Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis

G. Devouassoux*,**, V. Cottin#,**, H. Lioté¶, E. Marchand+, I. Frachon§, A. Schuller*, F. Béjui-Thivolet*f*, J-F. Cordier# and the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)

ABSTRACT: The characteristics of patients with rheumatoid arthritis (RA) who develop obliterative bronchiolitis characterised by severe airflow obstruction have been hitherto poorly investigated.

A retrospective study of 25 patients with RA and functional evidence of obliterative bronchiolitis (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <50% and/or residual volume (RV)/total lung capacity (TLC) >140% predicted) was conducted.

Patients (mean±SD age 64±11 yrs) included 17 never-smokers and eight ex-smokers (10.5±5.4 pack-yrs). The diagnosis of RA preceded respiratory symptoms in 88% of cases. Dyspnoea on exertion was present in all patients and bronchorrhea in 44%. High-resolution computed tomography findings included: bronchial wall thickening (96%), bronchiectasis (40%), mosaic pattern (40%), centrilobular emphysema (56%), and reticular and/or ground-glass opacities (32%). Pulmonary function tests showed: FEV_1 41±12% pred, FEV_1/FVC 49±14%, FVC 70±20% pred, RV 148±68% pred and RV/TLC 142±34% pred. Lung biopsy, available in nine patients, demonstrated constrictive, follicular and mixed bronchiolitis. Patients were followed for 48.2±49 months. Treatment was poorly effective. Chronic respiratory failure occurred in 40% of patients, and four patients died.

Obliterative bronchiolitis associated with rheumatoid arthritis is a severe and under-recognised condition leading to respiratory failure and death in a high proportion of patients.

AFFILIATIONS
*Hospices civils de Lyon, Centre Hospitalier Lyon Sud, Service de Pneumologie, Pierre-Bénite,
#Hospices civils de Lyon, Hôpital Louis Pradel, Service de pneumologie, Centre de Référence des maladies pulmonaires rares de l'adulte, Université de Lyon, Université Lyon I,
*f*Hospices civils de Lyon, Hôpital Louis Pradel, Service de Cytologie et Anatomie Pathologique, Lyon,
¶AP-HP, Hôpital Tenon, Service de Pneumologie et Réanimation, Centre de Compétence des maladies pulmonaires rares de l'adulte, Paris,
+Cliniques Universitaires UCL de Mont-Godinne, Yvoir,
§Service de Médecine Interne et Pneumologie, Hôpital de la Cavale Blanche, Brest, France.
**These authors contributed equally to this work.

CORRESPONDENCE
J-F. Cordier
Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires
Hôpital Louis Pradel, 69677 Lyon (Bron)
France
Fax: 33 472357653
E-mail: germop@univ-lyon1.fr

Received:
June 16 2008
Accepted after revision:
November 19 2008

Pulmonary manifestations may account for 10–20% 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; these were first reported in 1977 in six patients, five of whom had RA [3]. In the present manuscript, the following terminology is used: "bronchiolitis obliterans" (historically used for the histopathological lesions) to name the pathological 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). Herein it is shown 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. Furthermore, it is shown 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
The present retrospective study was conducted by the Groupe d'Etudes et de Recherche sur les Maladies ''Orphelines'' Pulmonaires (GERM''O''P), a collaborative group of >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 encountered between January 1987 and February 2007. Reports to the GERM''O''P registry were nominative for patients who gave their written consent, or were otherwise anonymous. 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 >4) [9]; and 2) presence of small airways disease demonstrated by severe airflow obstruction (OB) as defined by forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <50% and/or severe air trapping with residual volume (RV)/ total lung capacity (TLC) >140% predicted value. In addition, patients might have evidence of bronchiolitis on lung biopsy specimen.

In order to select cases in which small airways disease was confidently attributable to RA, only patients with a history of cumulative tobacco smoking of <20 pack-yrs 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 per cent of predicted, except for FEV_1/FVC, which was expressed as absolute per cent. FEV_1 and FEV_1/FVC were assessed before bronchodilators, then 10–15 min after the administration of short-acting inhaled β_2-agonist. Airflow obstruction was defined by a post-bronchodilator FEV_1/FVC ratio <70% pred with FEV_1 <80% pred, and severe airflow obstruction by post-bronchodilator FEV_1/FVC ratio <50% and/or RV/TLC >140% pred.

Data analysis
Data were reported as mean$\pm$SD, and were expressed as absolute values or as per cent of predicted values, as appropriate. Categorical variables were compared by the Chi-squared test and continuous variables by the paired t-test. A p-value of <0.05 was considered significant.

RESULTS
Patients characteristics
A total of 25 patients (18 females, seven males) were included in the study, with a mean$\pm$SD age of 64 ± 11 yrs (range 37–81 yrs). In total, 17 (68%) patients were never-smokers; eight were ex-smokers (10.5 ± 5.4 pack-yrs, with age of 62 ± 8 yrs), 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's colitis).

According to inclusion criteria, all patients had both RA and evidence of severe fixed airflow obstruction (18 patients with FEV_1/FVC <50%, two patients with RV/TLC >140% pred and five patients with both criteria), including nine 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 yrs (range 1–35 yrs); the mean interval between the diagnosis of RA and the diagnosis of bronchiolitis was 9.5 ± 10 yrs (range 1–45 yrs); and the mean interval between respiratory symptoms and diagnosis of bronchiolitis was 19 ± 32 months (range 1–73 months). Respiratory manifestations developed after the diagnosis of RA in 22 cases, were concomitant in one case, and preceded the rheumatoid disease in only two cases (by 8 and 20 months).

The major respiratory symptom was chronic dyspnoea on exertion, present in all patients, with six, 10 and nine cases classified as New York Heart Association II, III and IV,

respectively. A total of 16 (64%) patients complained of cough, and bronchorrhea was present in 11 (44%). Chest pain was reported in three patients. Crackles, wheezes and squeaks were found in 13, 13 and six 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 (six cases), and weight loss (12 cases). At the time of the onset of OB, RA was symptomatic in eight 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 two, one and two cases, respectively. Other disorders were present in three patients, with Hashimoto thyroiditis, Crohn's colitis and vitiligo. Additional systemic involvement by RA was diagnosed in five patients, affecting the heart (two cases), muscle (one case), and skin (two 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%, two patients with RV/TLC >140% pred, and five patients with both criteria). Transfer factor for carbon monoxide ($D_{L,CO}$) was 78 ± 16%, and transfer coefficient of the lung (K_{CO}) was 104 ± 24% pred.

Mean arterial oxygen tension (P_{a,O_2}) on room air was 8.8 ± 1.7 kPa, with P_{a,O_2} <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 (fig. 1), lobular areas of decreased attenuation with mosaic pattern indicative of air trapping, and bronchiectasis (fig. 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 four patients, and rheumatoid lung nodules in nine patients.

Biology and BAL

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%,

TABLE 1	Pulmonary function tests	
Parameter	Value	Patients tested
FEV1 mL	1000 ± 380	25
FEV1 % pred	41 ± 12	25
Post-bronchodilator FEV1 mL	1100 ± 403	20
Post-bronchodilator FEV1 % pred	46 ± 13	20
FVC mL	2119 ± 797	25
FVC % pred	70 ± 20	25
FEV1/FVC %	49 ± 14	25
FEF25–75% mL	518 ± 336	19
FEF25–75% % pred	17 ± 10	19
FEF25–75%/FVC %	16 ± 4	19
FEF25% mL	175 ± 74	20
FEF25% % pred	13 ± 5	20
FEF50% mL	424 ± 256	23
FEF50% % pred	13 ± 6	23
FEF75% mL	1033 ± 783	14
FEF75% % pred	21 ± 14	14
RV mL	2965 ± 1520	19
RV % pred	148 ± 68	19
TLC mL	5280 ± 1750	19
TLC % pred	103 ± 33	19
RV/TLC %	52 ± 13	19
RV/TLC % pred	142 ± 34	19
$D_{L,CO}$ mmol·mmHg^{-1}·min^{-1}	8.4 ± 5.1	14
$D_{L,CO}$ % pred	78 ± 16	14
K_{CO} mmol·mmHg^{-1}·min^{-1}·mL^{-1}	2.3 ± 1.2	14
K_{CO} % pred	104 ± 24	14
Resting P_{a,O_2} kPa	8.8 ± 1.7	23

Data are expressed as mean$\pm$SD or n. FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; FEF25–75%: mean forced expiratory flow between 25% and 75% of FVC; FEF25%: forced expiratory flow at 25% of FVC; FEF50%: forced expiratory flow at 50% of FVC; FEF75%: forced expiratory flow at 75% of FVC; RV: residual volume; TLC: total lung capacity; $D_{L,CO}$: transfer factor for carbon monoxide; K_{CO}: transfer coefficient for carbon monoxide; P_{a,O_2}: arterial oxygen tension. 1 mmHg=0.133 kPa.

lymphocytes 13 ± 12%, without eosinophils). Infectious pathogens were identified by BAL during the course of disease in nine patients (*Pseudomonas aeruginosa* in three; *Aspergillus fumigatus* in two; *Streptococcus pneumoniae* in two; *Haemophilus influenzae* in one; and *Staphylococcus aureus* in one), with presence of bronchiectasis at HRCT in eight out of nine 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^{-1}). Rheumatoid factor and anti-nuclear antibodies (without specificity for soluble nuclear antigens or native DNA) were present in 24 (96%) and 12 (48%) patients, respectively.

Lung pathology

Lung pathology of video-assisted thoracoscopic or open lung biopsy or explanted lung was available in eight and one case, respectively, and analysed by an experienced lung pathologist (FTB). A histopathological pattern of bronchiolitis was found
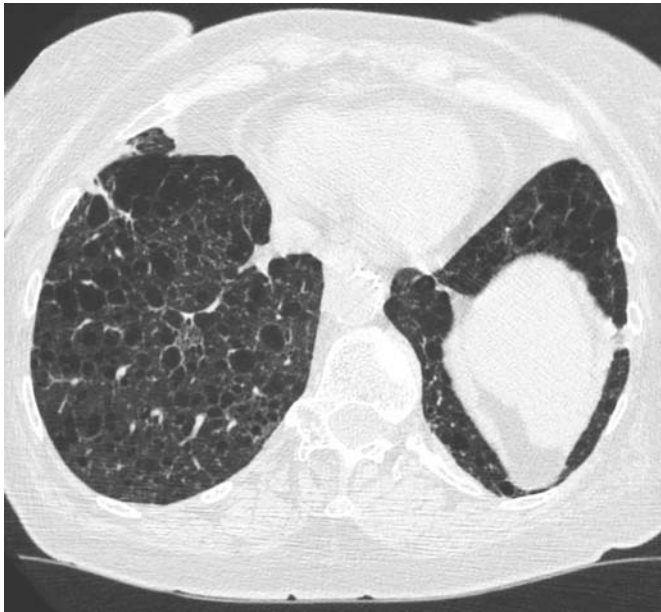
FIGURE 1. High-resolution computed tomography showing diffuse emphysema lesions in a nonsmoking patient with rheumatoid arthritis and severe airflow obstruction.

FIGURE 2. High-resolution computed tomography showing bronchiectasis and centrilobular micronodules in a nonsmoking patient with rheumatoid arthritis and severe obliterative bronchiolitis.

in all cases, occasionally associated with accessory lesions consistent with usual interstitial pneumonia or diffuse alveolar damage (one case each). Bronchiolar changes consisted in chronic constrictive bronchiolitis (six cases), follicular bronchiolitis (one case), and mixed constrictive/follicular bronchiolitis (two cases; fig. 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 four cases. Centrilobular emphysema adjacent to bronchiolar changes was further present in five cases.

Echocardiography
Echocardiography performed in 16 patients showed normal left ventricular function in all patients. The estimated systolic pulmonary artery pressure was >35 mmHg in six 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; of these, 24 (96%) were receiving oral corticosteroids, and 22 were taking nonsteroidal anti-inflammatory drugs. Of the study patients, 52% had received methotrexate for a mean duration of 46 months, 40% had received intramuscular gold salts (mean duration 20 months), 48% had received D-penicillamine (mean duration 25 months), 20% had received hydroxychloroquine (mean duration 62 months), 20% had received leflunomide (mean duration 19 months), 12% had received salazopyrine (mean duration 33 months), 12% had received anti-tumour necrosis factor (anti-TNF)-α regimens (mean duration 21 months) and 4% had received tiopronine. In order to evaluate the possible influence of
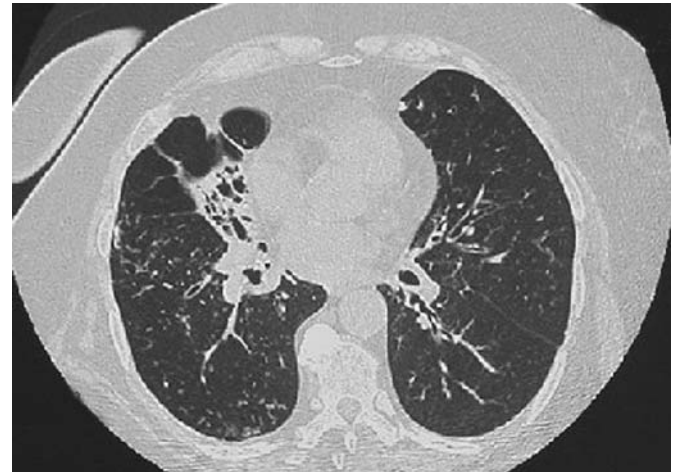
treatment of RA on the development or severity of OB, the main HRCT findings, pulmonary function tests and pathology findings were compared according to treatment and tobacco history (table 3). FEV1 was lower in patients who had ever received D-penicillamine as compared with those who had not been treated with this drug (800 ± 320 mL versus $1,240 \pm 320$ 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 ($119 \pm 27\%$ versus $151 \pm 23\%$, $p < 0.05$), 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 (96%) patients, associated with immunosuppressive treatment in 24 cases (methotrexate in nine patients; leflunomide in four; hydroxychloroquine in four; anti-TNF-α in three; azathioprine in one; and cyclophosphamide in three).

TABLE 2	High-resolution computed tomography findings
	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)[¶]

Data are presented as n (%). [#]: bilateral in one case; [¶]: multiple in six cases, excavated in one.
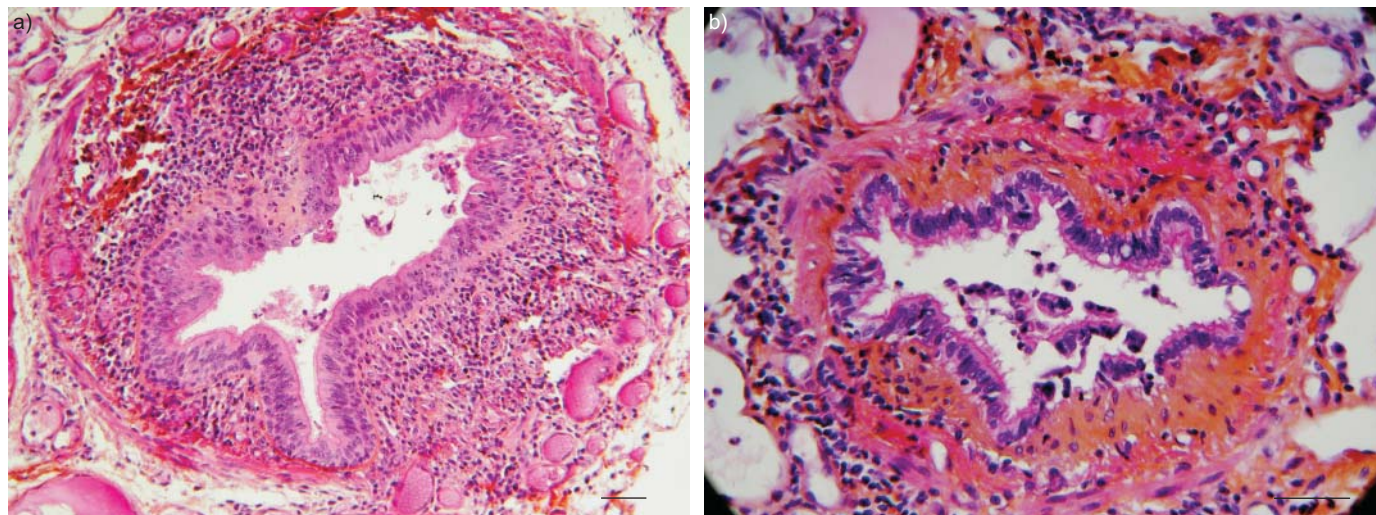
FIGURE 3. Histopathological analysis of lung biopsy specimen. a) Lymphocytic constrictive bronchiolitis with nonfollicular lymphocytic infiltrate of the bronchiolar wall. b) Chronic constrictive bronchiolitis, with thickening of the bronchiolar wall by collagen deposition, partial destruction of the muscular fibres, narrowing of the bronchiolar lumen and mild peribronchiolar lymphocytic infiltrates. Scale bars=40 μm.

D-Penicillamine was stopped after the emergence of airflow obstruction in two patients. Improvement of pulmonary symptoms was obtained in only four patients, three of whom received corticosteroids and two 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 48.2 ± 49 months. Symptoms worsened in 52% of patients, and were unchanged in 32% of patients. Bronchial and/or pulmonary infections occurred in 60% of patients and pneumothorax in 12%. Acute respiratory failure occurred in 48% of patients. Right cardiac failure developed in 16% of patients 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

The present study 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 $D_{L,CO}$. 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. [3] in six patients (five of whom had RA) with rapid progressive dyspnoea and airflow obstruction, with bronchiolitis obliterans demonstrated at necropsy in four cases. Most cases occur <5 yrs after the diagnosis of RA, but

OB may be a presenting manifestation of RA in 10–20% of patients [2], as in two of the current patient series.

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 the present study).

The patients reported in the present study, which is the largest series of patients with RA-related severe OB, presented with an abrupt or progressive onset of dyspnoea and dry cough, often with squeaks and crackles at auscultation, as previously reported [3]. However, the mean±SD 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 in those with OB presenting concomitantly or before the diagnosis of RA. Pulmonary function testing revealed airflow obstruction, which seemed to progress more rapidly than in COPD, as previously described [3, 15, 18], with mild to moderate hypoxaemia. In addition to airflow obstruction (with decreased $FEV1/FVC$), hyperinflation demonstrated by increased RV and RV/TLC was common. In order to improve early detection of disease, the current authors suggest sequential pulmonary function tests (including measurement of RV and RV/TLC) be performed in any RA patient with progressive dyspnoea on exertion. In addition, lung biopsy should be considered more frequently in this condition, except when contraindicated by the severity of disease or comorbidities, as it might provide access to definitive diagnosis and

TABLE 3	High-resolution computed tomography (HRCT) findings, pulmonary function and pathology findings, according to tobacco smoking and treatment of rheumatoid arthritis									
	Smokers		**Methotrexate**		**Gold salts**		**D-Penicillamine**		**Smokers on ARD**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Subjects n	8	17	13	12	10	15	12	13	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	8	10	20	17	15	0	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										
FEV$_1$ mL	1230±300	910±380	910±330	1160±380	930±430	1100±320	800±320**	1240±320**	1100±240	975±430
RV/TLC % 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	0	1	0	1	1	0	0	1	0	1
Mixed bronchiolitis n	1	1	1	1	2	0	2	0	2	0

Data are expressed as mean±SD, unless otherwise stated. HRCT, lung function and pathological characteristics are expressed in ex-smokers (compared with never-smokers), or in patients ever treated with methotrexate, gold salts or D-penicillamine, and in ex-smokers who had received anti-rheumatoid drugs (ARDs; as compared with the other patients). FEV$_1$: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity. *: $p<0.05$; **: $p<0.01$.

early therapy. However, the current authors consider that the diagnosis of OB may be obtained 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 previously described [3]. Some improvement was obtained in two patients who received off-label anti-TNF-α regimen for OB (one of these has been 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, will decrease progression of OB. Although not formally compared, overall survival seemed lower than that of COPD patients with similar airflow obstruction, and was almost similar to that in post-transplant bronchiolitis obliterans syndrome [21, 22]. No treatment recommendation can be provided from published data and the present study. However, it is 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 out of 25 patients had received previous therapy with D-penicillamine or

tiopronine, and 10 out of 25 had received gold salts, raising the concern of drug-induced bronchiolar disease. In addition, FEV$_1$ was significantly lower in patients who had ever been treated with D-penicillamine compared with 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 females [20], contrasting with the increased prevalence of interstitial lung disease associated with RA in males [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-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 the present patients.

Only eight out of 25 patients in the current series were ex-smokers, with a mean smoking history of only 10 pack-yrs. 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 $D_{L,CO}$). Hence, the Global Initiative for Obstructive Lung Disease functional definition of moderate, severe, and very severe COPD [25] was fulfilled in 20%, 56% and 24% of the 25 patients, respectively. Interestingly, cigarette smoking is associated with an increased risk of developing RA [26] and

with RA activity, an association probably 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 pre-existing 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 probably 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 can be affected by the presence and treatment of gastro-oesophageal 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, compared with 20–32% 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 the present study was the high frequency of diffuse emphysema lesions on HRCT (56% of patients, five of whom were smokers) and on histopathology (five out of nine cases with biopsy, including three smokers), a prevalence higher than in previous studies (*i.e.* 4–39% [7, 8, 31, 32]), which may be partly due to the inclusion criteria, which 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 one third of patients, both emphysema and infiltrative opacities were present, and was somewhat reminiscent of the syndrome of combined pulmonary fibrosis and emphysema identified in smokers [34, 35]. Taken together, the findings suggest that severe OB occurring in RA present significant similarity with COPD, especially with emphysema on chest imaging, and subtle changes suggestive of bronchiolar disease may be overlooked.

Bronchiectasis is present in 8–30% of patients with RA [7, 16, 31, 36] and has been associated with a higher risk of airflow obstruction, pulmonary infections and death [37]. Bronchiectasis, bronchial wall thickening, cough and bronchorrhea in the patients from the present study with OB suggest comprehensive airways disease, involving both bronchioles and bronchi of all size. Therefore, airway disease with OB occurring in RA compares to that complicating bone marrow transplantation [21, 38] and lung transplantation [21].

Pathological analysis of the lung biopsy available in nine out of 25 cases (a proportion possibly greater than that in 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, in a similar manner 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 of the present 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 probably occurred, with the most severe cases being referred to participating tertiary centres. Although inclusion bias may have occurred, as in any retrospective study, the current authors consider that it was limited by including patients in whom lung biopsy was not performed (with potentially more severe disease), therefore the 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, in order to improve the 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 yrs, image acquisition was not standardised. The limited number of patients did not allow multivariate statistical analysis.

In conclusion, the current authors describe a homogenous cohort of 25 patients with severe obliterative bronchiolitis attributable to rheumatoid arthritis, characterised by severe dyspnoea, lung hyperinflation, bronchial wall thickening, frequent bronchiectasis, and centrilobular emphysema on chest imaging. Disease presentation was somewhat similar to that of chronic obstructive pulmonary disease in tobacco smokers. Severity of disease was variable. Response to oral corticosteroids was poor, frequently leading to chronic respiratory failure and possible death.

REFERENCES

1 Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. *Scand J Rheumatol* 2004; 33: 221–227.

2 Brown KK. Rheumatoid lung disease. *Proc Am Thorac Soc* 2007; 4: 443–448.

3 Geddes DM, Corrin B, Brewerton DA, Davies RJ, Turner-Warwick M. Progressive airway obliteration in adults and

its association with rheumatoid disease. *Q J Med* 1977; 46: 427–444.

4 Leslie KO, Trahan S, Gruden J. Pulmonary pathology of the rheumatic diseases. *Semin Respir Crit Care Med* 2007; 28: 369–378.

5 Howling SJ, Hansell DM, Wells AU, Nicholson AG, Flint JD, Muller NL. Follicular bronchiolitis: thin-section CT and histologic findings. *Radiology* 1999; 212: 637–642.

6 Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med* 1996; 154: 1531–1536.

7 Cortet B, Perez T, Roux N, *et al.* Pulmonary function tests and high resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Ann Rheum Dis* 1997; 56: 596–600.

8 Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. *Am J Respir Crit Care Med* 1998; 157: 1658–1665.

9 Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315–324.

10 Cortot AB, Cottin V, Miossec P, Fauchon E, Thivolet-Bejui F, Cordier JF. Improvement of refractory rheumatoid arthritis-associated constrictive bronchiolitis with etanercept. *Respir Med* 2005; 99: 511–514.

11 King TE Jr. Bronchiolitis. *In:* Schwarz MI, King TE Jr, eds. Interstitial Lung Disease. Fourth Edn. Hamilton, B.C. Decker Inc., 2003; pp. 878–824.

12 Papiris SA, Maniati M, Constantopoulos SH, Roussos C, Moutsopoulos HM, Skopouli FN. Lung involvement in primary Sjogren's syndrome is mainly related to the small airway disease. *Ann Rheum Dis* 1999; 58: 61–64.

13 Tzeng DZ, Leslie KO, Shelton D, Chan A. Unusual dyspnoea in a woman with CREST syndrome. *Chest* 2008; 133: 286–290.

14 Collins RL, Turner RA, Johnson AM, Whitley NO, McLean RL. Obstructive pulmonary disease in rheumatoid arthritis. *Arthritis Rheum* 1976; 19: 623–628.

15 Geddes DM, Webley M, Emerson PA. Airways obstruction in rheumatoid arthritis. *Ann Rheum Dis* 1979; 38: 222–225.

16 Vergnenegre A, Pugnere N, Antonini MT, *et al.* Airway obstruction and rheumatoid arthritis. *Eur Respir J* 1997; 10: 1072–1078.

17 Fuld JP, Johnson MK, Cotton MM, *et al.* A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis. *Chest* 2003; 124: 1224–1231.

18 Begin R, Masse S, Cantin A, Menard HA, Bureau MA. Airway disease in a subset of nonsmoking rheumatoid patients. Characterization of the disease and evidence for an autoimmune pathogenesis. *Am J Med* 1982; 72: 743–750.

19 van de Laar MA, Westermann CJ, Wagenaar SS, Dinant HJ. Beneficial effect of intravenous cyclophosphamide and oral prednisone on D-penicillamine-associated bronchiolitis obliterans. *Arthritis Rheum* 1985; 28: 93–97.

20 Schwarz MI, Lynch DA, Tuder R. Bronchiolitis obliterans: the lone manifestation of rheumatoid arthritis? *Eur Respir J* 1994; 7: 817–820.

21 Philit F, Wiesendanger T, Archimbaud E, Mornex JF, Brune J, Cordier JF. Post-transplant obstructive lung disease (''bronchiolitis obliterans''): a clinical comparative study of bone marrow and lung transplant patients. *Eur Respir J* 1995; 8: 551–558.

22 Marras TK, Chan CK. Obliterative bronchiolitis complicating bone marrow transplantation. *Semin Respir Crit Care Med* 2003; 24: 531–542.

23 Andonopoulos AP, Constantopoulos SH, Drosos AA, Moutsopoulos HM. Pulmonary function of nonsmoking patients with rheumatoid arthritis in the presence and absence of secondary Sjogren's syndrome, a controlled study. *Respiration* 1988; 53: 251–258.

24 Sweatman MC, Markwick JR, Charles PJ, *et al.* Histocompatibility antigens in adult obliterative bronchiolitis with or without rheumatoid arthritis. *Dis Markers* 1986; 4: 19–26.

25 Rabe KF, Hurd S, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532–555.

26 Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. *Am J Med* 2006;119:503 e1–e9.

27 Klareskog L, Stolt P, Lundberg K, *et al.* A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006; 54: 38–46.

28 Rangel-Moreno J, Hartson L, Navarro C, Gaxiola M, Selman M, Randall TD. Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. *J Clin Invest* 2006; 116: 3183–3194.

29 Atkins SR, Turesson C, Myers JL, *et al.* Morphologic and quantitative assessment of CD20+ B cell infiltrates in rheumatoid arthritis-associated nonspecific interstitial pneumonia and usual interstitial pneumonia. *Arthritis Rheum* 2006; 54: 635–641.

30 Terasaki H, Fujimoto K, Hayabuchi N, Ogoh Y, Fukuda T, Muller NL. Respiratory symptoms in rheumatoid arthritis: relation between high resolution CT findings and functional impairment. *Radiat Med* 2004; 22: 179–185.

31 Tanaka N, Kim JS, Newell JD, *et al.* Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 2004; 232: 81–91.

32 Biederer J, Schnabel A, Muhle C, Gross WL, Heller M, Reuter M. Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. *Eur Radiol* 2004; 14: 272–280.

33 Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smoker's. *N Engl J Med* 1974; 291: 755–758.

34 Cottin V, Nunes H, Brillet PY, *et al.* Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005; 26: 586–593.

35 Cottin V, Hachulla E, Van Huffel S, *et al.* Combined pulmonary emphysema and fibrosis (CPFE) in connective tissue disease. *Proc Am Thorac Soc* 2007; 175: A144.

36 Kaushik VV, Hutchinson D, Desmond J, Lynch MP, Dawson JK. Association between bronchiectasis and

smoking in patients with rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 1001–1002.

37 Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. *Br J Rheumatol* 1997; 36: 689–691.

38 Ooi GC, Peh WC, Ip M. High-resolution computed tomography of bronchiolitis obliterans syndrome after bone marrow transplantation. *Respiration* 1998; 65: 187–191.

39 Cordier JF. Challenges in pulmonary fibrosis. 2: Bronchiolo-centric fibrosis. *Thorax* 2007; 62: 638–649.