

# Pulmonary involvement in systemic sclerosis due to therapy and as a complication

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**ABSTRACT:** *Pulmonary involvement in systemic sclerosis due to therapy and as a complication. F. Chiappini, A. Zoli, L. Maugeri.*

Lung involvement frequently occurs in systemic sclerosis (SS), similar to other connective tissue diseases. Sometimes lung disease may be a side effect of antirheumatic

drugs. We report a case of a patient affected by SS, with isolated pulmonary hypertension, who developed bronchiolitis secondary to penicillamine. The latter was treated by withdrawal of the drug without increasing the steroids. After one month, the patient's clinical conditions appeared improved. *Monaldi Arch Chest Dis 2005; 63: 2, 111-113.*

**Keywords:** *Systemic sclerosis, bronchiolitis, penicillamine, pulmonary hypertension.*

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## Introduction

Systemic sclerosis (SS) is a connective tissue disease characterised by thickening of the skin, Raynaud's phenomenon, telangiectasis and visceral involvement of various organs, especially the oesophagus and lungs.

The most frequent pulmonary complications in SS are pulmonary fibrosis and isolated pulmonary hypertension [1, 2, 3]. SS treatment should be individualised depending on the specific problems of each patient, and on the variability of the disease manifestations [4]. Advances in organ-specific therapy, particularly calcium channel blockers in Raynaud's phenomenon, proton pump inhibitors in esophageal reflux, intravenous iloprost and endothelin receptor antagonists in pulmonary hypertension, ACE inhibitors in renal crisis, decreased morbidity and mortality in patients affected by SS [4]. Studies on aggressive therapies to prevent or improve pulmonary fibrosis are still in progress. Penicillamine, methotrexate, photopheresis, relaxin, interferons, and cyclosporine have all been studied in controlled trials with variable outcomes [4]. So far an overall therapy for remission has not been determined, but new, potentially useful agents are being investigated. The possibility of iatrogenic complications, well documented in many cases [4], is an important aspect of anti-rheumatic therapy.

We report the case of a patient affected by SS and treated with penicillamine, who developed two distinct lung disorders: pulmonary hypertension, as a complication of the disease, and bronchiolitis obliterans, presumably as a consequence of the therapy.

## Case report

In January 2003, a 61-year-old woman, affected by SS (limited variant with anti-centromere antibodies) since 1996, was admitted to our division of Pneumology because of dyspnoea on mild exertion, cough and mild fever. The patient had been treated with enalapril, nifedipine, prednisone (24 mg/day), iloprost (a prostacycline analogue), penicillamine (450 mg/day) for many years. Her dyspnoea began in October 2002. In November 2002 the patient was admitted to the Rheumatology division of our Hospital for respiratory failure. Bronchiolitis was diagnosed on the basis of clinical, radiological and functional findings. A Computed tomography (CT) scan showed air trapping areas and bronchiectasis, without signs of interstitial involvement; pulmonary function tests revealed a restrictive pattern with reduced DLCO. The forced vital capacity (FVC) was 1.97 litres, increased at the end of September to 2.52 litres. Arterial blood gas analysis showed hypoxaemia, ( $\text{PaO}_2 = 55$  mmHg versus  $\text{PaO}_2 = 77$  mmHg in September). The patient was treated with methylprednisolone (80 mg/day i.v.) for ten days, and an increase in FVC of about 200 ml was observed.

However, dyspnoea, worsened until admission to our division. On physical examination bilateral crackles in lower lung lobes were detected. Blood tests showed neutrophilic leucocytosis (WBC  $16.500 \cdot \text{mm}^{-3}$ ); erythrocyte sedimentation rate was  $23 \text{ mm} \cdot \text{h}^{-1}$ . Arterial blood gas analysis showed hypoxaemia ( $\text{PaO}_2$  68.3 mmHg) with hypocapnia ( $\text{PaCO}_2$  23.2 mmHg) and respiratory alkalosis (pH 7.553). Sputum culture was negative. However, the patient was treated with antibi-

otics (amoxicilline and then piperacilline) for some days, with disappearance of fever and reduction of cough, while dyspnoea was persisting. Pulmonary function tests showed a mixed obstructive-restrictive pattern, with an important reduction in small airway flow and DLCO (tab. 1). Chest-X-ray was normal. High resolution CT scan revealed signs of airway pathology, with mosaic pattern bilateral hypodensities in expiratory scans and small areas of thickening in interlobular and intralobular septa (fig. 1). These findings were consistent with bronchiolitis. BAL analysis showed an important increase in lymphocytes, as seen in bronchiolitis and BOOP. B lymphocytes were predominant (CD3 91.6%). CD4/CD8 ratio was normal (1.67). The patient's history was negative for any kind of risk factor, except for penicillamine therapy. Serological tests confirmed anti-centromere antibodies; anti-pneumotropic viruses, anti-Mycoplasma, anti-Clamidia, anti-Legionella antibodies were negative. These findings excluded an infectious aetiology and any connective tissue disease except SS. On the basis of the patient's history, we suspected a iatrogenic aetiology of bronchiolitis and decided to withdraw penicillamine.

After one month of follow-up, the clinical condition of our patient appeared to have improved. In March, functional and arterial blood gas values

Table 1. - Trend of functional data between January to May

Date	01/17/03	03/10/03	05/27/03
<b>FVC (L)</b>	1.77	2.22	1.91
<b>FEV<sub>1</sub> (L)</b>	1.27	1.50	1.36
<b>PEF (L/sec)</b>	2.99	3.91	3.32
<b>FEF<sub>25-75%</sub> (L/sec)</b>	0.81	0.76	0.85
<b>DLCO (ml/mmHg/min)</b>	5.9	6.5	4.9
<b>DLCO (% pred.)</b>	25	28	21
<b>PaO<sub>2</sub> (mmHg)</b>	68.3	70.8	62.6



Fig. 1. - CT scan showing bronchiolitis (01/15/03).

were slightly improved (tab. 1). In May, they worsened again (tab. 1); another CT scan was performed at the beginning of June, but it did not reveal significant alterations.

Interestingly enough, our patient showed another SS-induced lung complication: isolated pulmonary hypertension. Echocardiography demonstrated a right ventricular hypertrophy and dilatation with moderate-severe pulmonary hypertension (pulmonary arterial systolic pressure was 65 mmHg). These findings could not be related to bronchiolitis and mild hypoxaemia shown by our patient and were suggestive of an isolated form of pulmonary hypertension secondary to SS. Diagnosis of pulmonary hypertension in SS must be confirmed by right catheterisation, which is useful also to test the response to vasodilators [3]. Therefore the patient was discharged with the indication to perform a right catheterisation.

### Discussion

This case is particularly interesting for the presence, in a single patient, of two different lung complications, presumably caused by different mechanisms. The most important symptom, that brought the patient to our observation, was dyspnoea. The differential diagnosis of this symptom is extensive and can be difficult. At the onset of dyspnoea, bronchiolitis was diagnosed. The aetiology was not investigated and steroid therapy was prescribed. When the patient came to our division, the diagnosis of bronchiolitis was confirmed by CT scan. BOOP is rarely reported as a complication of SS [5], but in our case CT findings were rather suggestive of bronchiolitis obliterans, with no alveolar involvement.

Our patient had been taking penicillamine for many years. It is well known that this drug can give several pulmonary complications, among which bronchiolitis obliterans [6, 7], probably with a hypersensitivity mechanism. Excluding other possible causes, we suspected that penicillamine could have a pivotal role in the genesis of this alteration. Even if it is difficult to distinguish between complications from connective tissue diseases and side effects of anti-rheumatic therapy,



Fig. 2. - CT scan showing absence of bronchiolitis (06/05/03).

because of the lack of specific markers of drug-induced lung diseases [8], penicillamine was withdrawn. In fact, in suspected drug-induced diseases, the discontinuation of the therapy is recommended and, if there are important alterations to pulmonary gas exchanges, corticosteroids can be useful [8]. Therefore, we did not increase the dose of prednisone that our patient was already taking, even though cases have been reported in which penicillamine-related bronchiolitis has worsened despite the drug suspension and steroid therapy, the only effective solution being lung transplantation [9].

Bronchiolitis, with the functional alterations found in our patient, could explain the symptoms, thus clarifying the case. It is known that in SS, after pulmonary fibrosis (excluded by CT), the second most frequent lung complication is pulmonary hypertension. Therefore echocardiography as a screening procedure is recommended in these patients, also if asymptomatic, [2].

In this case, the reduction of DLCO and the worsening dyspnoea could be explained by pulmonary hypertension rather than bronchiolitis. Unfortunately, pulmonary hypertension associated with SS has an adverse prognosis and is difficult to treat [10]. At present, new drugs, such as iloprost, a prostaciline analogue, and bosentan, a receptorial antagonist of endothelin seem to be effective [11]. Long-term follow-up will be useful to test the effectiveness of therapy.

In conclusion, in patients affected by SS lung parenchyma, airway and pulmonary vessels should always be examined while keeping in mind that also drugs, like penicillamine, commonly used to treat this disease can induce a lung damage.

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