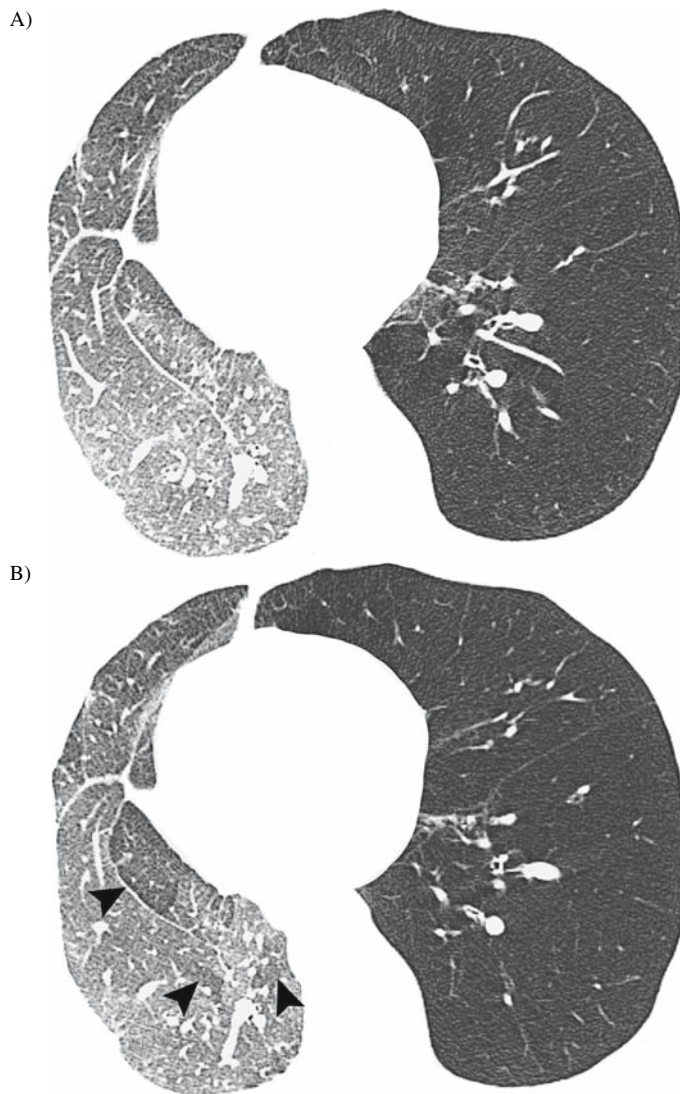
A)

B)

Fig. 18. Obliterative bronchiolitis following unilateral lung transplantation for severe panacinar emphysema. (**A**) Expiratory high-resolution CT image shortly after transplantation shows no definite abnormality in the transplanted lung. The native lung demonstrates diffuse decrease in attenuation and marked hyperinflation due to panacinar emphysema. (**B**) Expiratory image at the same level as (A) 1 year later demonstrates lobular air trapping in the right lower lobe (arrows). The patient was a 60-year-old man with bronchiolitis obliterans syndrome.

appearance and during the early stages of BOS is lower than previously reported *(154,156)*. The reported sensitivities and specificities of air trapping range from 44 to 91% and 80 to 100%, respectively *(46,154–158)*. This variability may be due to differences in the technique used to quantify the extent of air trapping, patient selection with inclusion of heart-lung or bilateral-lung and single-lung transplant recipients and predate the revised criteria for BOS, which are believed to be more sensitive for the detection of early-stage BOS *(132)*. Furthermore, most studies included high-resolution CT scans that were obtained after clinical diagnosis of OB. In a recent study, Konen et al. *(154)* assessed

the value of CT findings in predicting BOS before its clinical appearance and during the early stages of BOS. The authors found lower sensitivity for air trapping (44–50%) than previously reported (74–91%) *(155–158)*. The sensitivities of mosaic perfusion, bronchiectasis, and bronchial wall thickening were even lower, not exceeding 25% *(154,158,159)*. The limitations of high-resolution CT are also at least in part because of the inter- and intra-observer variability in the interpretation of the CT images and the different scoring systems used to quantify the extent of air trapping on CT *(154,156,157,160)*. A composite CT score system may have a potential role in the early detection of OB in lung transplant recipients, as demonstrated in a recent study with good intra- and inter-observer agreement *(161)*. Preliminary studies have shown that functional MR imaging using hyperpolarized 3-He detects BOS earlier than spirometry or high-resolution CT *(31,162)*. The main limitations of functional MR imaging are high cost and limited availability. It therefore currently remains an investigational modality.

7.3. Postinhalational Obliterative Bronchiolitis

Obliterative bronchiolitis is a well-described complication of inhalational injury being seen most commonly after inhalation of nitrogen dioxide (Silo filler's disease). The acute phase of Silo filler's disease typically manifests within minutes or hours after exposure and usually resolves within hours *(83)*. The main clinical symptoms consist of cough, dyspnea, fatigue, and cyanosis. Patients may develop pulmonary edema and acute respiratory distress syndrome (ARDS). If the patient survives, a progressive and irreversible obstructive ventilatory defect may be noted 2–5 weeks later *(83)*. At the late stage, the radiologic findings are similar to those of OB because of other causes. Other toxic gases associated with OB include ammonia, chlorine, hydrogen bromide, hydrogen selenide, sulfur dioxide, and fire smoke *(3,5)*. Recently, diacetyl (2,3-butanedione), a ketone with butter-flavor characteristics, was the predominant compound isolated in workers in a microwave popcorn plant *(163,164)*, who developed clinical, histologic, and imaging findings of OB *(163)*. Some of these patients developed severe symptoms and required lung transplantation.

7.4. Obliterative Bronchiolitis Associated with Connective Tissue Disorders

Several connective tissue diseases are associated with an increased risk of bronchiolitis, but OB is seen most commonly in patients with rheumatoid arthritis *(84,85,87,165,166)*. OB in rheumatoid arthritis usually occurs in patients with long-standing disease and is seen most commonly in women in their fifth to sixth decades of life *(84,85)*. OB as the sole and presenting feature of rheumatoid arthritis is rare *(86,167)*.

The course of disease is variable. Penicillamine therapy and, less commonly, gold therapy have been implicated as potential contributive causative agents of OB in some patients with rheumatoid arthritis *(167–169)*.

The radiologic findings of rheumatoid arthritis associated with OB are similar to those of patients with others forms of OB. The most common high-resolution CT findings are mosaic perfusion, air trapping, and bronchiectasis (Fig. 19) *(86,170,171)*.

Occasionally, OB may be seen in association with connective disorders other than rheumatoid arthritis, including Sjögren's syndrome *(172)*, systemic lupus erythematosus *(173)*, and scleroderma *(88–90)*.

7.5. Sauropous androgynus-Related Obliterative Bronchiolitis

Consumption of juice prepared from the uncooked leaves of the vegetable *Sauropous androgynus* (a member of the Euphorbiaceae family), which is alleged to help weight control, has a known association with OB *(92–94,174)*. *S. androgynus* is commonly found in Malaysia, Indonesia, southwest China, and Vietnam. It is not known whether OB results from cytotoxic effect, inflammatory reaction,
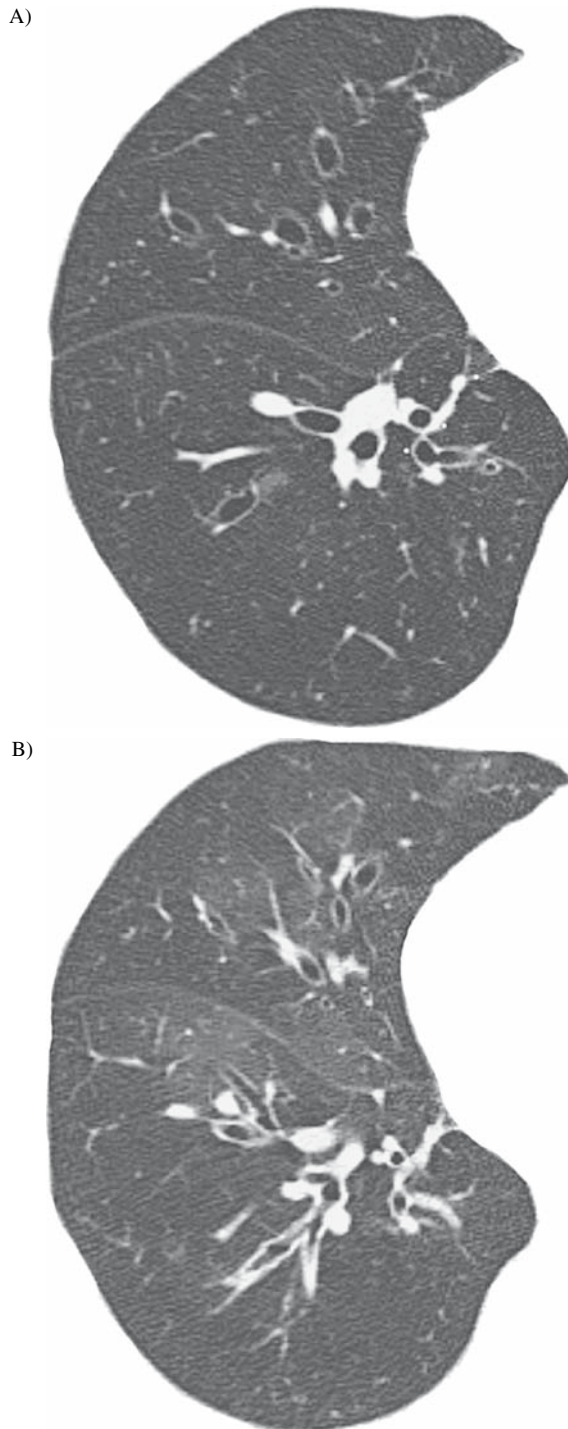
Fig. 19. Obliterative bronchiolitis in a 49-year-old woman with long-standing rheumatoid arthritis. (**A**) High-resolution CT image targeted to the right lung shows extensive areas of decreased attenuation and vascularity and bronchiectasis. (**B**) Expiratory image shows air trapping.

or immunological response. Lai et al. *(94)* reported the clinical and radiologic features of OB associated with consumption of uncooked *S. androgynus* in 23 patients during an outbreak in Taiwan. All patients were young or middle-aged nonsmoking women who developed rapidly progressive shortness of breath and persistent cough 3–4 months after ingestion of blended vegetable juice. The patients had moderate-to-severe airflow obstruction without response to bronchodilator therapy or prednisolone. The chest radiographs were normal, and high-resolution CT demonstrated bilateral bronchiectasis and patchy mosaic perfusion at inspiratory CT in 11 of 23 patients and air trapping at expiratory scans in all patients. Four patients had open lung biopsy findings of OB. OB associated with consumption of *S. androgynus* has a poor prognosis, some patients requiring lung transplantation *(175,176)*.

7.6. Obliterative Bronchiolitis Associated with Diffuse Neuroendocrine Cell Hyperplasia, Carcinoid Tumorlets, and Carcinoid Tumors

Neuroendocrine (Kulchitzky) cells are commonly found in the basal layer of the surface epithelium and in the bronchial glands from the level of the main bronchi to the proximal bronchioles. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare condition characterized by proliferation of neuroendocrine cells as clusters of cells or as linear arrays along the basement membrane *(95,177)*. DIPNECH is regarded as a precursor to the development of carcinoid tumorlets, which consist of nodular proliferations (diameter <5 mm) of airway neuroendocrine cells that extend beyond the epithelium into the adjacent wall or lung parenchyma. If such a lesion exceeds 5 mm in diameter, it is regarded as a carcinoid tumor *(177–179)*. Aguayo et al. *(95)* reported the clinical and pathologic findings of six lifelong nonsmokers who had diffuse hyperplasia of airway neuroendocrine cells and multiple pulmonary carcinoid tumorlets associated with OB and airway obstruction. The OB in these patients is postulated to be secondary to a combination of intraluminal obstruction by hyperplastic neuroendocrine cells and peribronchiolar fibrosis presumably secondary to peptide secretory products released by the proliferating neuroendocrine cells *(95,180)*. The patients are usually women in their fifth or sixth decade and have history of long-standing progressive respiratory distress (>10 years) and persistent cough with mild-to-moderate airflow obstruction at lung function tests *(96)*. The chest radiograph is usually normal. The most common high-resolution CT findings are mosaic perfusion at inspiratory CT and air trapping at expiratory images. Other high-resolution CT findings include bronchial wall thickening, a few dilated bronchi and occasional well-defined nodules measuring 0.2–1.5 mm in diameter that correspond to the carcinoid tumorlets and carcinoid tumors identified histologically (Fig. 20) *(96,97,178,181)*.

7.7. Cryptogenic Obliterative Bronchiolitis

Cryptogenic (idiopathic) OB is rare and has been described mainly in older women *(106,182)*. Patients with cryptogenic OB usually present with chronic cough, dyspnea, mild-to-severe airway obstruction that may progress to respiratory failure and does not respond to bronchodilators. The radiologic findings of cryptogenic OB are similar to those of patients with other forms of OB (see Fig. 6) *(35,47)*.

7.8. Obliterative Bronchiolitis Associated with Inflammatory Bowel Disease

The most frequent pulmonary complications associated with inflammatory bowel disease are tracheobronchitis, chronic bronchitis, and bronchiectasis *(183–186)*. Occasionally, patients with ulcerative colitis and Crohn's disease may develop OB *(187)*. Colectomy is believed to be a risk factor for the development of pulmonary disease in these patients *(99,183,184,186)*. In a study of 17 patients with inflammatory bowel disease (14 patients with ulcerative colitis and three patients with
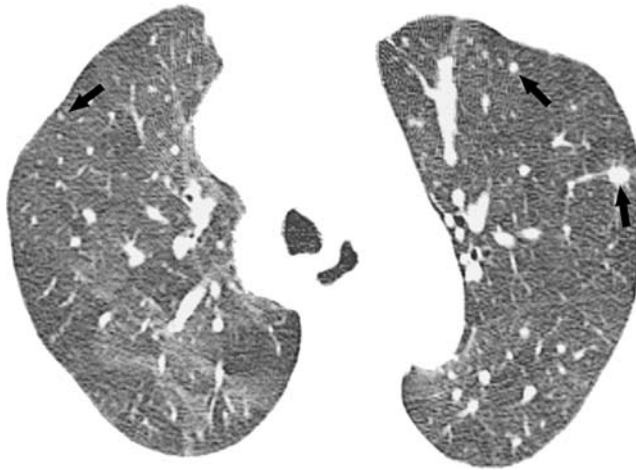
Fig. 20. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). Expiratory high-resolution CT image at the level or aortic arch shows patchy areas of air trapping and bilateral 2–8 mm well-defined soft tissue nodules (arrows). The patient was a 72-year-old woman with biopsy proven obliterative bronchiolitis and DIPNECH and multiple pulmonary carcinoid tumorlets and carcinoid tumors.

Crohn's disease) without active bowel disease at the time of the study, bronchiectasis was seen in 13 patients (76%) including 11 with ulcerative colitis and two with Crohn's disease, nine patients showed evidence of air trapping, and five had tree-in-bud opacities at high-resolution CT *(99)*.

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