Small airway disease: semiological and radiological evaluation. A pictorial review.

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Learning objectives

- To review direct and indirect radiological findings in small airway disease and its anatomical, semiological and pathological correlation.
- To remember the bronchiolar classification of bronchiolitis that includes the wide range of pathologies that manifest themselves as small airway disease and can be easily applied in everyday practice.
Background

Bronchioles are small airways that do not contain cartilage in their walls located at the center of the secondary pulmonary lobule, has an internal diameter less of 2 mm, therefore, they are not visible when are normal. The thickening of its walls and the variable intraluminal exudate reflecting an inflammatory process or fibrosis named bronchiolitis, term that encompasses a broad number of diseases [1, 2]

Bronchiolitis or small airway disease is a radiological finding very frequent in daily practice that requires an adequate anatomical knowledge for its correct identification. There is currently no radiological consensus for its classification generating confusion among clinicians, radiologists, and pathologists. However, we consider bronchiolar classification as a practical and complete way of remembering small air disease.

Anatomy of the secondary pulmonary lobule

The secondary pulmonary lobule is the smallest functional anatomic unit of the lung. It has a polyhedral morphology, bounded by interlobular septa which contain pulmonary venules and lymphatic channels and its center has an arteriole pulmonary, bronchiole and lymphatics. (Figure 1)

The lung is supported by a network of connective tissue called the lung interstitium, that could be visible on high-resolution computed tomography only if is thickening and has three components: the peribronchovascular interstitium that invests the pulmonary artery and bronchi, continuing with the centrilobular interstitium that envelops the bronchiole and centrilobular arteries, the subpleural interstitium locates in the visceral pleura and the intralobular interstitium a fine connective tissue between the center of the secondary pulmonary lobule and the interlobular septa. [3]

The structures of the secondary pulmonary lobule identified on high-resolution computed tomography are only the arteriole pulmonary because the normal bronchiole it's no visualized. Nevertheless exist computed findings suggestive of bronchiolar disorder: Ground-Glass centrilobular nodules, branching or Y-shaped centrilobular opacities ("tree-in-bud"), bronchiolectasis, mosaic attenuation, air trapping and bronchiolar wall thickening. [4]

Direct and indirect signs of small airway disease
• **Direct signs:**

The ground-glass centrilobular nodules of bronchiolitis are airspace nodules ill-defined with less dense than vessels and distribution limited to centrilobular regions, finding them usually centered 5 to 10 mm from the pleural surface, spared the fissures and interlobular septa. (Figure 2) [5]

The centrilobular nodules are not present only in airway disease, they can also be present in interstitial and vascular diseases, been important take into account the clinical history and the context of this patients. For example, when finding centrilobular peribronchovascular interstitial thickening and a lymphatic distribution of disease that include nodules in other locations like subpleural regions or interlobular septa think in interstitial disease but if the patient has a history of abusing pain medications and a new onset of pulmonary hypertension take in consideration Talcosis. [5, 6]

Centrilobular nodules are seen in acute bronchiolitis, diffuse panbronchiolitis, respiratory bronchiolitis, bronchiolitis related to toxic, gases, fumes, follicular bronchiolitis and hypersensitivity pneumonitis.

Another direct sign is branching or Y-shaped centrilobular opacities also named tree-in-bud opacities, consists of nodules centrilobular with soft tissue attenuation connected to multiple linear structures that originate a single stalk and represent impaction with mucus, pus or fluid of the centrilobular bronchioles. Tree-in-bud is indicative of small airway disease and its most frequently recognized in patients with endobronchial spread of tuberculosis, infectious bronchiolitis and noninfectious bronchiolitis (aspiration). (Figure 3) [5, 7]

Two less common direct signs are the bronchiolectasis and wall thickening. Bronchiolectasis is defined as dilatation of bronchioles by inflammatory airway disease or fibrosis and is considered dilated if the broncoarterial ratio exceed one (signet ring sign) and it is localized to 1 cm of the pleural surface. (Figure 4, 5) [8, 9]

• **Indirect sign:**

The mosaic attenuation pattern appears as a patchwork of regions of different attenuation and may represent: interstitial disease, airway disease or vascular disease. In a patient with airway disease, the inflamed bronchioles or mucus impaction leads a partial or complete obstruction with air trapping secondarily and poor ventilation of lung parenchyma. This area of less ventilation is poorly perfused because of reflex of vasoconstriction, then the pulmonary vessels appear smaller in the areas of decreased opacity with air trapping in comparison with the areas of more density, findings that are better visualized in expiratory high-resolution computed tomography. (Figure 6) [6, 8, 10]
The differentiation with vascular mosaic attenuation is not easy, but the dilated or thick-walled airway suggest the diagnostic of airway disease and the enlargement of the main pulmonary arteries a vascular etiology.
Fig. 1: Anatomy of the secondary pulmonary lobule. The secondary pulmonary lobule is the functional unit of the lung, has a polyhedral shape and are bounded by interlobular septa which contain lymphatic vessels and vein (green and blue). Each lobule is supplied by a lobular bronchiole and a pulmonary artery branch (orange, red).

Fig. 2: Drawing of ground-glass centrilobular nodules shows nodules ill-defined with less dense than vessels and distribution limited to centrilobular regions, finding them to a 10 mm from the pleural surface.

© Rivera A.L. 2017. Ground-glass centrilobular nodule
Fig. 3: Drawing of tree-in-bud opacities represent impaction with mucus, pus or fluid of the centrilobular bronchioles and is indicative of small airway disease.

© Rivera A.L. 2017. Tree-in-bud opacities

Fig. 4: Drawing of bronchiolar wall thickening.

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Fig. 5: Drawing of bronchiolectasis with a broncoarterial ratio that exceeds one (signet ring sign) and absence of normal bronchiolar tapering.

© Rivera A.L. 2017. Bronchiolectasis

Fig. 6: Drawing shows mosaic attenuation on inspiratory (a) and expiratory (b). The dark gray is represent air trapping that are more prominent on expiratory.
Findings and procedure details

We performed a retrospective search of patients with radiologic manifestations compatible with bronchiolitis, selecting the most representative cases, most of them with pathological correlation.

**BRONCHIOLAR CLASSIFICATION**

The bronchiolar classification of bronchiolitis classify the bronchiolar disorders into primary with the affection of the bronchiole and another disease with secondarily involved in the bronchiole. (Figure 7)

**PRIMARY BRONCHIOLAR DISORDERS**

*Constrictive bronchiolitis*

Also known as obliterative bronchiolitis is characterized histologically by peribronchiolar fibrosis secondary of a chronic inflammation and submucosal scarring with resulting bronchiolar narrowing and air trapping. The most common causes are idiopathic, infections (adenovirus, measles, pertussis, mycoplasma, and tuberculosis), toxic fume inhalation, connective tissue disease, graft-versus-host disease, lung transplantation and drug reactions. (Figure 8, 9, 10, 11) [4, 11, 12]

On high resolution computed tomography mosaic attenuation it's a characteristic finding and result from hypoventilation and decreased perfusion of the areas of less attenuation with redistribution of blood flow to areas with normal or increase attenuation; expiratory computed tomography and the use of minimum intensity projection reconstruction increase the contrast between the normal and abnormal lung and make evident air trapping. Other findings on computed tomography in constrictive bronchiolitis are bronchiectasis, bronchiolectasis and bronchial wall thickening. [2, 4]

Swyer-James- MacLeod syndrome represent a long-term complication of post infectious constrictive bronchiolitis particularly by adenovirus in early childhood with radiographic manifestations seen in adulthood. Asymmetric expiratory air trapping and a mosaic of attenuation are the typical features of this disease. [2, 4, 6]

**Acute Bronchiolitis**
Is the most common type of bronchiolitis and can be classified as acute or chronic. Acute infectious bronchiolitis is most often in infants and children with infection for respiratory syncytial virus, adenovirus, parainfluenza, influenza and less commonly mycoplasma and chlamydia. Chronic infections (Pseudomona aeruginosa, Aspergillus) and mycobacterial infections cause chronic bronchiolitis. [2, 4, 6, 13]

Histologically it is characterized by a severe process inflammatory in the walls of the bronchiole, edema, exudate, and necrosis of bronchiolar epithelium. These findings are seen on high resolution computed tomography like peribronchial areas of consolidation, ground-glass centrilobular nodules, tree-in-bud opacities and bronchial wall thickening. (Figures 12, 13, 14)

**Diffuse Panbronchiolitis**

It is most common in Asiatic patients and represents an idiopathic chronic bronchiolitis with chronic inflammation of paranasal sinus. Findings on histology evidence intraluminal exudate and chronic inflammatory cells in the walls. High resolution computed tomography demonstrates findings nonspecific: tree-in-bud pattern, centrilobular nodules, bronchiectasis, bronchiolectasis and mosaic of attenuation. [2, 4]

**Respiratory bronchiolitis**

It is a condition seen mostly in asymptomatic cigarette smokers, however, may occur with other inhalation exposure, is characterized by an accumulation of hemosiderin-like pigment-laden macrophages in peribronchiolar airspace and alveolar space, chronic inflammation and finally fibrosis of the bronchiolar walls. On High resolution computed tomography, respiratory bronchiolitis manifests as ground-glass opacities and centrilobular micronodules with ground-glass density predominantly on the upper lobules. (Figures 15) [2, 4]

**Bronchiolitis related to toxic, gases, fumes and dust**

There are other agents can cause bronchiolitis: acute exposure to smoke, nitrogen dioxide. Initially, these organic and organic agents produce an inflammatory process in the bronchiole wall that occasionally progress to obliterative bronchiolitis, represented histologically by fibrosis and chronic infiltrate of its walls. The findings on high resolution computed tomography are bronchiectasis, attenuation mosaic, and expiratory air trapping. (Figures 16, 17) [2]
Follicular bronchiolitis

Follicular bronchiolitis is part of a spectrum of lymphoproliferative disorders, almost mostly in association with autoimmune diseases, connective tissue diseases, infection and hypersensitivity reactions.

On histology demonstrates lymphoid hyperplasia with the formation of nodular lymphoid aggregates. These findings represent on high resolution computed tomography solid or ground-glass centrilobular nodules. (Figures 18) [2, 4, 6]

BRONCHIOLAR INVOLVEMENT IN INTERSTITIAL LUNG DISEASE

Hypersensitivity Pneumonitis

Also known as allergic bronchiolitis or extrinsic allergic alveolitis is characterized by the inhalation of organic dust that causes an immune-mediated inflammatory process in the peribronchiolar alveoli. For unknown causes, the smokers have a protective effect against hypersensitivity pneumonitis. Their findings in high-resolution tomography are similar to a respiratory bronchiolitis: bilateral ground-glass opacity, ill-defined centrilobular nodules with mosaic attenuation and air trapping, these last two findings present in their chronic evolution. (Figures 19) [2, 14]

Respiratory bronchiolitis associated with interstitial disease

Is there a strong relationship between the smokers and respiratory bronchiolitis, from this group of patients a little proportion may be seen associated with interstitial lung diseases. Histological features are pigmented macrophages intraluminal and intraalveolar with peribronchiolar interstitial fibrosis. The findings on high resolution computed tomography are no specific, however, some features include centrilobular nodules, ground-glass opacification, thickening of the interlobular septa, thickening of the bronchi walls, emphysema, and mosaic of attenuation. (Figures 20) [13, 14]

Pneumonia cryptogenic of organization

Previously known erroneously as bronchiolitis obliterans with organizing pneumonia (BOOP), it’s a pathology that no always is idiopathic, can be associated with an infection, inhalation injury, connective tissue disease, drugs, radiation, aspiration or autoimmune disease. On histology feature for a proliferation of connective tissue and granulation
tissue in alveolar space with lesser bronchiolar involvement. On high resolution computed tomography is associated with the unilateral or bilateral consolidation that can migrate on serial images with a tendency of central bronchovascular and subpleural distribution, another findings include ground glass opacity, bronchial wall thickening and reversed halo sign. (Figures 21) [6, 13, 14]

BRONCHIOLAR INVOLVEMENT IN LARGE AIRWAY DISEASE

Chronic bronchitis, bronchiectasis, asthma

Bronchial abnormalities affect the large airway and have histologically changed include smooth muscle hyperplasia, air wall edema, mucous gland hyperplasia and mucostasis. High resolution computed tomography findings atelectasis, centrilobular nodules with upper lobe predominance, bronchiolar wall thickening and air trapping. (Figures 22,23) [13]
**Fig. 7:** Bronchiolar classification

**Fig. 9:** Axial computed tomography of a 36-year-old woman with a history of rheumatoid arthritis, show mosaic attenuation due air trapping. Histologic specimen (Trichrome stain 10X) demonstrates extensive fibrosis and obliterated airway.

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**Fig. 10:** Axial computed tomography of a 17-year-old man with a history of recurrent bronchiolitis in his childhood, show segmental mosaic attenuation. Histologic specimen (Trichrome stain 4X) demonstrates submucosal fibrosis of the bronchiole and obliterated airway.

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Fig. 11: Axial computed tomography of a patient with a history of bone marrow transplantation shows mosaic attenuation, paraseptal emphysema, and bronchiectasis. Histologic specimen (hematoxylin and eosin stain 10X) evidence mucosal fibrosis with obliterated airway and inflammatory infiltrates.

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**Fig. 12:** Axial computed tomography of a 6-year-old child with bronchiolitis by the respiratory syncytial virus. On computed tomography demonstrate centrilobular nodules and tree-in-bud opacities. Histologic specimen (hematoxylin and eosin stain 10X) with necrosis of the bronchial epithelium and acute inflammation of the bronchiolar wall.

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**Fig. 13:** Coronal and sagittal computed tomography of a patient VIH presenting three months of cough and hemoptysis demonstrate a tree-in-bud pattern and a pulmonary cavity by tuberculosis. Histologic specimen (hematoxylin and eosin stain 10X) with necrosis of the terminal bronchiole and giant multinucleated cells.

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Fig. 14: Axial computed tomography of a 25-year-old man with a history of bone marrow transplantation presenting neutropenia, the CT show centrilobular nodules and tree-in-bud opacities. Histologic specimen (hematoxylin and eosin stain 10X) with Aspergillus septate hyphae in the bronchiolar wall.

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**Fig. 15:** Axial computed tomography of a 35-year-old man with a history of smoker asymptomatic with penetrating trauma in left hemithorax. The CT demonstrates centrilobular nodule. Histologic specimen (hematoxylin and eosin stain 10X) show epithelial hyperplasia of the respiratory bronchiole, inflammatory infiltrates in the bronchiolar wall and pigmented macrophages in the bronchiolar lumen and in the adjacent alveolus.

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**Fig. 16:** Axial computed tomography demonstrates micronodules of random distribution and predominantly on the superior lobules in a 50-year-old man marble polisher for 15 years presenting with progressive dyspnea (silicosis). Histologic specimen (hematoxylin and eosin stain 10X) show deposits of anthracotic pigment and submucosal fibrosis in the bronchial walls.

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Fig. 17: Axial computed tomography demonstrates centrilobular nodules and tree-in-bud opacities in a 49-year-old man with a history of working with iron for 20 years presenting with cough and progressive dyspnea (siderosis). Histologic specimen (Prussian blue 10X) show deposits of anthracotic pigment and iron deposits in the submucosa of the terminal bronchiole.

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**Fig. 18:** Axial computed tomography demonstrates centrilobular nodules in a 35-year-old woman with a history of 2 years of cough and dyspnea. Histologic specimen (hematoxylin and eosin stain 10X) show hyperplastic peribronchovascular lymphoid follicles with reactive germinal centers.

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**Fig. 19:** Axial computed tomography demonstrates centrilobular nodules in a 25-year-old patient, with a history of exposure to birds for 2 years. Histologic specimen (hematoxylin and eosin stain 10X) show chronic inflammatory infiltrates in the walls of the terminal bronchioles.

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**Fig. 20:** A 50-year-old man with a history of smoker and with dry cough of three years of evolution. The CT demonstrates centrilobular nodules, centrilobular emphysema and tree-in-bud opacities. Histologic specimen (hematoxylin and eosin stain 10X) show fibrosis of the terminal bronchioles and inflammatory infiltrates and macrophages with anthracotic pigment in the peribronchiolar walls.

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**Fig. 21:** A 26-year-old patient with a history three weeks of fever, cough and malaise after finished treatment for tuberculosis. The CT demonstrates bronchiectasis, centrilobular nodules and tree-in-bud opacities. Histologic specimen (Trichrome stain 10X) show fibroblastic polyps or Masson bodies, which obstruct the bronchiole lumen and extend to the adjacent alveolus.

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**Fig. 8:** A 2-year old patient with a history of viral bronchiolitis. CT images show bronchiectasis and mosaic attenuation. Histologic specimen (Trichrome stain) shows narrowing of the bronchiole by peribronchiolar fibrosis (yellow arrow) and intraluminal secretion.

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Fig. 22: A 65-year-old patient with a history of chronic exposure to wood smoke. The CT demonstrates centrilobular micronodules, bronchiectasis and tree-in-bud opacities. Histologic specimen (hematoxylin and eosin stain 10X) show a bronchiole trapped inside a fibroantracotic nodule.

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Fig. 23: A 12-year-old girl with a history of recurrent respiratory infections. The CT demonstrates bronchiectasis, bronchiolectasis, and tree-in-bud opacities. Histologic specimen (hematoxylin and eosin stain 10X) acute inflammatory infiltrates composed of neutrophils that surround the wall and the lumen of the respiratory bronchioles and adjacent alveolus.

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Conclusion

The previous knowledge of anatomy in high-resolution CT and its semiological correlation are necessary so that the radiologist can identify and understand direct and indirect signs present in small airway disease. Its classification etiologic and patient clinical data are key to decrease the differential diagnoses in this wide spectrum of pathologies.
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