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# Chronic bronchiolitis in ankylosing spondylitis

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**Abstract.** The pleuro-pulmonary signs of ankylosing spondylitis are generally asymptomatic, typically represented by biapical lung fibrosis. To our knowledge, the severe bronchiolitis which is sometimes observed in other spondyloarthropathies has not been described in ankylosing spondylitis. We report two cases of severe chronic bronchiolitis in ankylosing spondylitis patients. Their clinical and radiological presentation were similar, characterized by progressive deterioration of stage III-IV dyspnea, non-reversible obstructive ventilatory defect, and CT scan showing air trapping with mosaic attenuation and ground-glass opacity in expiration. Lung biopsies confirmed the diagnosis of severe follicular bronchiolitis in one patient and constrictive bronchiolitis is suspected in the other. Only the patient with follicular bronchiolitis responded positively to treatment with low doses of macrolides. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 231-236)*

**Key words:** ankylosing spondylitis, bronchiolitis, dyspnea

**Abbrevation list**

AS: ankylosing spondylitis
CB: chronic bronchiolitis
ESSG: European Spondylitis Study Group
FEV1: forced expired volume in one second
FVC: forced vital capacity
PFTs: Pulmonary function tests
TLC: total lung capacity
RV: residual volume

Ankylosing spondylitis (AS) belongs to the group of spondyloarthropathies which includes psoriatic arthritis, Crohn's Disease and ulcerative colitis. The main symptoms are pain and stiffness in the spine. Diagnosis is based on the criteria of the European Spondylitis Study Group (ESSG) (1). To our knowledge, the severe bronchiolitis sometimes observed in other spondyloarthropathies has not been described in AS. We report the cases of two AS patients presenting with respiratory symptoms which led to the diagnosis of bronchiolitis.

## Case no. 1

A 51-year-old woman (Mrs R), who was hospitalized in January 2009 for dyspnoea which had become progressively worse over several weeks. The patient had been diagnosed with AS following pain in the joints associated chronic seronegative arthritis

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with HLA-B27 positivity, and was receiving treatment with non-steroidal anti-inflammatory drugs and methotrexate. She had been treated with sulfasalazine from 1990 to 2004. PFTs in 2005 were normal (table 1). The patient was an ex-smoker (8 pack-years) and had not smoked for one year. There was no history of genetic predisposition or occupational exposure. When the patient was admitted in February 2009, the class III dyspnoea was associated with a temperature of 38° and a productive cough. There were any sign of sinus disease or gastrointestinal symptoms. Auscultation revealed bilateral crackles. Clinical examination revealed no other abnormalities. Biological evaluation was normal apart from an increased C-reactive protein (CRP 116 mg/L). Serum protein electrophoresis and immunoelectrophoresis were normal. Chest X-ray revealed a bibasilar interstitial syndrome. The thoracic CT scan during inspiration revealed rare bronchiolar nodules with tree in buds and bronchiectasis in the two bases. In expiration, they were associated with extensive expiratory air-trapping which was predominant in the lower fields (Fig. 1a and 1b). Bronchial fibroscopy revealed 242,000 cells/ml, 82% macrophages, 10% polynuclear neutrophils, 7% lymphocytes and 1% polynuclear eosinophils on bronchoalveolar lavage. Bacteriological and mycological tests were negative. PFTs revealed an obstructive syndrome (table 1). Arterial blood gas analysis carried out in ambient air revealed isolated hypoxaemia (PaO2 at 58 mmHg). The patient was initially treated with amoxicillin and clavulanic acid, and then with oral corticosteroids at 1 mg/kg per day for several days, with no improvement. It was then decided to carry out a surgical lung biopsy of the right middle and lower lobes in May 2009. Histopathological examination revealed abraded bronchiolar epithelium replaced by a CD20, CD23, CD79a, CD3+ lymphocyte infiltrate occasionally forming lymphoid follicles (Figures 1c and 1d). These data suggested follicular bronchiolitis, and treatment with 250 mg/day azithromycin every other day was started in July 2009. Assessment in January 2010 showed an improvement of the dyspnoea, the cough and respiratory function (table 1).

## Case no. 2

A 37-year-old woman (Mrs S) presented in 2008 with progressive dyspnoea. AS had been diagnosed in 1995 following a combination of chronic inflammatory lumbar and sacro-iliac pain and HLA-B27 positivity. She had been treated with infliximab from February 2004 to June 2007, and then adalimumab from July 2007, with a satisfactory outcome. There was no history of occupational exposure to air pollutants, of genetic predisposition, or smoking. Following the onset of an NYHA class II dyspnoea, the patient consulted a chest physician for the first time in 2006. Clinical examination, in-

**Table 1.** Changes in respiratory function in the two patients

| Value (percentage of perdicted value) | Mrs R (case 1) | | | | Mrs S (case 2) | | | |
|---|---|---|---|---|---|---|---|---|
| | 09/2005 | 02/2009 | 07/2009 | 01/2010 | 06/2006 | 07/2008 | 04/2009 | 10/2009 |
| | | Diagnosis of CB | M0: start of Macrolides treatment | M6 | Onset of dyspnea | Diagnosis of CB | M0: start of Macrolides treatment | M6 |
| FVC | 3,3 (99) | 2,94 (72) | 2,92 (72) | 2,88 (89) | 2,29 (78) | 2,33 (80) | 2,13 (74) | 1,95 (70) |
| FEV1 | 2,54 (88) | 2,16 (66) | 2,22 (69) | 2,24 (81) | 1,4 (55) | 1,19 (48) | 1,18 (48) | 0,99 (41) |
| FEV1/FVC | 0,77 | 0,74 | 0,76 | 0,78 | 0,61 | 0,51 | 0,55 | 0,51 |
| FEV 25-75 | 2,17 (64) | 1,52 (40) | 1,72 (46) | 2 (61) | 0,71(20) | 0,46 (13) | 0,57 (16) | 0,4 (12) |
| TLC | 5,28 (98) | 5,33 (84) | 4,91 (77) | 5,07 (80) | 5,25 (122) | 5,41 (126) | 5,64 (131) | 5,47 (127) |
| RV | 1,98 (108) | 2,4 (114) | 1,99 (94) | 2,02 (96) | 2,96 (217) | 3,07 (223) | 3,79 (272) | 3,66 (263) |
| RV/TLC | 0,37 | 0,45 | 0,4 | 0,4 | 0,56 | 0,57 | 0,67 | 0,67 |
| DLCO | | 23(83) | 19,1 (70) | 21,5 (78) | 15,8 (67) | 12,8 (54) | | |

CB: chronic bronchiolitis; FVC: forced vital capacity; FEV1: forced expired volume in one second; FEV 25-75: forced expired volume 25-75; TLC: total lung capacity; RV: residual volume; DLCO: Diffusion capacity Lung Carbon Monoxide

cluding pulmonary auscultation, revealed no abnormalities. Chest X-ray was normal. Serum protein electrophoresis was normal. Pulmonary function tests (PFTs) revealed severe airway obstruction (table 1) with no reversibility following bronchodilator therapy. Arterial blood gas analysis car-

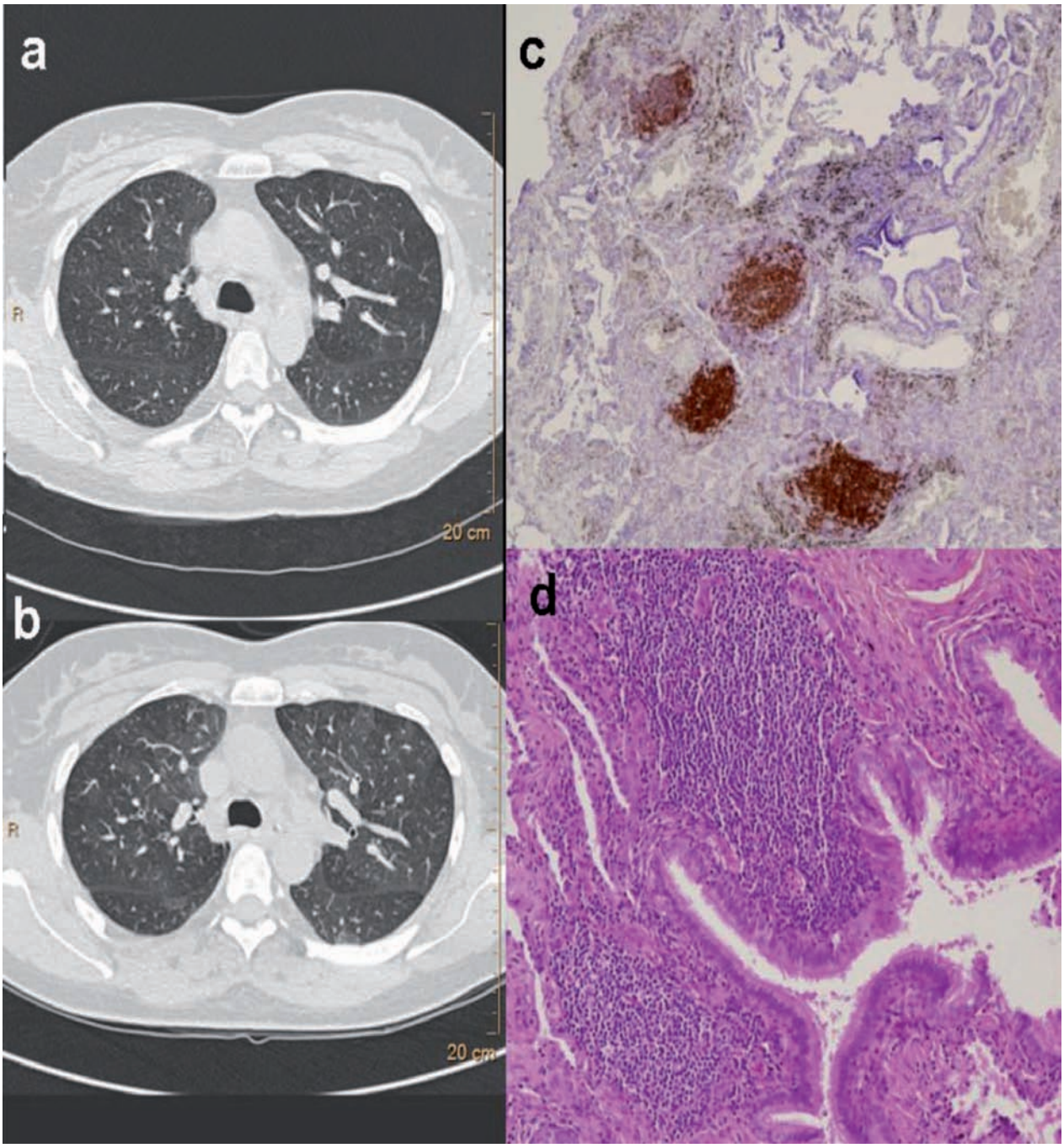


**Fig. 1.** Case 1: Millimetric sections of CT scan on inspiration (a) and expiration (b): mosaic pattern with alternation of air-trapping and "ground-glass" zones suggesting bronchiolar disease. (c) Histopathological analysis of lung biopsy. Magnification x 20, anti-CD20 labeling: clusters of peribronchiolar lymphocyte infiltrate. Presence of hyperplastic lymphoid follicles with reactive germinal centers distributed along bronchovascular bundles. peribronchiolar lymphocytic infiltration into the interstitium often accompanies the peribronchiolar lymphoid aggregates. (d) HES stain, magnification x 200: presence of peribronchiolar lymphoid follicles

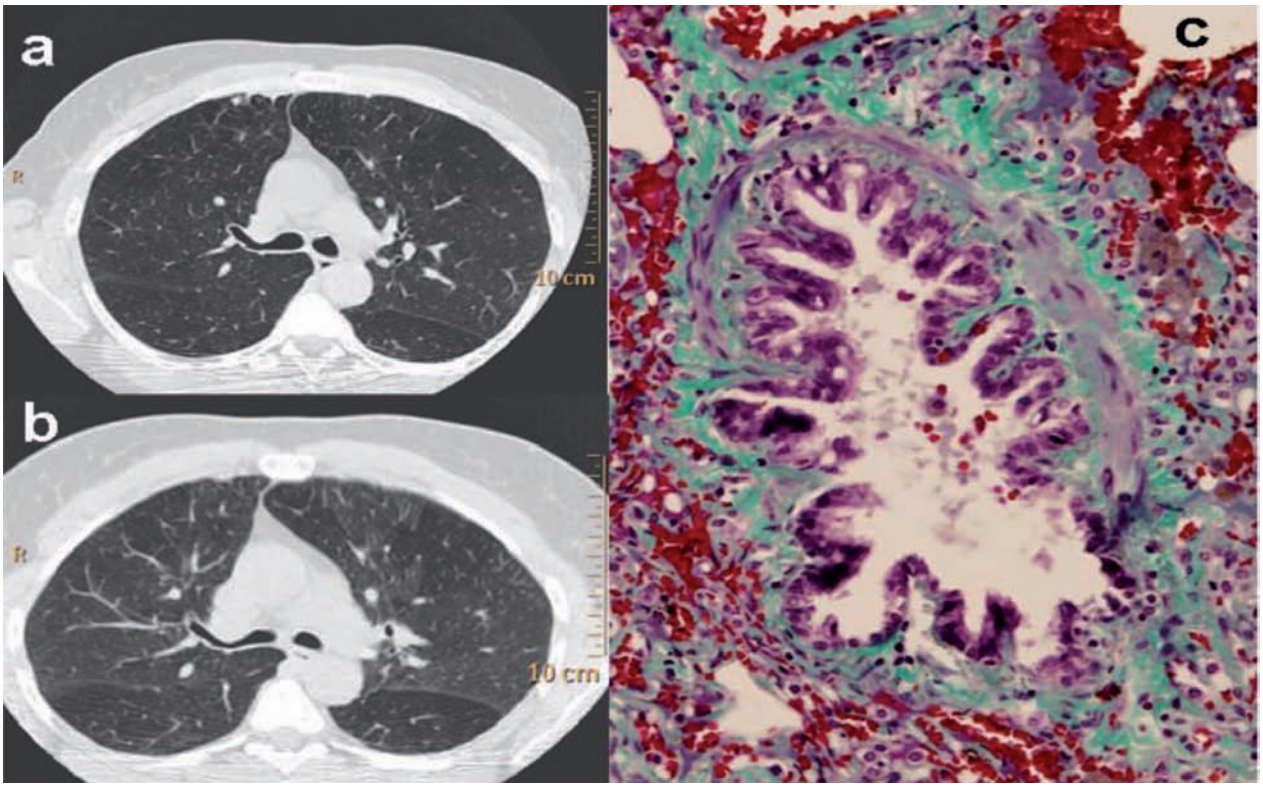


**Fig. 2.** Case 2: Millimetric sections of thoracic CT scan on inspiration (a) and expiration (b): mosaic pattern with alternation of air-trapping and "ground-glass" zones suggesting bronchiolar disease. (c) Histopathological analysis of lung biopsy. Magnification: x200, Masson's trichrome stain: constrictive bronchiolitis with thickening of the bronchiolar wall due to collagen deposit (in green), partial destruction of muscular fibres and minimal peribronchiolar lymphocyte infiltration.

ried out in ambient air and at rest was normal. There was no improvement following treatment with fluticasone plus salmeterol followed by systemic corticotherapy with 0.5 mg/kg prednisolone per day for 3 months. The dyspnoea worsened, reaching NYHA class III/IV, and the patient was reassessed in October 2008. There were any sign of sinus disease or gastrointestinal symptoms. Clinical examination and chest radiography were unchanged. Serum protein electrophoresis and immunoelectrophoresis were normal. Airway obstruction had worsened (table 1). Thin-section inspiratory CT scan revealed rare bronchiectasis. The analysis in expiration revealed area of air trapping with ground glass in mosaïc predominating in anterior regions, at the upper and middle lobes (Figures 2a and 2b). Bronchial fibroscopic examination revealed alveolitis in bronchoalveolar lavage (147,000 cells/ml, 80% macrophages and 20% lymphocytes, CD4/CD8 ratio = 1.83). Microbiological samples were negative. It was decided to carry out surgical lung biopsy of the middle lobe. This revealed rare lesions characterized by small alterations in the walls of bronchiole (collagen deposits and fibroblastic infiltration) (Fig 2c). It was mostly an aspect of "disappearance" of bronchioles suggesting to a late stage of constrictive bronchiolitis. Treatment with 250 mg azithromycin every other day was started in April 2009 for six months, but produced neither clinical nor functional improvement (table 1).

## Discussion

We report the cases of two patients with ankylosing spondylitis who developed severe histologically proven bronchiolitis. The clinical-functional and radiological picture was identical, but in one case the bronchiolitis was follicular and in the other case, it was suspected to be constrictive. Response to anti-

inflammatory therapy with low-dose macrolides differed in the two cases.

AS belongs to the group of spondyloarthropathies (2-5). The pulmonary disorders of AS are often asymptomatic (6). Respiratory function tests generally reveal moderate defects, with an obstructive syndrome (0 to 13% of patients) or a restrictive syndrome (20 to 57% of patients) (2-5, 7-13). Radiography reveals pulmonary opacities in 1.3 to 30% of patients (4). CT studies (2-5, 7-10, 13) have found frequent anomalies (40 to 85% of patients) in patients with few or no symptoms. These abnormalities are essentially apical fibrosis and emphysema. Mosaic ground-glass pattern (4 to 36%), centrilobular micro-nodules (13 to 25%), bronchial thickening (4 to 26%) and expiratory air-trapping (39 to 48%) have frequently been found, suggesting airway disease, and particularly chronic bronchiolitis (2-5). Expiratory air-trapping, a characteristic sign of bronchiolitis, is associated 7 out of 10 times with mosaic ground-glass pattern on inspiratory CT scan (3). However, while this diagnosis is often suggested, constrictive bronchiolitis has only been histologically proved once in the literature (14). The few symptoms generally shown by these patients in whom air-trapping is found on CT scan could explain the lack of invasive investigation required for histological diagnosis of chronic bronchiolitis. Our two AS patients had a severe, progressive respiratory disability, characterized by a class III-IV dyspnoea, a severe obstructive ventilatory disorder, and signs of air-trapping on CT scan associated with lack of response to corticosteroid treatment. These elements led us to carry out a surgical pulmonary biopsy confirming the follicular bronchiolitis diagnosis, in one case. Histologically, the constrictive bronchiolitis is often patchy and focal, making difficult diagnosis in small samples. This fibrotic constrictive lesion develops externally to the airway lumen, constricting the airway in a concentric manner with eventual obliteration of the lumen.Advanced cases may be especially inconspicuous because of lack of active inflammation and disappearance of bronchioles. This could explain only probable diagnosis of constrictive bronchiolitis in the other patient. After eliminating other aetiologies of bronchiolitis such as viral infections, connective tissue disorders, medication-induced causes, and immune deficiencies, we hypothesized a link between the severe bronchiolitis and ankylosing spondylitis.

Bronchiolitis can be found in certain spondyloarthropathies other than AS includes psoriatic arthritis (15, 16). Similarly, in Crohn's disease and ulcerative colitis that can be associated with spondylarthropathy signs, 0.2% of patients present with respiratory symptoms related to severe bronchiolitis (17). Mahadeva et al. studied the clinical and CT respiratory symptoms in 14 patients with ulcerative colitis and 3 with Crohn's Disease (18). Nine of the 17 patients presented with expiratory air-trapping associated with a tree-in-bud pattern. Our patients provided no evidence of chronic inflammatory disorders of the intestine associated with their AS which could have been responsible for the respiratory picture.

There is no agreed treatment for chronic bronchiolitis. Immunosuppressors such as corticosteroids or cyclophosphamide have been proposed, but with very mixed results (19). Follicular bronchiolitis clinical course with treatment and the prognosis are relatively good (20). Macrolides with a macrocycle of 14 or 15 atoms have been successfully given as an alternative therapy to some patients with follicular bronchiolitis in a context other than AS (19, 21, 22). Macrolides seem to act on the inflammation induced by the polynuclear neutrophils by inhibiting their activity and recruitment (23). Verleden found that patients with post-lung transplant bronchiolitis obliterans who had neutrophil alveolitis responded better to low doses of macrolides (24). Our patient who responded well to macrolides presented with neutrophil alveolitis on bronchoalveolar lavage in a context of follicular bronchiolitis. The lack of response to macrolides in the other patient could be explained by the histological picture, lung samples revealing a proliferation of fibroblasts and collagen deposits, characteristic of constrictive bronchiolitis. Irreversibility is one of the common characteristics of constrictive bronchiolitis (25) and usually do not respond to treatment (20). Vanaudenaerde et al found that post-lung transplant patients with bronchiolitis obliterans who did not respond to macrolides showed aspects of fibroproliferative bronchiolitis (23).

In conclusion, observations of our two patients demonstrate that AS, like other spondyloarthropathies, can be complicated by severe bronchiolitis. This disorder has rarely been reported, possibly due to the fact that diagnosis is suspected on

expiratory CT scan, which is not always carried out on account of the paucity of clinical symptoms. The effectiveness of treatment with low-dose macrolides requires further investigation. The response to macrolides could depend on the histopathological type or the extent of neutrophilic inflammation.

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