Case Report

Postinfectious bronchiolitis obliterans accompanied by pulmonary hemosiderosis in childhood*

LEONARDO ARAÚJO PINTO[1], ANICK OLIVEIRA[2], SINTIA COLLAZIOL[2], PAULO MÁRCIO PITREZ[3], MARCUS JONES[3], JOÃO CARLOS PROLLA[3], MARISA DOLHNIKOFF[4], RENATO T. STEIN[3]

ABSTRACT

In the present report, we describe an unusual presentation of post-infectious bronchiolitis obliterans accompanied by pulmonary hemosiderosis in a nine-year-old boy with persistent respiratory symptoms subsequent to an episode of acute bronchiolitis occurring at the age of seven months. After the episode, the persistent respiratory symptoms worsened significantly, and, by the age of seven, the patient began to have difficulty breathing after minimal exertion. Computed tomography of the chest presented findings consistent with bronchiolitis obliterans. Open lung biopsy revealed numerous hemosiderin-laden macrophages, as well as other findings consistent with bronchiolitis obliterans. Pulmonary hemosiderosis can occasionally be accompanied by bronchiolitis obliterans in children with severe sequelae after an episode of viral infection.

Keywords: Bronchoalveolar lavage; Bronchiolitis obliterans; Hemosiderosis; Case reports [Publication type]

INTRODUCTION

Bronchiolitis obliterans (BO) is characterized by intense inflammation of the lower airway secondary to some previous injury, resulting in airway obstruction. It is common in children after an episode of acute viral bronchitis. Although its prevalence is unknown, it is not an illness commonly seen in clinical practice.[1-2] Cases of BO have been described in suckling infants, typically following an episode of acute viral bronchiolitis caused by adenovirus. It causes damage to the respiratory

epithelium, with total or partial obliteration of the secondary to the thickening of the mucosa caused by inflammatory cells and fibrosis.[3]

Factors other than bronchiolitis from adenovirus can trigger BO. Such factors include inhaled toxins, aspiration syndrome and lung transplant.[1] It has been estimated that the prevalence of BO is relatively high in the southern region of Latin America, especially in relation to respiratory infections.

Pulmonary hemosiderosis (PH) is a rare condition that can occur in individuals of any age, from neonates to adults. However, in 80% of the cases, its first manifestation occurs in the first decade of life, especially between the ages of one and seven years.[4-5] The primary morphological characteristic is the presence of chronic and recurrent intra-alveolar hemorrhage with consequent intra-alveolar accumulation of hemosiderin and interstitial fibrosis.[6] Most cases of HP are considered idiopathic. There are reports of HP cases associated with auto-immune diseases such as lactose intolerance, some types of vasculitis, and celiac disease. Some cases involving familial inheritance have also been reported, suggesting that genetic predisposition has a significant impact.[4,7-8]

Herein, we describe a rare case of BO accompanied by HP in a nine-year-old child. There have been no previous reports of this combination.

CASE REPORT

A nine-year old male patient was referred to the University Hospital of the Pontifical Catholic University of Rio Grande do Sul for assessment of persistent respiratory symptoms that began after an episode of severe acute viral bronchiolitis at the age of seven months. In this first incident, the suckling infant was admitted to a pediatric intensive care unit and, due to respiratory failure resulting from an upper-airway infection, remained on mechanical ventilation for a period of three weeks. During the time on mechanical ventilation, the most severe complication described was a pneumothorax, which was promptly treated with the use of a thoracic drain. Although the pathogen had not yet been identified, a diagnosis of acute viral bronchiolitis was made based on clinical criteria.

After the acute episode, the patient presented partial improvement of symptoms and was discharged from the hospital without the need for supplemental oxygen. The patient continued to present persistent respiratory symptoms after having been discharged, with frequent crises that were principally characterized by breathing difficulties due to the upper-airway infection. However, a second admission to the hospital did not become necessary until the patient had reached the age of six. Although the patient was treated with several antibiotics, corticosteroids and inhaled ß2-agonists during this period, the basic clinical profile remained unresolved.

The clinical profile worsened when the patient was seven years of age, at which point he was treated with an additional course of systemic corticosteroids during the exacerbations. Since the patient presented persistent difficulty in breathing, even upon minimal exertion, together with a persistent productive cough that had worsened progressively, especially over the preceding four months, the case was directed to the Pediatric Pulmonology department of the Pontifical Catholic University of Rio Grande do Sul.

In the physical examination, the patient presented tachypnea, breathing difficulty, noted increase of anteroposterior thoracic diameter and significant digital clubbing. Pulmonary auscultation revealed breath sounds that were abnormal and reduced bilaterally, especially on the left side. Oxygen saturation was 87%, and arterial carbon dioxide tension was 43 mmHg on room air.

Laboratory tests showed that hematocrit was 41%, hemoglobin was 13.5 g%, and the platelet count was 414,000/mm3 (subsequent collections revealed no signs of anemia). The pulmonary function tests revealed severe obstructive pulmonary disease with significant air trapping: forced expiratory volume in one second of 0.5 L (21% of predicted); forced vital capacity of 0.6 L (22% of predicted); ratio of forced expiratory volume in one second to forced vital capacity of 87%; and residual volume of 1.5 L (207% of predicted). The pulmonary function test findings remained unchanged throughout the follow-up period.

Pulmonary perfusion scintigraphy revealed bilateral alteration of pulmonary perfusion that was more intense on the left. A computed tomography scan of the chest showed diffuse areas of air trapping (discrete mosaic pattern), atelectasis and

cylindrical bronchiectasis in the upper left lobe and upper segment of the lower left lobe (Figure 1). The results of the computed tomography scan of the chest were consistent with BO.

The results of the sweat test of electrolyte concentrations (used to identify cystic fibrosis), as well as those of the tests for congenital or acquired immunodeficiencies, were normal. In the cardiac evaluation, the patient presented no abnormalities, and the echocardiogram showed no evidence of pulmonary hypertension. Other laboratory tests, such as those for the antinuclear factor, anti-DNA antibody, rheumatoid factor and bovine milk anti-protein antibody, were all negative. Clinical and laboratory test histories did not suggest a diagnosis of chronic pulmonary aspiration, whether due to a swallowing disorder or to gastroesophageal reflux (normal esophageal pHmetry).

After two weeks of treatment with broad-spectrum antibiotics, corticosteroids and bronchodilators, the patient was discharged from the hospital with a prescription for home oxygen therapy due to persistent hypoxemia. Since patient presented no improvement with the use of oral corticosteroids, two courses of pulse therapy with endovenous methylprednisolone were performed as a treatment for BO (1 g/day for three consecutive days), with an interval of one month between the two.

A bronchoalveolar lavage (BAL) revealed a predominantly neutrophilic inflammatory profile (55% neutrophils, 10% lymphocytes, 31% macrophages and 4% eosinophils) The cultures were negative for bacteria, mycobacteria and fungi. Hemosiderin-stained macrophages were seen in more than 20% of the BAL sample tested (Figure 2). The techniques standardized by the European Respiratory Society(9) were applied in the BAL.

A second BAL confirmed the finding as being consistent with PH, with a great number of hemosiderin-stained macrophages (more than 90%). After the BAL, treatment with chloroquine was started. However, no clinical or pulmonary function improvement was observed. Considering the severity of the case and the difficulty in making the diagnosis, an open lung biopsy was performed. The biopsy revealed hemorrhagic disease with a great quantity of hemosiderin-stained macrophages.

The biopsy also revealed discrete septal and peribronchial thickening, secondary to a monocytic inflammatory infiltrate and septal fibrosis Electron

microscopy revealed high quantity of macrophages and pneumocytes without significant alterations (Figure 3). Areas of microhemorrhage were observed in both lungs. The peribronchial alveolar tissue presented signs of collapse, and there was intra-alveolar accumulation of hemosiderin-stained alveolar macrophages. The bronchioles presented a constrictive aspect with thickening of the mucosa and discrete inflammation extending to the lung parenchyma. These findings are consistent with BO.

The patient continued to present a severe obstructive status, remaining oxygen dependant, with no response to any of the treatments, and
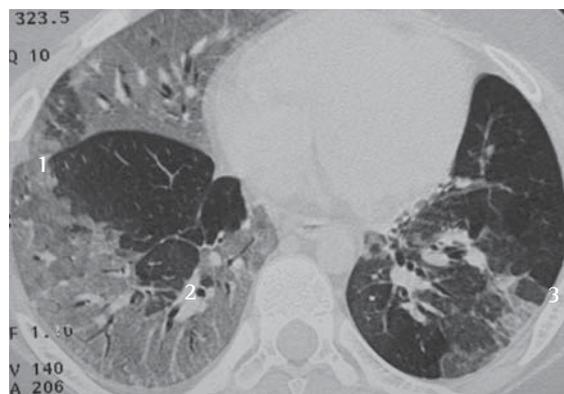

Figure 1 - Tomography scan of the chest showing diffuse areas of air trapping (1), together with areas of opacity presenting signs of a 'ground-glass' pattern and cylindrical atelectasis (2), in the upper left lobe and superior segment of inferior left lobe. A mosaic pattern can be observed (3) (areas of hyper- and hypo-attenuation in the lungs), consistent with a state of post-viral bronchiolitis obliterans
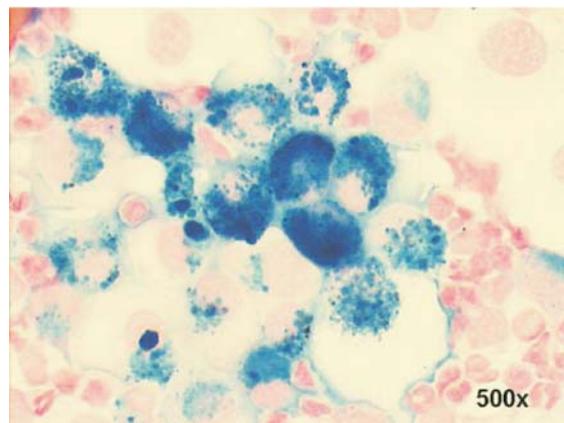

Figure 2 - Slide from the bronchoalveolar lavage presenting alveolar macrophages stained with hemosiderin
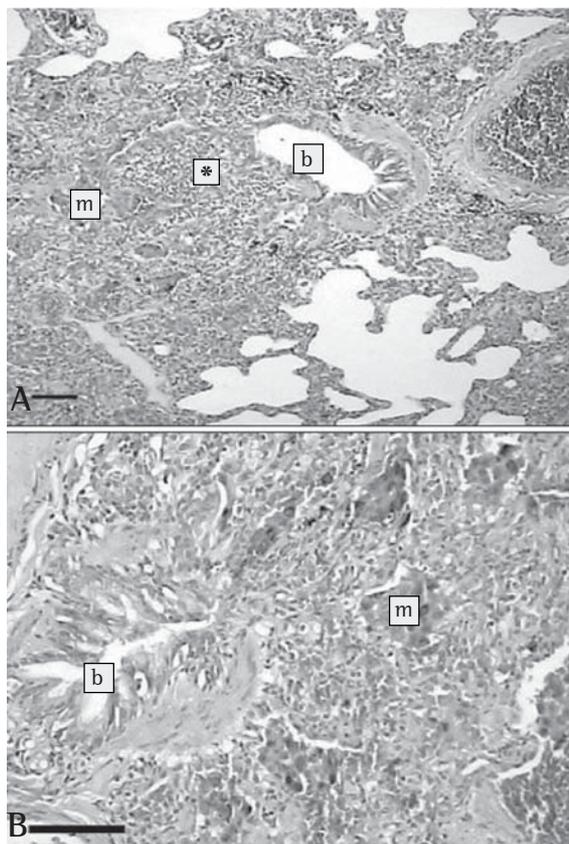
Figure 3 - Optical photomicrographs of pulmonary tissue presenting: A) a constricted bronchiole (b) with partial reduction of the lumen and signs of mild/moderate chronic inflammation in the walls (*), extending to the pulmonary parenchyma; B) Peribronchial alveolar tissue presenting signs of collapse and intra-alveolar accumulation of hemosiderin-stained alveolar macrophages (m). A) H&E, ×100; B) H&E, ×200. Bar scale = 100; m

was under evaluation for the possibility of lung transplant.

DISCUSSION

The case reported herein received an initial diagnosis of post-viral BO due to the previous clinical history of the patient related to the respiratory event occurring in the first year of life and to the pulmonary tests performed when he was nine years old, as well as to the fact that the computed tomography scan of the chest produced findings that were consistent with the disease. However, the lung biopsy and BAL revealed, in addition to findings also consistent with BO, signs characteristic of PH.

It can be suspected that the residual pulmonary damage after the acute event in the first year of life led to the persistent hypoxemia, which can be accompanied by hemorrhage in the bronchial wall. However, it can also be considered that the initial insult, which led to BO, is related to a severe inflammatory response related to PH. It is known that this illness has idiopathic causes, and the viral insult might therefore have provoked the bronchial mucosa bleeding. Therefore, it is not possible to reject the hypothesis that PH was present since the first episode, which was initially characterized by acute respiratory failure.

The combination of these two diagnoses is unusual and leads to the suspicion that the chronic status resulting from the initial injury, typically designated post-viral BO, can predispose a patient to other diseases and can mask their symptoms. It is important to consider other diagnoses accompanying viral post-injury BO. Based on this case, we suggest that PH always be included in the differential diagnosis of BO.

Common manifestations of PH are iron deficiency anemia, hemoptysis, cough, breathing difficulty, recurrent sibilance, low weight, and transitory pulmonary infiltrate on chest X-rays.[4] However, the classic triad of anemia, hemoptysis and pulmonary infiltrate is uncommon in children.[8] Although the finding of hemosiderin-stained alveolar macrophages suggests PH, it should also be interpreted with caution, since other pathologies, such as heart failure, bacterial pneumonia, primary pulmonary hypertension, and pulmonary veno-occlusive disease, can also be present.[7]

It should also be taken into consideration that the chronic inflammatory injury seen in BO[2] can provoke bleeding in the bronchial mucosa and the consequent findings observed in the BAL and lung biopsy. However, these findings have never before been described in reports of post-infectious BO.

Many cases described as PH could represent misdiagnoses, being in fact diffuse alveolar hemorrhage caused by any one of a number of illnesses. Since hemosiderin-containing macrophages can remain in the lungs for four to eight weeks, it has been suggested that the term PH be reserved only for cases in which there is persistent or recurrent alveolar bleeding.(10) Considering that this patient presented this finding at three different points (two BALs and one biopsy), we found it appropriate to

make a diagnosis of concomitant PH.

Treatment with high doses of corticosteroids can alter cytological findings, resulting in a predominantly neutrophilic pattern, or predispose to pulmonary hemorrhage, systemically influencing the production of coagulation factors, as well as the fragility of the pulmonary capillaries. However, the use of systemic corticosteroids has never been described as a cause of persistent or recurrent alveolar hemorrhage and might be one of the first therapeutic options for patients with PH, principally for cases related to auto-immune phenomena.

The concomitant occurrence of these two rare diseases in a child could be mere coincidence, but is notable due to its rarity. Therefore, a common pathogenic mechanism cannot be ruled out. The combination of idiopathic PH and celiac disease has been described in only a few more than ten cases. However, it remains unknown whether there is a common pathogenic mechanism.[10]

Despite being suggestive of a diagnosis of BO,[11] the isolated findings of the open lung biopsy do not explain the severity of the case. Lung biopsy is considered the gold standard for the diagnosis of BO. However, it has not been widely used, since high-resolution computed tomography of the chest combined with the taking of a clinical history present high sensitivity and specificity for reaching a sound final diagnosis.[12-13]

Based on the case reported herein, we suspect that a diagnosis of concomitant PH could be made with greater frequency in children presenting post-viral BO sequelae. This finding suggests that, even in the absence of anemia or hemoptysis, children with severe post-injury viral chronic pulmonary diseases be investigated for PH.

REFERENCES

1. Ferkol Jr TW, Davis PB. Bronchiectasis and bronchiolitis obliterans. In; Taussig LM, Landau Ll, editors. Pediatric respiratory medicine. St. Louis, Missouri: Mosby; 1998. p. 784-92.

2. Zhang L, Irion K, Kozakewich H, Reid L, Camargo JJ, da Silva Porto N, et al. Clinical course of postinfectious bronchiolitis obliterans. Pediatr Pulmonol. 2000;29(5):341-50.

3. Mauad T, Dolhnikoff M; Sao Paulo Bronchiolitis Obliterans Study Group. Histology of childhood bronchiolitis obliterans. Pediatr Pulmonol. 2002;33(6):466-74.

4. Kiper N, Gocmen A, Ozcelik U, Dilber E, Anadol D. Long-term clinical course of patients with idiopathic pulmonary hemosiderosis (1979-1994): prolonged survival with low-dose corticosteroid therapy. Pediatr Pulmonol. 1999;27(3):180-4.

5. Ferrari GF, Fioretto JR, Alves AFR, Brandão GS. Hemossiderose pulmonar idiopatica. Relato de Caso. J Pediatr (Rio de J). 2000;76(2):149-52.

6. Saeed MM, Woo MS, MacLaughlin EF, Margetis MF, Keens TG. Prognosis in pediatric idiopathic pulmonary hemosiderosis. Chest. 1999;116(3):721-5.

7. McCoy K. Hemosiderosis. In: Taussig LM, Landau Ll, editors. Pediatric respiratory medicine. St. Louis, Missouri: Mosby; 1998. p. 835-41.

8. Bush A, Sheppard MN, Warner JO. Chloroquine in idiopathic pulmonary haemosiderosis. Arch Dis Child. 1992;67(5):625-7.

9. de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, et al. Bronchoalveolar lavage in children. ERS Task Force on bronchoalveolar lavage in children. European Respiratory Society. Eur Respir J. 2000;15(1):217-31.

10. Ioachimescu OC, Sieber S, Kotch A. Idiopathic pulmonary haemosiderosis revisited. Eur Respir J. 2004;24(1):162-70.

11. Mauad T, van Schadewijk A, Schrumpf J, Hack CE, Fernezlian S, Garippo AL, Ejzenberg B, Hiemstra PS, Rabe KF, Dolhnikoff M; Sao Paulo BO Study Group. Lymphocytic inflammation in childhood bronchiolitis obliterans. Pediatr Pulmonol. 2004;38(3):233-9.

12. Jensen SP, Lynch DA, Brown KK, Wenzel SE, Newell JD. High-resolution CT features of severe asthma and bronchiolitis obliterans. Clin Radiol. 2002;57(12):1078-85.

13. Hardy KA, Schidlow DV, Zaeri N. Obliterative bronchiolitis in children. Chest. 1988;93(3):460-6.