J Bras Pneumol. 2016;42(3):228-231
http://dx.doi.org/10.1590/S1806-37562016000000043

CASE REPORT

Impact of long-term treatment with inhaled corticosteroids and bronchodilators on lung function in a patient with post-infectious bronchiolitis obliterans

Cecilia Calabrese[1], Nadia Corcione[1], Gaetano Rea[2], Francesco Stefanelli[3], Ilernando Meoli[3], Alessandro Vatrella[4]

1. Dipartimento di Scienze Cardio-Toraciche e Respiratorie, Seconda Università degli Studi di Napoli, Italia.
2. Dipartimento di Radiologia, A. O. dei Colli, Ospedale Monaldi, Napoli, Italia.
3. Divisione di Pneumologia, A. O. dei Colli, Ospedale Monaldi, Napoli, Italia.
4. Dipartimento di Medicina e Chirurgia, Sezione di Malattie Respiratorie, Università degli Studi di Salerno, Italia.

Submitted: 11 February 2016.
Accepted: 9 May 2016.

Study carried out at the A. O. dei Colli, Ospedale Monaldi di Napoli, Italia.

ABSTRACT

Post-infectious bronchiolitis obliterans (PIBO) is a small airways disease characterized by fixed airflow limitation. Therefore, inhaled bronchodilators and corticosteroids are not recommended as maintenance therapy options. The management of PIBO currently consists only of close monitoring of affected patients, aimed at the prevention and early treatment of pulmonary infections. In recent years, there has been an increase in the incidence of PIBO in the pediatric population. Patients with PIBO are characterized by a progressive decline in lung function, accompanied by a decrease in overall functional capacity. Here, we report the case of a relatively young man diagnosed with PIBO and followed for three years. After short- and long-term therapy with an inhaled corticosteroid/long-acting β_2 agonist combination, together with an inhaled long-acting antimuscarinic, the patient showed relevant improvement of airway obstruction that had been irreversible at the time of the bronchodilator test. The lung function of the patient worsened when he interrupted the triple inhaled therapy. In addition, a 3-week pulmonary rehabilitation program markedly improved his physical performance.

Keywords: Bronchiolitis obliterans/therapy; Infection/complications; Adrenergic beta-2 receptor antagonists/therapeutic use; Administration, inhalation; Anti-inflammatory agents/therapeutic use; Muscarinic antagonists/therapeutic use; Lung diseases/rehabilitation.

INTRODUCTION

Post-infectious bronchiolitis obliterans (PIBO) is currently recognized as an acquired disorder that is usually consequent to severe bronchiolitis occurring during infancy.[1,2] The incidence of PIBO in the pediatric population has increased over the last few years, and some cases are also incidentally diagnosed in adulthood.[3-8] PIBO is characterized by small-airway obstruction that is generally unresponsive or poorly responsive to bronchodilators.[9] We report the case of a relatively young man diagnosed with PIBO, whose airway obstruction improved after long-term treatment with inhaled bronchodilators and corticosteroids. In addition, a short-term pulmonary rehabilitation program resulted in better physical performance.

CASE REPORT

A 36-year-old man, exhibiting apparent good health, was referred to our outpatient clinic for pulmonary function testing before undergoing a surgical procedure (vocal cord polypectomy). The flow-volume curve showed moderate airflow limitation that was irreversible after inhalation of 400 µg of albuterol. In particular, the FEV_1 was 2.36 L (58% of the predicted value); the FVC was 3.15 L (65% of the predicted value); the FEV_1/FVC ratio was 69.6%; and the post-bronchodilator FEV_1 was 2.4 L (2% increase). The patient history was then carefully collected. The patient reported no respiratory symptoms or previous lung disease, with the exception of intermittent allergic rhinitis and an episode of bronchiolitis (requiring hospitalization) during the first months of life. He categorized himself as a nonsmoker and reported no occupational exposure to toxic substances. On physical examination, crackles were heard at both lung bases. Therefore, whole-body plethysmography was performed. The plethysmography showed static lung hyperinflation characterized by an increased RV (3.05 L, 161% of the predicted value), although the TLC was normal (6.89 L, 99% of the predicted value). The DLCO was within the normal range. Arterial blood gas analysis demonstrated mild hypoxemia and a normal acid-base balance (PaO_2: 72.2 mmHg; $PaCO_2$: 40.6 mmHg; pH: 7.41; and HCO_3^-: 25.6 mmol/L). The patient underwent HRCT, scans being obtained at the end of inspiration, as well as during the so-called "expiratory hold" respiratory maneuver (Figures 1A and 1B). The HRCT scans showed heterogeneous lung tissue density, characterized by areas of reduced attenuation in the absence of tissue destruction, located in the middle lobe, lingula, and lower lobes, which featured a "patchy distribution" pattern suggestive of small airways disease, accompanied by air trapping. In the areas of lowest density, a significant reduction in both the number and size of pulmonary vessels was

Corresponding author:
Cecilia Calabrese. Dipartimento di Scienze Cardio-Toraciche e Respiratorie, Seconda Università degli Studi di Napoli, Via Posillipo 276, 80123, Napoli, Italia.
Tel.: 39 3473 675572. Fax: 39 0817 062365. E-mail: cecilia.calabrese@unina2.it
Financial support: None.

ISSN 1806-3713

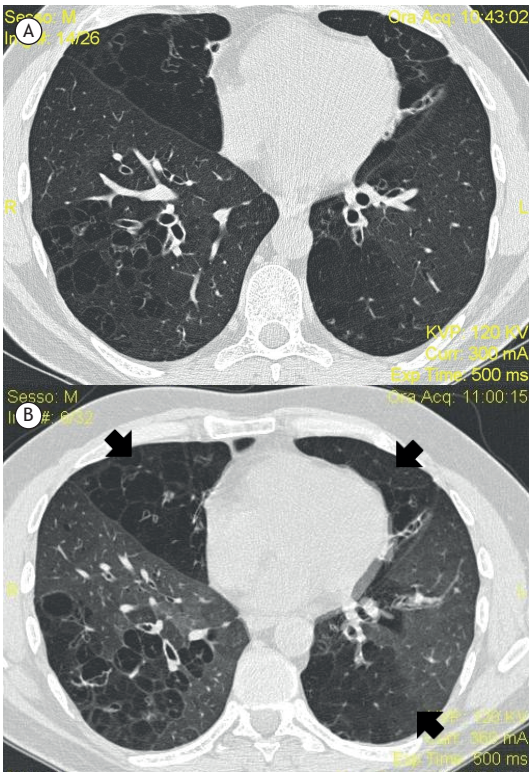

Figure 1. (A) HRCT scan of the chest, acquired in the inspiratory phase, showing marked bilateral heterogeneity of lung tissue density, characterized by extensive areas of reduced attenuation, located in the middle lobe, lingula, and lower lobes; some areas of bronchiectasis are also evident. The patchy distribution pattern and the absence of lung tissue destruction are suggestive of a small airways disease, with multifocal areas of air trapping. In the lower density areas, the significant decrease in the number and size of pulmonary vessels can be seen. (B) HRCT scan of the chest, acquired in the expiratory phase, showing a moderate reduction in lung volumes, with areas of air trapping caused by hypoxic vasoconstriction subsequent to alterations due to post-infectious bronchiolitis obliterans (black arrows).

also evident. Lung perfusion scintigraphy showed segmental and subsegmental defects in both lung fields, particularly in the lower lobes. Analysis of the BAL fluid demonstrated an increased proportion of neutrophils (36%), the proportions of lymphocytes and macrophages being 10% and 54%, respectively.

The history of bronchiolitis during the first months of life, together with the abovementioned clinical, functional, and CT scan features, suggested a diagnosis of PIBO. Although PIBO is regarded as a small airways disease characterized by fixed airway obstruction, empirical treatment with an inhaled corticosteroid/long-acting β_2 agonist (ICS/LABA) combination, together with an inhaled, long-acting antimuscarinic (LAMA), was prescribed. The ICS/LABA combination consisted of beclomethasone dipropionate and formoterol (at 100 µg and 6 µg, respectively), delivered via a pressurized metered dose inhaler (two puffs twice a day). The LAMA was tiotropium (at 18 µg), delivered via a dry powder inhaler (one inhalation a day). After two months of treatment, we observed an improvement in lung function, consisting of increases of 360 mL and 550 mL in FEV_1 and FVC, respectively. Therefore, the inhaled therapy was continued. During a 3-year follow-up period, we detected a worsening of lung function when the patient spontaneously interrupted the inhaled treatment; in particular, FEV_1 reached the lowest value of 1.84 L (47% of the predicted value) when the ICS/LABA+LAMA therapy was interrupted and gradually increased to 2.52 L (63% of the predicted value) when the therapy was started again (Figure 2). Over the course of the study period, the TLC remained substantially unchanged and the RV decreased, whereas FEV_1 and FVC improved.

At the end of the 3-year follow-up period, cardiopulmonary exercise testing (CPET) showed reduced physical performance—a maximum workload of 85 W (39% of the predicted value) and peak oxygen consumption of 21.1 mL/kg/min (55% of the predicted value)—and the patient therefore underwent a 3-week pulmonary rehabilitation program. The rehabilitation plan consisted of high-intensity training of legs and arms on a cycle ergometer, treadmill, and arm ergometer at a workload of 75-80% of the maximal workload calculated in the CPET; the endurance time of the exercises was progressively increased up to a maximum of 30 min. After the patient had completed the rehabilitation program, there was a relevant improvement in his physical performance—peak oxygen consumption of 27.3 mL/kg/min (71.0 of the predicted value; 29.3% increase) and a maximum workload of 118 W (54.0 of the predicted value; 38.2% increase).

DISCUSSION

Here, we have reported the case of a patient with PIBO who was followed for three years. We found that short- and long-term ICS/LABA+LAMA therapy, in combination with a pulmonary rehabilitation program, produced a beneficial response.

Currently, the management of PIBO consists in close monitoring aimed at the prevention and early treatment of pulmonary infections. Influenza and pneumococcal vaccinations are strongly recommended for patients with PIBO. Antibiotics, preferably macrolides, together with systemic corticosteroids and inhaled bronchodilators, are administered during acute disease exacerbations.[9] In patients with reversible airflow limitation, β_2 agonists are prescribed as maintenance therapy.[10] In fact, most studies have shown that patients with PIBO show no response to bronchodilators. In a study of 19 patients with PIBO and severe airway obstruction, conducted in Australia, albuterol was found to induce no improvement.[11] Similarly, in a study of 13 infants with PIBO, evaluated by plethysmography, there was no response to albuterol or ipratropium bromide.[12] However, in a study involving 17 adults suffering from bronchiolitis obliterans after bone marrow transplant and treated with inhaled albuterol plus tiotropium, the treatment resulted in half of the enrolled patients

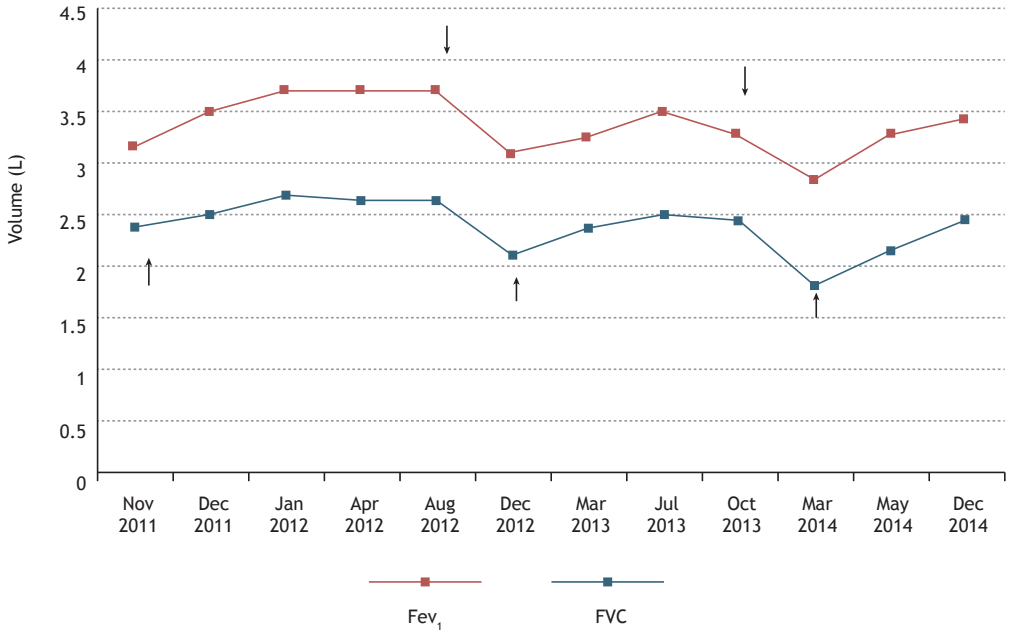

Figure 2. Graph showing the trends for FEV_1 and FVC in relation to the introduction (↑) and withdrawal (↓) of therapy with an inhaled corticosteroid/long-acting β_2 agonist combination, together with an inhaled long-acting antimuscarinic, in a patient with post-infectious bronchiolitis obliterans.

meeting the standard criteria for FEV_1 or FVC reversibility, whereas some patients exhibited either an increase in partial forced expiratory flows or a decrease in RV.[13] In addition, a recent study of children with PIBO showed that, within the first 24 h of treatment, tiotropium acutely decreased airway obstruction and air trapping.[14] The usefulness of treatment with the combination of inhaled bronchodilators and corticosteroids is also supported by the results of a recent study showing that most children with PIBO show bronchial hyperresponsiveness to methacholine, although the mechanisms underlying bronchial hyperresponsiveness in such patients remain unclear.[15]

To date, studies of patients with PIBO have evaluated only the acute effects of inhaled bronchodilators on lung function parameters, and none of those studies have evaluated the long-term impact that inhaled bronchodilator treatment has on functional and clinical outcomes such as symptoms, exercise tolerance, and quality of life. In addition, because of the low prevalence of the disease, there have been no well-designed randomized clinical trials. However, we believe that it is important to investigate the pharmacological treatment of PIBO, because the incidence of the disease is increasing, the patients are usually young, and the impairment of pulmonary function can be severe. In fact, it has been reported that most children and adolescents with PIBO show reduced functional capacity during CPET and the six-minute walk test.[16] Nevertheless, to our knowledge, the potential effects of rehabilitation plans on lung function have never been evaluated in individuals with PIBO.

In the case presented here, the ICS/LABA+LAMA therapy had a beneficial effect on lung function over the course of a 3-year follow-up period. Although our patient did not report respiratory symptoms, we prescribed the inhaled therapy because a progressive FEV_1 decline has been shown in patients with PIBO.[17] We suggested the ICS because the analysis of bronchoalveolar cellularity in patients with PIBO has indicated that such patients show an ongoing inflammatory process over time.[17] Combining an LABA and an ICS has synergistic effects, potentiating their anti-inflammatory and bronchodilating actions. Adding a LAMA to a LABA can further improve bronchodilation through positive pharmacological interactions via distinct mechanisms of action operating at different levels in the airways.[18] In our patient, we observed that the post-treatment improvement in FVC was greater than was the post-treatment improvement in FEV_1, which is probably because patients with increased peripheral airway resistance and lung hyperinflation, such as those with PIBO, are more likely to be volume responders than flow responders after bronchodilator administration.[19] We decided not to use a step-down approach, because our patient had persistent pulmonary function impairment and did not exhibit any adverse reactions to the treatment. Although he suffered from allergic rhinitis, we excluded underlying bronchial asthma because he did not complain of any symptoms suggestive of asthma and did not meet the standard criteria for reversibility in FEV_1. Because some patients with PIBO show hyperresponsiveness to methacholine,[15] we did not perform a bronchoprovocation test.

There is a need for further studies of pharmacological treatment in patients with PIBO. Such studies should evaluate the long-term effectiveness of inhaled ICS/LABA+LAMA therapy.

REFERENCES

1. Swyer PR, James GC. A case of unilateral pulmonary emphysema. Thorax 1953;8(2):133-6. http://dx.doi.org/10.1136/thx.8.2.133
2. Moore AD, Godwin JD, Dietrich PA, Verschakelen JA, Henderson WR Jr. Swyer-James syndrome: CT findings in eight patients. AJR Am J Roentgenol 1992;158(6):1211-5. http://dx.doi.org/10.2214/ajr.158.6.1590109
3. Boyacı N, Karakaş Ö, Yalçin F, Yildiz S, Çeçe H. A case of Swyer-James-MacLeod syndrome diagnosed in adulthood. Tuberk Toraks. 2013;61(4):355-6. http://dx.doi.org/10.5578/tt.6131
4. Capela C, Gouveia P, Sousa M, Regadas MJ. Adult diagnosis of Swyer-James-MacLeod syndrome: a case report. J Med Case Rep. 2011;5:2. http://dx.doi.org/10.1186/1752-1947-5-2
5. Desai NR, Palomino J, Hayek H, Shames J, Simeone F. A 63-year-old man with recurrent pulmonary infections: a case of Swyer-James Macleod syndrome. J La State Med Soc. 2010;162(6):346-9.
6. Garg R, Aga P, Saheer S, Jabeed P, Singh A, Hassan G, et al. Swyer-James-MacLeod syndrome with ipsilateral herniation of hyperinflated hyperlucent lung. BMJ Case Rep. 2011;2011. pii: bcr0520114191. http://dx.doi.org/10.1136/bcr.05.2011.4191
7. Metin B, Özkan E, Sariçam M, Ariba OK. Swyer-James-MacLeod syndrome with renal ectopy misdiagnosed as pneumothorax and chest tube drained: Case study. J Thorac Cardiovasc Surg. 2013;145(5):e44-7. http://dx.doi.org/10.1016/j.jtcvs.2013.01.035
8. Sen HS, Taylan M, Abakay O, Sezgi C, Cetincakmak MG. Adult diagnosis of Swyer-James-Macleod syndrome: retrospective analysis of four cases. Respir Care. 2014;59(4):e51-4. http://dx.doi.org/10.4187/respcare.02552
9. Lino CA, Batista AK, Soares MA, de Freitas AE, Gomes LC, M Filho JH, et al. Bronchiolitis obliterans: clinical and radiological profile of children followed-up in a reference outpatient clinic. Rev Paul Pediatr. 2013;31(1):10-6. http://dx.doi.org/10.1590/S0103-05822013000100003
10. Champs NS, Lasmar LM, Camargos PA, Marguet C, Fischer GB, Mocelin HT. Post-infectious bronchiolitis obliterans in children. J Pediatr (Rio J). 2011;87(3):187-98. http://dx.doi.org/10.2223/jped.2083
11. Chang AB, Masel JP, Masters B. Post-infectious bronchiolitis obliterans: clinical, radiological and pulmonary function sequelae. Pediatr Radiol. 1998;28(1):23-9. http://dx.doi.org/10.1007/s002470050286
12. Teper AM, Kofman CD, Maffey AF, Vidaurreta SM. Lung function in infants with chronic pulmonary disease after severe adenoviral illness. J Pediatr. 1999;134(6):730-3. http://dx.doi.org/10.1016/S0022-3476(99)70289-1
13. Barisione G, Bacigalupo A, Crimi E, Brusasco V. Acute bronchodilator responsiveness in bronchiolitis obliterans syndrome following hematopoietic stem cell transplantation. Chest. 2011;139(3):633-9. http://dx.doi.org/10.1378/chest.10-1442
14. Teixeira MF, Rodrigues JC, Leone C, Adde FV. Acute bronchodilator responsiveness to tiotropium in postinfectious bronchiolitis obliterans in children. Chest. 2013;144(3):974-80. http://dx.doi.org/10.1378/chest.12-2280
15. Yoo Y, Yu J, Kim DK, Choi SH, Kim CK, Koh YY. Methacholine and adenosine 5'-monophosphate challenges in children with post-infectious bronchiolitis obliterans. Eur Respir J. 2006;27(1):36-41. http://dx.doi.org/10.1183/09031936.06.00019605
16. Mattiello R, Sarria EE, Stein R, Fischer GB, Mocelin HT, Barreto SS, et al. Functional capacity assessment in children and adolescents with post-infectious bronchiolitis obliterans. J Pediatr (Rio J). 2008;84(4):337-43. http://dx.doi.org/10.2223/jped.1807
17. Cazzato S, Poletti V, Bernardi F, Loroni L, Bertelli L, Colonna S, et al. Airway inflammation and lung function decline in childhood post-infectious bronchiolitis obliterans. Pediatr Pulmonol. 2008;43(4):381-90. http://dx.doi.org/10.1002/ppul.20784
18. Pelaia G, Vatrella A, Busceti MT, Gallelli L, Calabrese C, Terracciano R, et al. Pharmacologic rationale underlying the therapeutic effects of tiotropium/olodaterol in COPD. Ther Clin Risk Manag. 2015;11:1563-72. http://dx.doi.org/10.2147/TCRM.S84151
19. Pisi R, Aiello M, Zanini A, Tzani P, Paleari D, Marangio E, et al. Small airway dysfunction and flow and volume bronchodilator responsiveness in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:1191-7. http://dx.doi.org/10.1183/13993003.congress-2015.pa3357