ERJ Express. Published on January 7, 2009 as doi: 10.1183/09031936.00091608

Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis

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Running head

Bronchiolitis and rheumatoid arthritis (Character count 38)

Word count 4 217

Abstract (194 words, word limit 200)

The characteristics of patients with rheumatoid arthritis (RA) who develop obliterative bronchiolitis characterised by severe airflow obstruction have been hitherto poorly investigated. We conducted a retrospective study of 25 patients with RA and functional evidence of obliterative bronchiolitis (FEV1/FVC <50% and/or RV/TLC >140% of predicted). Patients (64 ± 11 years) included 17 never-smokers and 8 ex-smokers (10.5 ± 5.4 pack-years). The diagnosis of RA preceded respiratory symptoms in 88% of cases. Dyspnea on exertion was present in all patients and bronchorrhea in 44%. HRCT findings included: bronchial wall thickening (96%), bronchiectasis (40%), mosaic pattern (40%), centrilobular emphysema (56%), reticular and/or ground glass opacities (32%). Pulmonary function tests showed: FEV1 41 ±12% of predicted, FEV1/FVC 49 ±14%, FVC 70 ±20% of predicted, RV 148 ±68% of predicted, and RV/TLC 142 ±34% of predicted. Lung biopsy available in 9 patients demonstrated constrictive, follicular, and mixed bronchiolitis. Patients were followed for a mean of 48.2 ± 49 months. Treatment was poorly effective. Chronic respiratory failure occurred in 40% of patients, and 4 patients died. Obliterative bronchiolitis associated with RA is a severe and underrecognised condition leading to respiratory failure and death in a high proportion of patients.

Keywords

Rheumatoid arthritis; airflow obstruction; small airways disease; bronchiectasis; emphysema; obliterative bronchiolitis.

Introduction

Pulmonary manifestations may account for 10 to 20% of all rheumatoid arthritis (RA)-related deaths, ranking second after cardiovascular disease (1). These include opportunistic pulmonary infections, drug-induced lung disease, and pulmonary manifestations directly associated with RA, which may affect all anatomic compartments of the lung, with the exception of pulmonary hypertension, which is distinctly rare in RA (2). Pleural disease (with or without effusion), interstitial lung disease (most commonly with a histopathological pattern of usual interstitial pneumonia), and rheumatoid (necrobiotic) lung nodules, are the most frequent manifestations, with a prevalence varying according to the investigation employed.

Airway complications include cricoarytenoid arthritis, bronchiectasis (often not clinically significant), and small airways disease, which may cause airflow obstruction first reported in 1977 in six patients, five of whom had RA (3). We use the terminology of *bronchiolitis obliterans* (historically used for the histopathological lesions) to name the pathologic feature of reduced lumen of the bronchioles, and *obliterative bronchiolitis* (OB) to name its functional counterpart with airflow obstruction. The estimated prevalence of bronchiolar disease in RA varies widely (from 8% to 65%) between studies (4-8) depending on the criteria used. It may correspond pathologically to either fibrosing (constrictive bronchiolitis obliterans) or cellular bronchiolitis (follicular bronchiolitis, or less commonly diffuse panbronchiolitis) (2, 4, 5).

Although some of the characteristics of bronchiolar disease have been reported in systematic studies of consecutive patients with RA undergoing pulmonary function tests and (or) high-resolution computed tomography (HRCT) of the chest, regardless of pulmonary symptoms (6-8), the small subgroup of RA patients with severe airflow obstruction remains poorly investigated. The current study provides a detailed analysis of a homogenous group of 25

patients with functional evidence of OB (as defined by severe airflow obstruction without clinically relevant tobacco smoking, and with or without pathological diagnosis). Here, we show that the clinical radiological presentation of RA-associated severe OB may be nonspecific and resemble chronic obstructive pulmonary disease (COPD) with emphysema, with inconstant direct signs of bronchiolitis at HRCT. Further, we show that some features of interstitial lung disease may be present in addition to the airways disease in as many as one third of the cases.

Patients and methods

Case recruitment

This retrospective study was conducted by the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P), a collaborative group of over 200 physicians dedicated to the study of rare (so-called orphan) pulmonary diseases. Members keep in regular contact through newsletters and an annual meeting, and constitute a motivated group with experience in orphan and systemic diseases. A letter was sent to participating physicians, asking them to report cases of airways disease with severe airflow obstruction associated with RA according to the following inclusion criteria and encountered between January 1987 and February 2007. Reports to the GERM"O"P registry were nominative for patients who gave their written consent, or anonymous otherwise. The clinical data were collected through a detailed questionnaire sent to each participating physician who had reported cases. Queries were sent for missing data.

Inclusion criteria

Patients were included in the study if they fulfilled the following two criteria: 1) RA diagnosed according to the American Rheumatism Association (score greater than 4) (9), and 2) presence of small airways disease demonstrated by severe airflow obstruction (obliterative

bronchiolitis) as defined by forced expiratory volume in one second (FEV1) / forced vital capacity (FVC) less than 50% and (or) severe air trapping with residual volume (RV) / total lung capacity (TLC) higher than 140% of predicted value. In addition, patients might have evidence of bronchiolitis on lung biopsy specimen.

To select cases in which small airways disease was confidently attributable to RA, only patients with a history of cumulative tobacco smoking of less than 20 pack-years were included. Only cases for which pulmonary function data and chest imaging were available for review were included. Bronchoalveolar lavage (BAL) and echocardiography were performed as part of the patients evaluation according to the judgement of the physician.

Clinical analysis

Medical records were reviewed for clinical manifestations, including respiratory and extra-respiratory symptoms with a special focus on respiratory symptoms, subcutaneous rheumatoid nodules, Raynaud phenomenon, Sjögren syndrome, pulmonary function tests, and laboratory tests. Chest radiographs and HRCT scans of the chest were reviewed by participating physicians, and assessed for presence of hyperinflation, reticulation (irregular linear opacities), areas of ground glass opacification, consolidation, nodules, bronchiectasis, bronchiolectasis, expiratory air trapping (lobular areas with decreased attenuation, and mosaic pattern), and bronchial wall thickening. Reports of histopathological analysis of open lung biopsy were collected. The authors also reviewed drug therapies received by the patients and their potential impact on respiratory symptoms and lung function, including anti-rheumatoid regimens, and outcome.

Pulmonary function tests

Pulmonary function tests were performed with standard protocols, and following European Respiratory Society guidelines. Values were expressed as a percentage of predicted values, except for forced expiratory volume in one second (FEV1) / forced vital capacity (FVC) which was expressed as absolute percentage. FEV1 and FEV1/FVC were assessed before bronchodilators, then 10-15 min after the administration of short acting inhaled beta-2-agonist. Airflow obstruction was defined by a post-bronchodilator FEV1/FVC ratio <70% of predicted with FEV1 <80% of predicted, and severe airflow obstruction by post-bronchodilator FEV1/FVC ratio <50% and/or RV/TLC > 140%.

Data analysis

Data were reported as mean ± standard deviation, and were expressed as absolute values or as percent of predicted values as appropriate. Categorical variables were compared by the Chi-2 test and continuous variables by the Student' t test. A p value of < 0.05 was considered significant. Microsoft Excel 2003 and SPSS 13.0 were used for data analysis.

Results

Patients characteristics

Twenty five patients (18 females, 7 males) were included in the study, with a mean age of 64 ± 11 years (range 37-81). Seventeen patients (68%) were never smokers; 8 were ex-smokers (10.5 ± 5.4 pack-years, with a mean age of 62 ± 8 years), but none had been diagnosed with COPD before the diagnosis of RA-related airways disease. Respiratory occupational exposure was present in a single patient who had worked in a gasoline service station with some exposure to petrol extracts. None of the patients had a history of atopy, asthma, severe

respiratory infection during childhood, or other significant chronic disease other than RA, which may have affected pulmonary lung function (except for one patient with Crohn colitis).

According to inclusion criteria, all patients had both RA and evidence of severe fixed airflow obstruction (18 patients with FEV1/FVC < 50%, 2 patients with RV/TLC > 140%, and 5 patients with both criteria), including 9 patients with further pathological evidence of bronchiolitis on lung biopsy.

Clinical presentation

The mean interval between the diagnosis of RA and the onset of respiratory symptoms was 7.8 ± 8.2 years (range, 1-35); the mean interval between the diagnosis of RA and the diagnosis of bronchiolitis was 9.5 ± 10 years (range, 1-45); and the mean interval between respiratory symptoms and diagnosis of bronchilitis was 19 ± 32 months (range, 1-73). Respiratory manifestations developed after the diagnosis of RA in 22 cases, were concomitant in 1 case, and preceded the rheumatoid disease in only 2 cases (by 8 and 20 months, respectively).

The major respiratory symptom was chronic dyspnea on exertion, present in all patients, with 6, 10, and 9 cases classified as New York Heart Association II, III, and IV, respectively. Sixteen patients (64%) were complaining of cough, and bronchorrhea was present in 11 (44%). Chest pain was reported in 3 patients. Crackles, wheezes, and squeaks, were found in 13, 13, and 6 patients, respectively. Chest hyperinflation was present clinically in 11 patients. Finger clubbing was not reported.

The mean body mass index was 22.5 ± 4 kg/m^2. The most frequent extra-respiratory symptoms were asthenia (17 cases), fever (6 cases), and weight loss (12 cases). At the time of the onset of OB, RA was symptomatic in 8 of 25 patients, who complained of morning joint

stiffness, soft tissue swelling, and symmetrical peripheral joint pain. Subcutaneous rheumatoid nodules, Raynaud phenomenon, and Sjögren syndrome were present in 2, 1 and 2 cases, respectively. Another disorder was present in 3 patients, with Hashimoto thyroiditis, Crohn colitis, and vitiligo, respectively. Additional systemic involvement by RA was diagnosed in 5 patients, affecting the heart (2 cases), muscle (1 case), and skin (2 cases). No patient had RA-associated vasculitis.

Pulmonary function tests

The pulmonary function parameters are listed in table 1. According to inclusion criteria, all patients had both RA and evidence of severe fixed airflow obstruction (18 patients with FEV1/FVC < 50%, 2 patients with RV/TLC > 140%, and 5 patients with both criteria). Transfer factor for carbon monoxide (DLco) was 78 ± 16%, and transfer coefficient of the lung (Kco) was 104 ± 24% of predicted.

Mean PaO_2 on room air was 8.8 kPa ± 1.7, with PaO_2 less than 7.5 kPa in 34% of patients, without significant change depending upon position or exercise (table 1). The mean 6-min walk distance was 335 ± 145 m, with a mean decrease of pulse oxygen saturation of 9% (from 94 ± 2.6% initially to 85% ± 6.2% at the end of the test).

Chest imaging

The most common findings on chest radiograph were pulmonary hyperinflation (64%), diffuse lung infiltrates (44%), and bronchiectasis (40%). Diffuse alveolar opacities and nodular shadows were reported less frequently (32% and 16% of cases, respectively).

Bronchial wall thickening, centrilobular emphysema (figure 1), lobular areas of decreased attenuation with mosaic pattern indicative of air trapping, and bronchiectasis (figure 2) were the most frequent HRCT findings, present in 96%, 56%, 42%, and 40%, respectively (Table

2). Areas of ground glass attenuation were found in 44% of cases, and reticular opacities with mild honeycombing in the lower lobes were present in 16% of cases. An association of diffuse emphysema and interstitial opacities of the lower lobes (including ground glass attenuation) was present in 32% of cases; infiltrative opacities were bilateral and diffuse, without central or peripheral predominance. Pleural effusion was observed in 4 patients, and rheumatoid lung nodules in 9 patients.

Biology and broncho-alveolar lavage

BAL performed in 12 patients showed increased leukocyte count in 10 patients, with a predominant increase of neutrophils at differential cell count (neutrophils 29 ± 35%, lymphocytes 13 ± 12%, without eosinophils). Infectious pathogens were identified by BAL during the course of disease in 9 patients (*Pseudomonas aeruginosa*, 3; *Aspergillus fumigatus*, 2; *Streptococcus pneumoniae*, 2; *Haemophilus influenzae*, 1; *Staphylococcus aureus*, 1), with presence of bronchiectasis at HRCT in 8 of 9 cases.

Erythrocyte sediment rate was increased in all patients (46 ± 28 mm at 1 h), and serum C-reactive protein was elevated (29 ± 30 mg/L). Rheumatoid factor and anti-nuclear antibodies (without specificity for soluble nuclear antigens or native DNA) were present in 24 (96%) and 12 patients (48%), respectively.

Lung pathology

Lung pathology of video-assisted thoracoscopic or open lung biopsy or explanted lung was available in 8 and 1 case, respectively, and analysed by an experienced lung pathologist (FTB). A histopathological pattern of bronchiolitis was found in all cases, occasionally associated with accessory lesions consistent with usual interstitial pneumonia or diffuse alveolar damage (1 case each). Bronchiolar changes consisted in chronic constrictive

bronchiolitis (6 cases), follicular bronchiolitis (1 case), and mixed constrictive/follicular bronchiolitis (2 cases) (Figure 3). Constrictive bronchiolitis was characterised by the presence of concentric fibrosis of the bronchial wall, with severe narrowing of the bronchiolar lumen and (or) bronchiolectasis. Inflammatory infiltrates (predominantly lymphocytic) were present within the wall of bronchioles in 4 cases. Centrilobular emphysema adjacent to bronchiolar changes was further present in 5 cases.

Echocardiography

Echocardiography performed in 16 patients showed normal left ventricular function in all patients. The estimated systolic pulmonary artery pressure was above 35 mmHg in 6 patients, with a mean of 52.6 ± 13.3 mmHg, and was normal in the remaining patients. No patient had clinical evidence of right heart failure at diagnosis.

Treatment and outcome

All patients were receiving treatment for RA at the onset of the airways disease. Twenty-four (96%) were receiving oral corticosteroids, and 22 were taking non-steroidal anti-inflammatory drugs. Fifty two percent of patients had received methotrexate for a mean duration of 46 months, 40% intra-muscular gold salts (mean duration 20 months), 48% D-penicillamine (mean duration 25 months), 20% hydroxychloroquine (mean duration 62 months), 20% leflunomide (mean duration 19 months), 12% salazopyrine (mean duration 33 months), 12% anti-TNF-α regimens (mean duration 21 months), and 4% tiopronine. To evaluate the possible influence of treatment of rheumatoid arthritis on the development or severity of OB, the main HRCT findings, pulmonary function tests, and pathology findings were compared according to treatment and tobacco history (table 3). FEV1 was lower in patients who had ever received D-penicillamine as compared to those who had not been treated with this drug (800 ± 320 ml versus 1240 ± 320 ml, $p<0.01$). There was also a trend

toward lower FEV1 in patients who had been treated with methotrexate or gold salts. Ex-smokers had lower RV/TLC than never-smokers (119 ± 27 versus 151 ± 23 %, $p<0.05$), with a trend toward higher FEV1 in smokers. RA treatment and smoking history had no effect on HRCT and pathology findings.

Treatment of the respiratory disease included oral corticosteroids in 24 patients (96%), associated with immunosuppressive treatment in 24 cases (methotrexate, 9 patients; leflunomide, 4; hydroxychloroquine, 4; anti-TNF-α, 3; azathioprine, 1; cyclophosphamide, 3). D-penicillamine was stopped consecutively to the emergence of airflow obstruction in 2 patients. Improvement of pulmonary symptoms was obtained in only 4 patients, 3 of whom received corticosteroids, and 2 received anti-TNF-α regimens. Pulmonary function tests improved in one patient treated with etanercept (10), with stabilisation in another patient. However, imaging and pulmonary function parameters were not significantly modified by treatment in the remaining patients.

Patients were followed for a mean of 48.2 ± 49 months. Symptoms worsened in 52% of patients, and were unchanged in 32% patients. Bronchial and (or) pulmonary infections occurred in 60% of patients, and pneumothorax in 12%. Acute respiratory failure occurred in 48% of patients. Sixteen percent of patients developed right cardiac failure during follow-up, all of them with pulmonary hypertension at echocardiography. Chronic respiratory failure requiring oxygen supplementation occurred in 40% of patients One patient underwent single lung transplantation. Four patients died of respiratory failure.

Discussion

Here, we showed that OB associated with RA is a severe condition, with imaging and functional features resembling those of COPD, with the exception of less impaired carbon

monoxide transfer capacity of the lung. Typical imaging features of bronchiolitis were inconstant at HRCT, and interstitial lung disease was occasionally associated. Respiratory failure was common.

Among the connective tissue diseases, OB has been reported mostly in RA (11), although it may also be encountered in Sjögren disease (12), and only exceptionally in systemic sclerosis (13). The association of OB and RA was initially described by Geddes *et al* in 6 patients (5 of whom had RA) with rapid progressive dyspnea and airflow obstruction (3), with bronchiolitis obliterans demonstrated at necropsy in 4 cases. Most cases occur within five years after the diagnosis of RA, but OB may be a presenting manifestation of RA in 10 to 20% of patients (2), as in 2 of our patients.

Since the original description, several studies reported that mild to moderate airways involvement is frequent in patients with RA regardless of pulmonary symptoms (8, 14, 15). Hence, airways obstruction (reduced FEV1/FVC) was present in 13.6% of consecutive nonsmoking patients undergoing systematic evaluation in one study (16), and some HRCT abnormalities suggestive of airways disease were present in 34% of patients in another study (8). The disease course is usually uneventful in poorly symptomatic patients with only mild airflow obstruction and (or) isolated bronchiectasis detected by systematic evaluation (17), a condition distinct from that of symptomatic patients with severe OB (as in this study).

The patients reported in the present study – the largest series of patients with RA-related severe OB - presented with an abrupt or progressive onset of dyspnea and dry cough, often with squeaks and crackles at auscultation, as previously reported (3). However, the mean delay between respiratory symptoms and diagnosis was 19 ± 32 months, further delaying onset of treatment. The diagnosis may be especially delayed in patients with progressive onset of symptoms, and those with OB presenting concomitantly or before the diagnosis of RA.

Pulmonary function test revealed airflow obstruction, which seemed to progress more rapidly than in COPD, as described (3, 15, 18), with mild to moderate hypoxemia. In addition to airflow obstruction (with decreased FEV1/FVC), hyperinflation demonstrated by increased RV and RV/TLC was common. To improve early detection of disease, we suggest sequential pulmonary function tests (including measurement of RV and RV/TLC) be performed in any RA patient with progressive dyspnea on exertion. In addition, lung biopsy should be considered more frequently in this condition, except when contra-indicated by the severity of disease or comorbidities, as it might provide access to definitive diagnosis and early therapy. However, we consider that the diagnosis of OB may be done without a lung biopsy in a patient with RA and progressive severe airflow obstruction in the absence of significant tobacco smoking and no other cause of airflow obstruction. Treatment with bronchodilators and oral corticosteroids was ineffective in most (84%) of the patients, as described (3). Some improvement was obtained in two patients who received off-label anti-TNFα regimen for OB (one was previously reported (10)). Lung function further deteriorated in half of the patients, despite therapy, with chronic respiratory failure in 40%, and death in 16%. The use of high-dose corticosteroids, cyclophosphamide, and of erythromycin, has been suggested (6, 19, 20), but has been poorly evaluated. It is not known whether early diagnosis and treatment with inhaled or high-dose oral corticosteroids or cyclophosphamide might decrease progression of OB. Although not formally compared, overall survival seemed lower than that of COPD with similar airflow obstruction, and was almost similar to that of post-transplant bronchiolitis obliterans syndrome (21, 22). No treatment recommendation can be provided from published data and the present study. However, it is our current experience-based practice in patients with documented and progressive severe RA-associated OB (and especially those with cellular bronchiolitis at biopsy) to propose combination therapy with bronchodilators, inhaled

and oral corticosteroids; macrolides, pulse intravenous cyclophosphamide, or etanercept (with methotrexate) may be considered as second line therapy.

Consistent with previous studies (3, 11, 15), 13 of 25 patients had received previous therapy with D-penicillamine or tiopronine, and 10 of 25 had received gold salts, respectively, raising the concern of drug-induced bronchiolar disease. In addition, FEV1 was significantly lower in patients who had ever been treated with D-penicillamine as compared to those who had not, with a similar trend of more severe impairment of lung function in patients ever treated with methotrexate or gold salts. A majority of patients with RA and OB are women (20), contrasting with the increased prevalence of interstitial lung disease associated with RA in men (11). Whether associated Sjögren disease affects the development of OB is controversial (8, 16, 23). In addition, one study reported a higher frequency of OB in patients with human leukocyte antigen (HLA)-B40 and –DR4 (24). The risk of OB was not related to the severity of rheumatic disease, as RA was controlled by treatment in two thirds of our patients.

Only 8 of 25 patients in this series were ex-smokers, with a mean of only 10 pack-years. It is therefore the conviction of the present authors that progressive and severe airflow obstruction could be explained in them neither by tobacco smoking, nor by any known cause other than RA (11). In fact, pulmonary function was less severely impaired in ex-smokers than in never-smokers. Most patients had isolated, unexplained, and progressive obstructive lung disease, somewhat similar to COPD (although usually with more rapid functional worsening and less impaired carbon monoxide transfer capacity of the lung). Hence, the GOLD functional definition of moderate, severe, and very severe COPD (25), was fulfilled in 20%, 56%, and 24% of our 25 patients, respectively. Interestingly, cigarette smoking is associated with an increased risk of developing RA (26) and with RA activity, an association likely due to post-translational protein modifications induced by tobacco-derived products (27). The relationship

between tobacco smoking and the development of lung disease in RA is unclear (2). Although severe OB may develop without tobacco smoking in patients with RA, it is conceivable that smoking might have contributed to preexisting small airways disease in ex-smokers, and all RA patients should be discouraged from smoking. Lymphocytic activation within bronchus-associated lymphoid tissue (where the immunopathology of RA mostly takes place within the lung) also likely contributes to bronchiolar disease in RA (28), with involvement of both B lymphocytes and CD4+ T lymphocytes (28, 29). Whether the onset or outcome of OB may be affected by the presence and treatment of gastro-esophageal reflux in patients with RA is unknown and would require specific investigation.

HRCT features consisted mostly of indirect signs of bronchiolitis, with a mosaic pattern reflecting air trapping in 44% of cases, comparing with 20 to 32% in studies conducted in RA patients regardless of symptoms (7, 8). The frequency of mosaic pattern was probably underestimated, however, since expiratory images were not systematically obtained. Part of the imaging was performed using single detector row scanners. Direct signs of bronchiolitis (centrilobular micronodules and tree-in-bud opacities) and thin-walled cysts were also reported in previous imaging studies of consecutive patients with RA, with centrilobular opacities reported in 6% (8), 28% (7), and 71% (30) of patients.

One unexpected finding of our series was the high-frequency of diffuse emphysema lesions at HRCT (56% of patients, 5 of them were smokers) and on histopathology (5 of 9 cases with biopsy, including 3 smokers), a prevalence higher than in previous studies (i.e. 4% to 39% (7, 8, 31, 32)), which may be partly due to the inclusion criteria that included air trapping. Centrilobular emphysema was not influenced by a history of moderate tobacco smoking in 32% of patients ; it may conceivably develop as a late result of chronic bronchiolitis, as in smokers (33), and / or be related to air trapping. Interstitial lung disease was also present in

more than half of the patients with OB, consistent with previous reports (5, 28); interstitial lung disease was mild in most patients but evolved to severe pulmonary fibrosis and death in one patient. In about a third of patients, both emphysema and infiltrative opacities were present, somewhat reminiscent of the syndrome of combined pulmonary fibrosis and emphysema identified in smokers (34, 35). Taken together, our findings suggest that severe OB occurring in RA present significant similarity with COPD, especially with emphysema at chest imaging, and subtle changes suggestive of bronchiolar disease may be overlooked.

Bronchiectasis present in 8 to 30% of patients with RA (7, 16, 31, 36) has been associated with a higher risk of airflow obstruction, pulmonary infections, and death (37). Bronchiectasis, bronchial wall thickening, cough, and bronchorrhea in our patients with OB suggests comprehensive airways disease, involving both bronchioles and bronchi of all size. Airway disease with OB occurring in RA therefore compares to that complicating bone marrow transplantation (21)(38) and lung transplantation (21).

Pathological analysis of the lung biopsy available in 9 of 25 cases (a proportion possibly greater than that of current clinical practice) demonstrated bronchiolitis in all cases, predominantly with constrictive fibrotic bronchiolitis obliterans and peribronchiolar fibrosis (so-called bronchiolocentric fibrosis (39)), and occasionally follicular or mixed constrictive/follicular bronchiolitis, similar to previous studies (5, 6). Both pathological patterns often coexist in patients with RA (6). Although constrictive and follicular bronchiolitis share common clinical, functional, and imaging characteristics, follicular bronchiolitis might theoretically respond better to therapy.

The limitations to our study are its retrospective and multicentric nature; the management of patients was not uniform, limiting interpretation of effect of therapy. Expiratory chest HRCT was not performed in all patients. Referral bias likely occurred, with the most severe cases

being referred to participating tertiary centers. Although inclusion bias may have occurred as in any retrospective study, we consider that it was limited by our including patients in whom lung biopsy was not performed (with potentially more severe disease), therefore our series reflects current clinical practice. The design of the study did not allow an evaluation of the epidemiology of disease (and especially its actual prevalence), and evaluation of the spectrum of severity of disease (and especially patients with mild or moderate disease were not included), but rather focused specifically on describing the subpopulation of patients with severe OB, to improve our knowledge regarding the manifestations, chest imaging, outcome, and possibly therapy of this orphan condition, and to further justify and promote an earlier detection. While only severe cases were included, it cannot be ruled out that inclusion may be skewed toward cases with less progressive disease and better outcome (with ensuing longer follow-up facilitating recollection by the physician). As patients included were diagnosed over a period of 20 years, image acquisition was not standardised. The limited number of patients did not allow multivariate statistical analysis.

In conclusion, we describe a homogenous cohort of 25 patients with severe OB attributable to RA, characterized by severe dyspnea, lung hyperinflation, bronchial wall thickening, frequent bronchiectasis, and centrilobular emphysema at chest imaging. Disease presentation was somewhat similar to that of COPD in tobacco-smokers. Severity of disease was variable. Response to oral corticosteroids was poor, frequently leading to chronic respiratory failure and possible death.

Table 1. Pulmonary function tests.

	mean ± SD	% of predicted	Number of patients tested
FEV1, mL	1000 ± 380	41 ± 12	25
FEV1 post bronchodilator, mL	1100 ± 403	46 ± 13	20
FVC, mL	2119 ± 797	70 ± 20	25
FEV1/FVC, %	49 ± 14	-	25
FEF_{25-75}, mL	518 ± 336	17 ± 10	19
FEF_{25-75}/FVC, %	16 ± 4	-	19
FEF_{25}, mL	175 ± 74	13 ± 5	20
FEF_{50}, mL	424 ± 256	13 ± 6	23
FEF_{75}, mL	1033 ± 783	21 ± 14	14
RV, mL	2965 ± 1520	148 ± 68	19
TLC, mL	5280 ± 1750	103 ± 33	19
RV/TLC, %	52 ± 13	142 ± 34	19
DLco, mmol/mmHg/min	8.4 ± 5.1	78 ± 16	14
Kco, mmol/mmHg/min/ml	2.3 ± 1.2	104 ± 24	14
PaO_2 at rest, kPa	8.8 ± 1.7	-	23

DLco, transfer factor for carbon monoxide ; FEF, forced expiratory flow FEV1, forced expiratory volume in one second ; FVC, forced vital capacity ; Kco, transfer coefficient for carbon monoxide ; TLC, total lung capacity ; RV, residual volume.

Table 2. High resolution computed tomography (HRCT) findings.

	Number of patients (%)
Bronchial wall thickening	24 (96%)
Bronchiectasis	10 (40%)
Lobular areas of decreased attenuation (mosaic pattern)	13 (42%)
Centrilobular emphysema	14 (56%)
Irregular linear opacities, reticulation	8 (32%)
Ground glass opacification	11 (44%)
Areas of alveolar consolidation	7 (28%)
Honeycombing	4 (16%)
Pleural effusion	4 (16%) (*)
Rheumatoid nodule(s)	9 (36%) (**)

(*) bilateral in one case

(**) multiple in 6 cases, excavated in one case.

Table 3. HRCT findings, pulmonary function, and pathology findings, according to tobacco smoking and treatment of rheumatoid arthritis.

	Smoking +/- (n = 8/17)	**methotrexate +/- (n = 13/12)**	**Gold salts +/- (n = 10/15)**	**D-penicillamine +/- (n = 12/13)**	**Smoking + ARD +/- (n = 5/20)**
HRCT findings					
Emphysema (%)	62 / 53	69 / 41	60 / 53	66 / 46	60 / 55
Alveolar consolidation (%)	25 / 29	23 / 33	20 / 33	17 / 38	20 / 35
Ground glass attenuation (%)	50 / 41	61 / 25	50 /40	50 / 38	60 / 40
Honeycombing (%)	12.5 / 17	230/08	10 / 20	17 / 15	- / 20
Mosaic pattern (%)	50 / 53	61 / 41	40 / 60	50 / 53	40 / 55
Bronchiectasis (%)	37.5 / 41	53 / 25	30 / 46	42 / 38	40 / 40
Bronchial wall thickening (%)	100 / 94	92 / 100	80 / 100	91 / 100	100 / 95
Lung function findings					
FEV1 (mean ± SD), ml	1230 ± 300 / 910 ± 380	910 ± 330 / 1160 ± 380	930 ± 430 / 1100 ± 320	800 ± 320 / 1240 ± 320 §	1100 ± 240 / 975 ± 430
RV/TLC (mean ± SD), % of pred	119 ± 27 / 151 ±23 *	146 ± 24 / 129 ± 14	144 ± 21 / 139 ± 26	155 ± 25 / 128 ± 26	119 ± 31 / 145 ± 23
Pathological findings					
Constrictive bronchiolitis (n)	3 / 3	4 / 2	2 / 4	4 / 2	4 / 2
Follicular bronchiolitis (n)	- / 1	- / 1	1 / -	- / 1	- / 1
Mixed bronchiolitis (n)	1 / 1	1 / 1	2 / -	2 / -	2 / -

HRCT, lung function and pathological characteristics are expressed in ex-smokers (as compared to never-smokers), or in patients ever treated with methotrexate, gold salts, or D-penicillamine, and in ex-smokers who had received anti-rheumatoid drug (as compared to the other patients). FEV1, forced expiratory volume in one second; TLC, total lung capacity; RV, residual volume; ARD, anti-rheumatoid drug.

* $p<0.05$; § $p<0.01$

Figure 1. HRCT showing diffuse emphysema lesions in a non-smoking patient with rheumatoid arthritis and severe airflow obstruction.

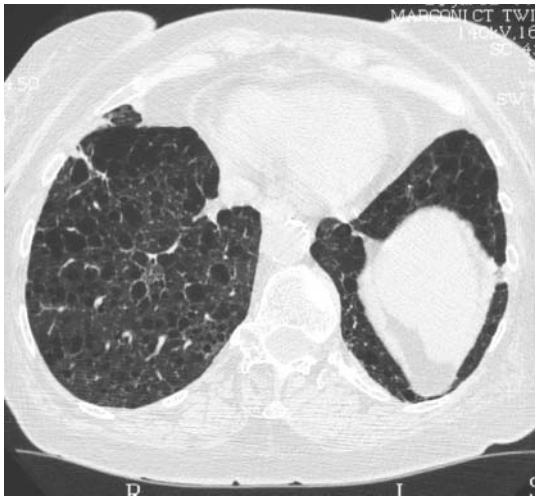


Figure 2. HRCT showing bronchiectasis and centrilobular micronodules in a non-smoking patient with rheumatoid arthritis and severe obliterative bronchiolitis.

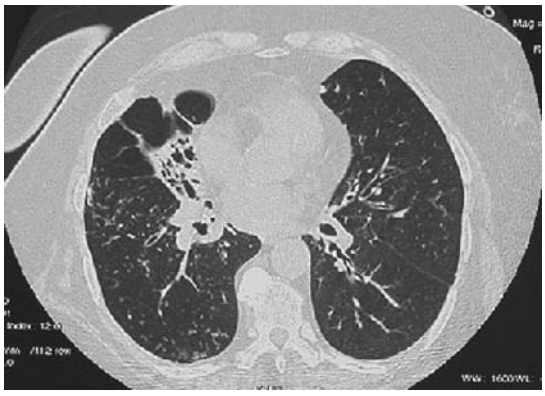
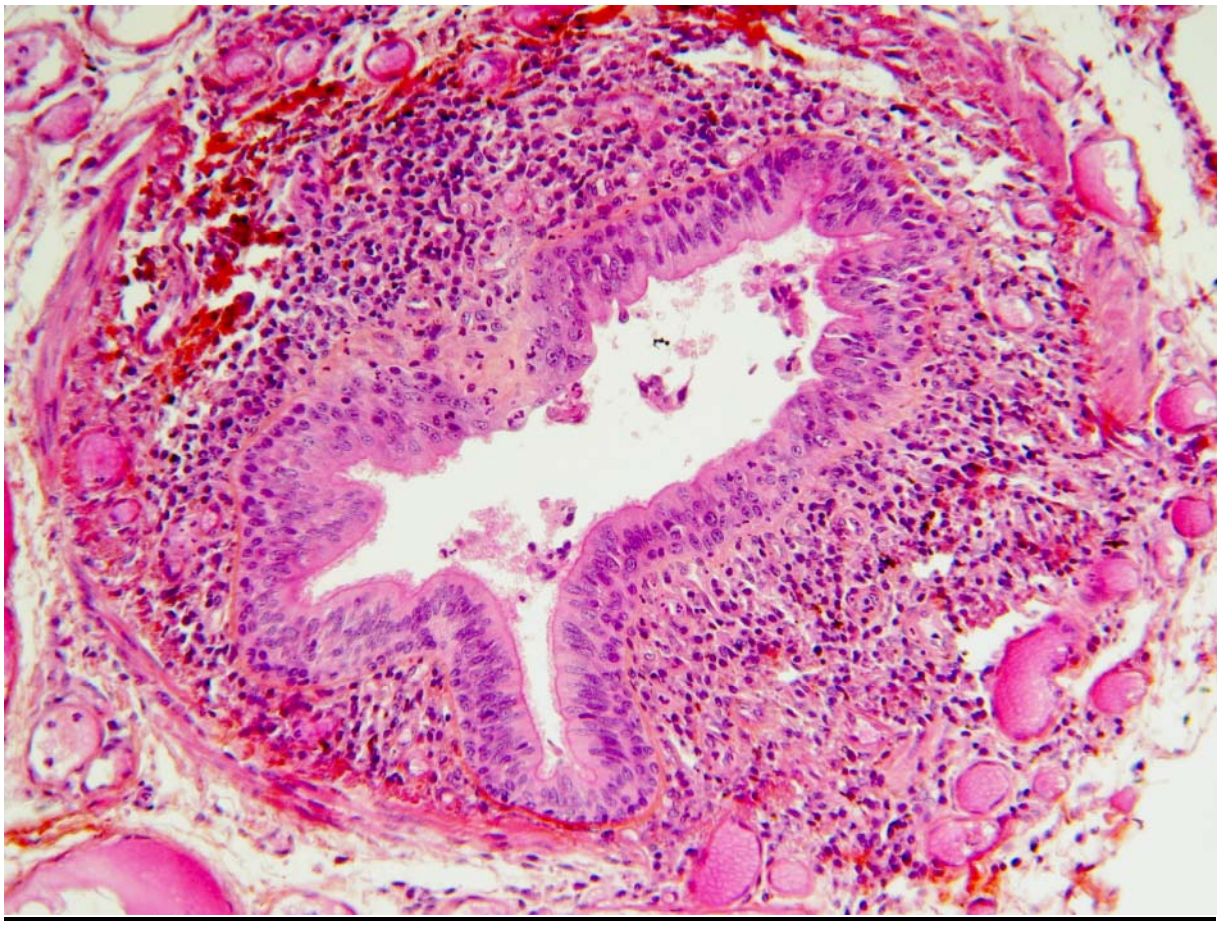
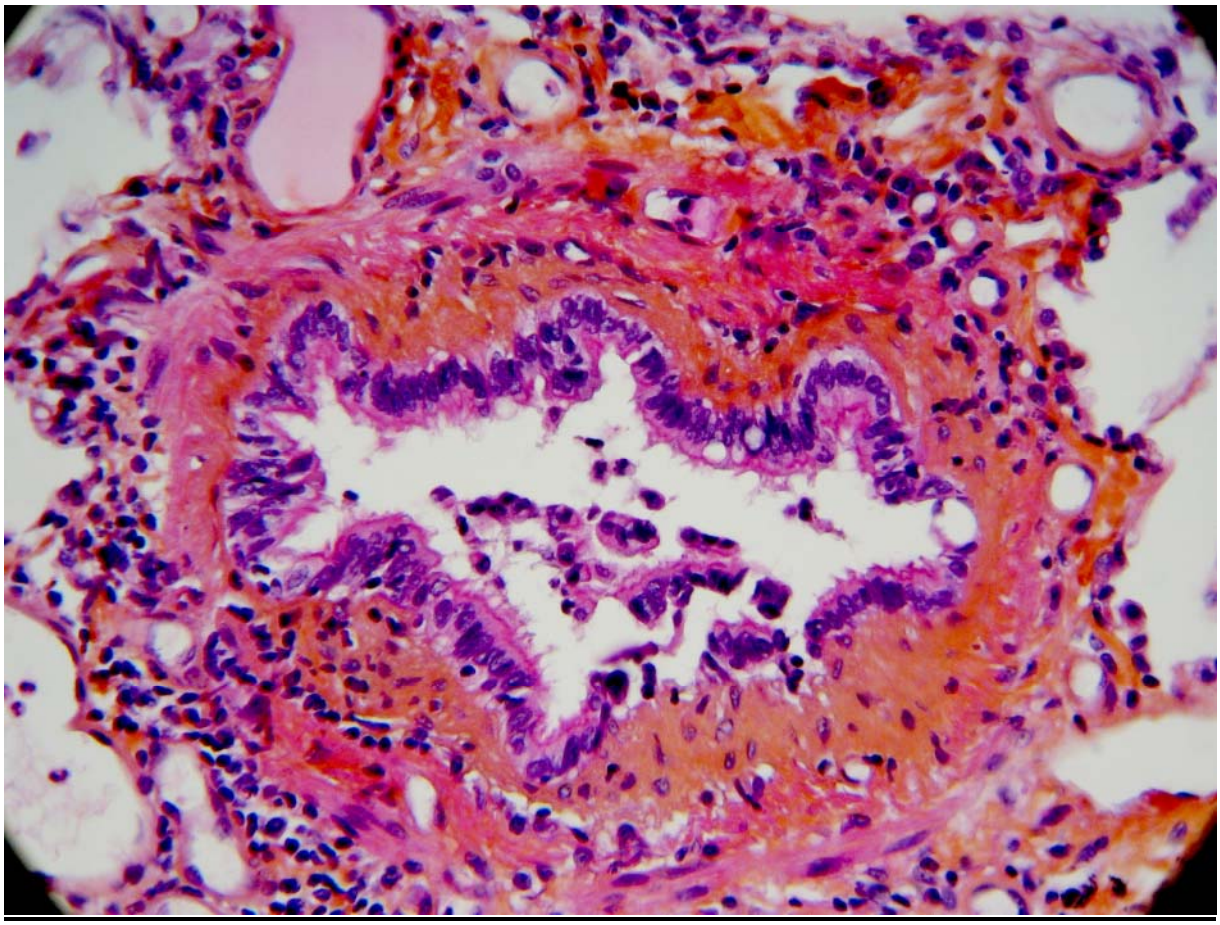


Figure 3. Histopathological analysis of lung biopsy specimen. A, lymphocytic constrictive bronchiolitis with nonfollicular lymphocytic infiltrate of the bronchiolar wall; B, chronic constrictive bronchiolitis, with thickening of the bronchiolar wall by collagen deposition, partial destruction of the muscular fibers, narrowing of the bronchiolar lumen, and mild peribronchiolar lymphocytic infiltrates.





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