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*CASE REPORT*

# Bronchiolitis obliterans: the lone manifestation of rheumatoid arthritis?

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*Bronchiolitis obliterans: the lone manifestation of rheumatoid arthritis? M.I. Schwarz, D.A. Lynch, R. Tuder. ©ERS Journals Ltd 1994.*

**ABSTRACT: The patient was a 62 year old man, who suddenly developed obstructive lung disease without a readily definable cause. He had a remarkable family history of deforming rheumatoid arthritis, and a serum rheumatoid factor of 1:1,256, but with no evidence of active rheumatological disease.**

**Clinical, physiological and radiologic features suggested bronchiolitis obliterans, and this was confirmed by open lung biopsy. Immune staining of tissue revealed immunoglobulin M (IgM) as well as rare immunoglobulin (IgG) containing plasma cells in a peribronchiolar location. Because of these findings, we suggest that this case represents bronchiolitis obliterans secondary to a rheumatoid process.**

**This case is unusual since it appeared in a man and is the first and, so far, the only manifestation of rheumatoid arthritis. Prior studies indicate that the bronchiolitis obliterans of rheumatoid arthritis occurs primarily in women and only in ongoing cases.**

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Bronchiolitis obliterans (obliterative bronchiolitis) refers to a mural concentric narrowing of the lumina of the membranous bronchioles producing an often fatal obstructive lung disease [1]. Both inflammatory and connective tissue elements are responsible for this luminal obliteration [1, 2]. Most cases, which are not associated with either solid organ and bone marrow transplantation or toxic inhalation, occur in the setting of a connective tissue disease, most often rheumatoid arthritis [2]. The bronchiolitis obliterans which complicates rheumatoid arthritis primarily affects women some of whom are receiving penicillamine at the time [2–4]. Furthermore, whilst other pleuropulmonary manifestations are sometimes the signal event of rheumatoid arthritis and, therefore, precede or occur simultaneously with the joint manifestations, bronchiolitis obliterans has only been reported in well-established cases [3, 5, 6]. There is also an idiopathic variety of bronchiolitis obliterans (cryptogenic obliterative bronchiolitis), which appears more commonly in women [7–9].

We present the case of a previously healthy man who developed an obstructive lung disease secondary to bronchiolitis obliterans but without a readily identifiable cause. He had a remarkable family history of deforming rheumatoid arthritis, and high titres of serum rheumatoid factor, but no articular disease. Histopathology indicated concentric luminal narrowing of membranous bronchioles by lymphoplasmocytic cells, as well as mural connective tissue elements. Immunoglobulin M (IgM) containing plasma cells were prominent in the peribronchiolar inflammatory infiltrates. We suggest that in this man bronchiolitis obliterans possibly represents the first and the only manifestation of the rheumatoid process.

## Case report

A 62 year old man who jogged 5 miles daily was first seen in June 1991. In the previous month he experienced the sudden onset of dry cough, chest tightness, and progressive dyspnoea. The symptoms were not preceded by an upper respiratory tract infection and immediately caused significant exercise limitation. He denied chest pain, wheezing, nocturnal exacerbations, dry eyes and mouth, or arthritic symptoms. Over the next 8 months an intermittently productive cough appeared, which responded to several courses of antibiotics. However, in spite of treatment with both oral and inhaled bronchodilators, inhaled ipratropium bromide, and low doses of an inhaled corticosteroid preparation, the dyspnoea progressed. He had smoked at a level of 40 pack-years, but not for the last 18 yrs. His only medication at the time of symptom onset was an angiotensin converting enzyme inhibitor prescribed for mild hypertension. Discontinuation of this drug did not affect symptoms. There was no environmental exposure to gases or fumes. He was retired from the air force and was presently employed as a production manager in the space industry but worked in an office distant from the manufacturing facilities. His past history was negative except for asymptomatic aortic stenosis, diagnosed 25 yrs ago. Prior to their deaths, his mother and a maternal aunt were diagnosed as having long-standing deforming rheumatoid arthritis.

He was afebrile with normal vital signs. Examination of the skin, head, eyes, ears and throat, and salivary glands and lymph nodes were normal. Lung examination revealed a bilateral decrease in breath sounds, with

faint crackles at both bases but without wheezes or an inspiratory squeak. There was a 3/6 systolic ejection murmur over the precordium, which radiated to the neck. Abdominal examination was normal, and there was no joint deformity or active synovitis. Complete blood count was normal, as were serum electrolytes, glucose, creatinine, urinalysis and liver function tests. The following were negative: anti-smooth muscle, anti-ribonucleo protein (anti-RNP), anti-single strand A and B (anti-ssA and anti-ssB), anticentromere, and anti-native double strand deoxyribonucleic acid (dsDNA) antibodies. The antinuclear antibody was 1:256, in a speckled pattern, and the serum rheumatoid factor was 1:1,256. The chest radiograph showed mild overdistention, a normal heart size, and no parenchymal infiltrates. Computed tomographic features indicated no evidence for parenchymal infiltration but rather marked inhomogenity of lung density, with alternating increased and decreased density in adjacent pulmonary lobules.

Table 1 summarizes the patient's lung function. Between December 6, 1991, and November 5, 1992, there was progressive and moderately severe airflow limitation, with minimal bronchodilator response, overdistention, and preservation of the diffusing capacity. A room air arterial blood gas revealed pH 7.48, arterial carbon dioxide tension ($Paco_2$) 34 mmHg (4.5 kPa), and arterial oxygen tension ($Pao_2$) 55 mmHg (7.3 kPa). The resting room air oxygen saturation was 89%, and after 3 min of exercise on a 10% gradient at 2.5 mph, it fell to 83%. A transoesophageal echocardiogram showed a calcified aortic valve. Cardiac catheterization disclosed a 25 mmHg gradient across the aortic valve, an aortic valve mean surface area of 1.6 $cm^2$, a pulmonary artery pressure of 25/8 mmHg, and normal coronary arteries.

An open lung biopsy demonstrated that the majority of the terminal and respiratory bronchioles showed intense inflammatory infiltration, composed predominately of lymphocytes and plasma cells (fig. 1). The inflammatory cells clustered around the airways, whilst sparing the alveolar walls. This infiltrate caused reduction of the bronchial lumen, resulting in a polypoid appearance to the bronchial lining. There was also medial and intimal thickening by fibrosclerotic tissue of the muscular pulmonary arteries. The inflammatory infiltrate extended to the adventitia and focally into the media of the compromised blood vessels. The peribronchial elastic tissue exhibited multiple sites of partial or complete fragmentation (fig. 2). IgM (rabbit anti-mu chain, Signet, Bedhem, MA, USA) and immunoglobulin G (IgG) (rabbit anti-gamma chain, Signet) immunostaining was detected on paraffin-embedded sections with rabbit anti-mouse or swine anti-rabbit antibody (1/40 dilution, for 5 min) followed by peroxidase anti-peroxidase antibody (1/100 dilution, 10 min, Dakko, Carpinteria, CA, USA). The plasma cells displayed cytoplasmic staining for IgM, whilst IgG positive cells were rarely found.


Fig. 1. – Low power view demonstrating an intense inflammatory infiltrate of the membranous bronchioles (b). Note the medial thickening of the accompanying pulmonary artery (V). (Haematoxylin and eosin staining; magnification 40×).

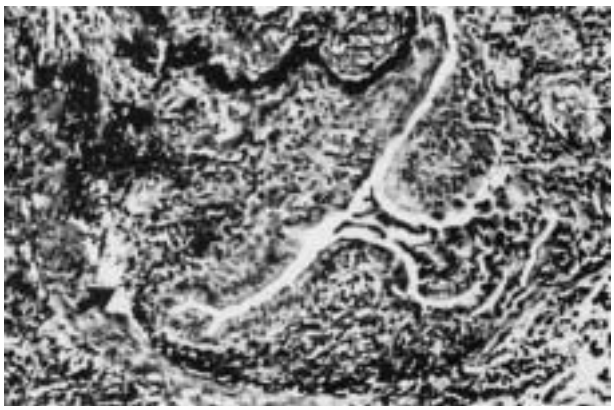

Fig. 2. – Terminal bronchiole demonstrating partial obliteration by the chronic infiltrate composed of primarily lymphocytes and plasma cells. The inflammatory infiltrate clusters between the elastic tissue and the bronchial epithelium. Note the fragmentation and interruption of the elastic layer (arrow). (Verhoeff van Gieson elastic stain, 150×).

Table 1. – Summary of pulmonary function measurements

| Date | FVC *l* | $FEV_1$ *l* | $FEV_1$/FVC %* | TGV *l* | TLC *l* | DLCO $ml \cdot min^{-1} \cdot mmHg^{-1}$ |
|---|---|---|---|---|---|---|
| Dec 1991 | 4.3 (101) | 2.4 (62) | 57–59 | 4.2 (118) | 7.4 (115) | 32 (102) |
| Nov 1992 | 3.6 (75) | 1.5 (41) | 46–48 | 4.6 (120) | 7.4 (115) | 25 (81) |
| April 1993 | 4.6 (110) | 2.1 (56) | 46–49 | 4.0 (116) | 7.2 (114) | 34 (101) |

Percentage predicted data are presented in parenthesis. *: Pre- and post-bronchodilator values. FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second; TGV: thoracic gas volume; TLC: total lung capacity; DLCO: diffusing capacity of the lungs for carbon monoxide.

Following biopsy, the patient received intravenous methylprednisolone, 500 mg *q.i.d.* for three days, followed by 80 mg of prednisone daily, which was slowly tapered over the next three months; he now remains on 10 mg daily. Oral cyclophosphamide, 175 mg, was initiated in the hospital, but was discontinued on September 25, 1992, because of severe diarrhoea. His medications at present include 10 mg of prednisone and four puffs *q.i.d.* of an inhaled corticosteroid preparation. The patient has had no further progression of symptoms, the cough has resolved and he rides a stationary bicycle for 30 min a day without difficulty. Follow-up lung function is shown in table 1 (April 1993). At the present time, there has been no further progression of his airflow limitation. His room air arterial oxygen saturation is now 93%, which falls to 91% after 3 min of exercise on a 10% gradient at 2.5 mph. His serum antinuclear and rheumatoid factors are no longer detectable, and he has not developed arthritis.

## Discussion

This report describes a man who suddenly developed progressive airflow obstruction without a readily identifiable cause. He had a remarkable family history of rheumatoid arthritis and a serum rheumatoid factor of 1:1,256, but without clinical evidence of rheumatoid arthritis either initially or during the 22 months follow-up period. This clinical presentation, combined with physiological tests and the computed tomographic scans, suggested the diagnosis of bronchiolitis obliterans. This diagnosis was confirmed by open lung biopsy, which demonstrated a peribronchiolar inflammatory infiltrate with destruction of the subepithelial elastic layer. Respiratory bronchiolitis has to be considered, as a result of a prior cigarette smoking history. However, both the time of onset of symptoms (18 yrs after cessation of smoking) and the extent and nature of the histological changes exclude this diagnosis. In respiratory bronchiolitis symptoms would occur in the active smoker with mild airflow limitation; histologically, this degree and type of inflammation and luminal obliteration is not seen [8]. The histological hallmark of respiratory bronchiolitis is filling of the respiratory bronchioles and adjacent alveoli with clusters of pigmented macrophages.

We suggest that the bronchiolitis obliterans in this reported case may be the first, or possibly the only, manifestation of rheumatoid arthritis. There is an increased incidence of rheumatoid arthritis in first degree relatives of similarly affected patients [10]. At present, the disease progression has abated after anti-inflammatory and immunosuppressive therapy. Further, immunoperoxidase staining revealing the presence of IgM-containing plasma cells in the bronchiolar lesions further supports this contention.

When pleuropulmonary disease precedes the joint disease in rheumatoid arthritis, it presents as either pleuritis or interstitial pneumonitis [2, 3, 5]. This is an infrequent occurrence, and the joint manifestations appear within months to several years. However, all previous reports of bronchiolitis obliterans complicating rheumatoid arthritis occurred in ongoing, well-established disease [3, 4, 7, 11–20]. Of these 31 cases, which included 13 patients who were receiving penicillamine and three patients receiving gold treatment, all but two were in women. In this respect, the bronchiolitis obliterans in the present case is unusual, occurring in a man and being the first, and so far the only, manifestation of rheumatoid arthritis.

Two other clinical situations of altered immunity result in a lymphocytic bronchiolitis with bronchoalveolar epithelial destruction. Chronic lung rejection is characterized by a progressive destruction of terminal and respiratory bronchioles [21]. Early in the process, there is an intense inflammatory infiltrate of host cells directed against the graft bronchiolar epithelium, similar to the pattern seen in the present case. The lymphocytic bronchiolitis then evolves into fibrous obliteration of compromised bronchioles. In addition, bronchiolar epithelial injury also occurs in bone marrow graft recipients, as a manifestation of the graft-*versus*-host reaction.

The possibility remains that this case represents idiopathic bronchiolitis obliterans. Of the reported cases of idiopathic bronchiolitis obliterans, only two had increased serum autoantibodies [3, 7, 8, 22]. JACOBS *et al*. [22] described a 57 year old woman with rapidly fatal bronchiolitis obliterans (8 months), who had circulating antinuclear (1:2,050) and rheumatoid (1:112) factors but without pre- or postmortem evidence of a systemic disease [4]. They suggested that the serological abnormalities resulted from the bronchiolar inflammation. GEDDES *et al*. [3] described a 62 year old woman, who had a positive antinuclear (1:80) but a negative rheumatoid factor. In neither case was the family history commented on, and both were unresponsive to corticosteroid treatment, dying within 2 yrs of disease onset. In the present case, in addition to the family history of rheumatoid arthritis, the serum rheumatoid factors were of higher titre and there was a response to treatment.

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