

Bronchiolitis obliterans and BOOP: what relevance in pediatric?

¹ Philippe Reix, MD-PhD

¹Service de pédiatrie, pneumologie, allergologie, mucoviscidose

Université Claude Bernard Lyon-1, INSERM U628

LYON, France

Tel: 33 + 4 72 38 56 11

Fax: 33 + 4 72 38 55 72

Email: philippe.reix@chu-lyon.fr

Introduction

Bronchiolitis obliterans (BO) and bronchiolitis obliterans with organizing pneumoniae (BOOP) are rare respiratory disorders involving distal airways (i.e. bronchioles). Although some etiology may be common to those conditions, they are distinct clinico-anatomo-radiological entities, with very distinct therapeutic responses to steroids. In pediatrics, infectious or post-infectious and post transplantation (either lung or bone marrow) represent the leading causes ¹.

While BO is mainly a primary bronchiolar disorder, the pathological hallmark of BOOP is the presence of foci of organized pneumoniae, describing buds of granulation tissue, taking place in the alveolar spaces and extending in the distal air spaces. However, this pathological pattern is not specific, and could be seen in many other diseases, including idiopathic BOOP ². Because idiopathic BOOP is a well defined clinicoradiological, and in order to avoid confusion with other bronchiolar disorders, the term cryptogenic organized pneumoniae (COP) is more appropriated ^{3,4}.

Nevertheless, in both BO and BOOP partial or complete obstruction of bronchioles is observed, in reaction to an epithelial injury (at the alveolar or the bronchiolar levels in case of BOOP and BO respectively) and an unusual immuno-inflammatory reaction and subsequent excessive fibroblastic and myofibroblastic local recruitment and connective tissue formation. In the first situation (BO), the connective tissue is disposed around the bronchioles and defined the constrictive form of bronchiolitis – also called obliterative or obliterans bronchiolitis-. In the second situation (BOOP), bronchioles lumens are obstructed by a polypoids intraalveolar fibroblastic plugs with a varying degree of bronchiolar involvement ^{2,3}.

Clinical symptoms

The pathological situations in which BO and BOOP may appear are responsible for specific clinical signs that are of major interest to orient the diagnosis. Rarely, BO or BOOP are revelatory of the underlying disease ⁵. In COP, flu-like illness is frequent (70%) as reported in the seminal description by Epler ⁶.

At the initial stages, BO and BOOP will present with unspecific presenting symptoms and signs such as cough, progressively increasing dyspnea with exercise intolerance, tachypnea ^{7,8}. In addition, BO has a marked obstructive clinical presentation and wheezing is common, while it is not the case in BOOP. Chest examination usually reveals crackles in BOOP associated to wheezing in BO. In the advanced stages of BO, symptoms related to bronchiectasis are present (chronic wet cough, bronchorrhea and recurrent pulmonary exacerbations), and chronic respiratory insufficiency is the ultimate evolutionary stage.

Conditions known to be responsible for BO or BOOP in children

In adults, many different situations have been described to be responsible for BO or BOOP development^{3,4}.

While in most cases, clinical scene, biological, radiological are helpful (but not always determinant) in finding the origin of BO or BOOP, some cases remained idiopathic.

In children BOOP could occur during a variety of immuno-inflammatory processes including auto-immune disease, infections, hypersensitivity reactions or toxic agents³. Numerous reports have also pointed out the possibility of BOOP as a lung manifestation of rejection in lung transplanted patients, or a graft vs. host reaction in bone marrow transplanted patients. In those latter cases, BOOP may be multifactorial and the synergistic role of iatrogenic or infectious agents must be systematically evaluated.

From far, the leading causes of BO in children are infectious agents. BO may occur during the post infectious period following *Mycoplasma pneumoniae* and some viruses (adenoviruses, influenzae, parainfluenzae, measles) infections⁹. Some populations are known to be particularly susceptible in developing BO after adenoviral infections probably because of specific host immunologic response to infection.

Autoimmune disorders and vasculitis are discussed causes of BO in children, since it was not always possible to differentiate the respective role of the underlying disease from the toxicity of the administered treatments.

Finally, BO is widely recognized to be the chronic rejection manifestation after lung transplantation, occurring in around 35 to 60 % of long term survivors (review in¹). It could also rarely (less than 10%) complicate autologous and more frequently allogenic bone marrow transplantation as a late manifestation of the graft versus host reaction¹⁰.

Pulmonary function tests (PFT) features

Pulmonary function tests are useful during the diagnosis process and the regular follow-up of patients at risk of developing BO or BOOP (transplanted patients).

During BO, the main characteristic is the presence of a fixed airflow obstruction. Air trapping and lung distension are frequently associated.

During BOOP, PFT typically show a predominantly restrictive defect (usually mild to moderate) associated with diminished diffusing capacity of the lungs for carbon monoxide. Occasionally, PFT are normal.

Imaging features

Routine Chest X-rays will show lung hyperinflation during BO, with lungs appearing clear. Because of lung distension, complications such as pneumothorax or pneumomediastinum could be seen. Unique or multiple

alveolar opacities, interstitial lung disease could be seen on the Chest X-ray of patients with BOOP. High Resolution CT scans (HRCT) is always indicated in both situations. During BO, images with full expiration should be done when possible (around 6 years of age) to highlight indirect signs of the bronchiolar disease. In non cooperative children lateral decubitus HRCT have been used as a surrogate of expiratory images ¹¹. Lesions of BO could be bilateral or localized to one lung (whole lung or lung lobe or segment) such in Swyer James-Mac leod syndromes. The “tree in buds” images (direct signs of bronchiolar disease) are not always easily detectable in young children. Indirect signs, and typically mosaic pattern of lung attenuation is more easily observed and increased by expiratory images. However, it should be kept in mind that mosaic pattern is not specific for bronchiolar diseases and has also been described in pulmonary vascular disease and diffuse parenchymal disease ³. Larger airways lesions (bronchial wall thickening, bronchiectasis) are common during BO. Lung ventilation-perfusion scan will provide informations on regional and global lung function.

In adults, three different radiological findings have been described during COP ⁴. The most frequent and typical imaging is multiples alveolar opacities, usually bilateral, peripheral and migratory. Solitary focal opacity and infiltrative BOOP represents the two others radiological aspects. In children, the three radiological patterns have been reported indifferently in some cases reports of BOOP.

Cytological and Histological findings

Bronchoalveolar lavage is almost always indicated when BO or BOOP is suspected. First it helps in excluding others cause of airflow obstruction or organized pneumoniae, second it may disclose active infection, and rarely in the pediatric situation, neoplastic disorders, especially lymphoma. While neutrophils count elevation in BAL is common during BO, typically, in adult's COP, a mixed pattern of differential cell count may orientates toward the diagnosis (mixed alveolitis with increased lymphocytes, neutrophils and eosinophils, with the level of lymphocytes higher thanthat of eosinophils) ⁴. This has however rarely been described in the same terms in pediatric BOOP, particularly in patients treated for neoplastic hematologic diseases ¹².

“A part” for lung transplanted patients where transbronchial lung biopsy are indicated as part of the routine follow-up, there is no consensus statement regarding lung biopsy realization in other clinical situations evocating BO. When the clinico-physiologico-radiological scene is highly suggestive of BO, it seems to be the common attitude to not perform lung biopsy, and to reserve this procedure to doubtable cases. Open lung biopsy has a highest sensitivity and is preferable to transbronchial biopsy, in order to obtain pieces of tissue of sufficient size, without artifacts induced by the forceps. It shows the classical histopathological pattern of the constrictive

bronchiolitis with a fibrosing process that surrounds the lumen, resulting in an extrinsic compression and obliteration of the airway.

The diagnosis of BOOP requires the establishment of a diagnosis of organising pneumoniae. As mentioned earlier, the hallmark of BOOP is the presence of buds of granulation tissue consisting of fibroblasts-myofibroblasts embedded in connective tissue. These buds extend from an alveoli to the other through the pores of Khon, they may also extend to the bronchioles and may obstruct the lumen (proliferative type of obliterative bronchiolitis). Histopathological examination is also needed to differentiate BOOP from other interstitial lung diseases where buds of granulation could be present.

Treatment and outcomes

Different patterns of evolution have been identified depending of the origin of BO, and the extension of lung lesions. In “post infectious” BO, in children, according to Zhang et al, three ways of evolution are possible: two-third of patients have persistent respiratory symptoms and signs, less than the third had clinical and radiological remission and less than ten percent died ¹³. In the “post transplantation” BO (either lung or bone marrow), the clinical evolution is usually worsen, and transplantation or re- transplantation is the only curable solution.

Numerous treatment options (immunosuppressive or not) have been explored in lung and bone marrow graft recipients to prevent or cure BO, however strong evidence-based data are lacking on their efficiency before their routine application is widespread. While altering immunosuppression with specific immunosuppressive agents could slow the progression of the disease, the treatment of BO is difficult and often unsuccessful ¹.

To the opposite, BOOP is fundamentally an inflammatory lesion and has usually a dramatic positive initial response to oral steroids, whatever its origin. However, in adult series of COP, relapses were frequent in around half cases. In rare cases, immunosuppressive agents were needed to properly control the disease ⁴.

References

1. Kurland G, Michelson P. Bronchiolitis obliterans in children. *Pediatr Pulmonol* 2005;39(3):193-208.
2. Cordier JF. Organising pneumonia. *Thorax* 2000;55(4):318-328.
3. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med* 2003;168(11):1277-1292.
4. Cordier JF. Cryptogenic organising pneumonia. *Eur Respir J* 2006;28(2):422-446.
5. Takada H, Saito Y, Nomura A, Ohga S, Kuwano K, Nakashima N, Aishima S, Tsuru N, Hara T. Bronchiolitis obliterans organizing pneumonia as an initial manifestation in systemic lupus erythematosus. *Pediatr Pulmonol* 2005;40(3):257-260.
6. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. *N Engl J Med* 1985;312(3):152-158.
7. Kim CK, Kim SW, Kim JS, Koh YY, Cohen AH, Deterding RR, White CW. Bronchiolitis obliterans in the 1990s in Korea and the United States. *Chest* 2001;120(4):1101-1106.
8. Chan PW, Muridan R, Debruyne JA. Bronchiolitis obliterans in children: clinical profile and diagnosis. *Respirology* 2000;5(4):369-375.
9. Hardy KA, Schidlow DV, Zaeri N. Obliterative bronchiolitis in children. *Chest* 1988;93(3):460-466.
10. Khurshid I, Anderson LC. Non-infectious pulmonary complications after bone marrow transplantation. *Postgrad Med J* 2002;78(919):257-262.
11. Choi SJ, Choi BK, Kim HJ, Lee SH, Choi SH, Park SJ, Goo HW, Lee JS, Yoon CH. Lateral decubitus HRCT: a simple technique to replace expiratory CT in children with air trapping. *Pediatr Radiol* 2002;32(3):179-182.
12. Battistini E, Dini G, Savioli C, Morando A, Gandolfo A, Kotitsa Z, Garaventa A, Rossi GA. Bronchiolitis obliterans organizing pneumonia in three children with acute leukaemias treated with cytosine arabinoside and anthracyclines. *Eur Respir J* 1997;10(5):1187-1190.
13. Zhang L, Irion K, Kozakewich H, Reid L, Camargo JJ, da Silva Porto N, Abreu e Silva FA. Clinical course of postinfectious bronchiolitis obliterans. *Pediatr Pulmonol* 2000;29(5):341-350.