

## CASE STUDY

# Accelerated obstructive pulmonary disease in HIV infected patients with bronchiectasis

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*Accelerated obstructive airway disease in HIV infected patients with bronchiectasis. M. Bard, L-J. Couderc, A.G. Saimot, A. Scherrer, I. Frachon, F. Seigneur, I. Caubarrere. ©ERS Journals Ltd 1998.*

**ABSTRACT:** Human immunodeficiency virus (HIV) infection has been associated with a wide spectrum of pulmonary disease. We report three HIV-seropositive patients with rapidly worsening airway obstruction associated with bronchiectasis.

All subjects (age range 33–39 yrs) were cigarette smokers. Two had previously used intravenous drugs. The CD4 lymphocyte count ranged 40–250 cells·mm<sup>-3</sup>. All individuals had complained of increasing dyspnoea for 3–6 months.

Within 1 yr, they all developed severe airway obstruction with a decrease in both forced expiratory volume in one second (FEV<sub>1</sub>) and ratio of FEV<sub>1</sub> to forced vital capacity (FEV<sub>1</sub>/FVC) to less than 60% of predicted value, and a decrease in mean forced expiratory flow at 25–75% of the forced vital capacity (FEF<sub>25–75</sub>) to less than 35% of predicted value. Computed tomography of the chest disclosed bilateral dilated and thickened bronchi. No classical causes of genetic or acquired bronchiectasis were identified in our patients. Recurrent bacterial bronchitis occurred in the follow-up period of the three patients.

In conclusion, unusually rapid airway obstruction associated with bronchiectasis should be added to the wide spectrum of respiratory complications of human immunodeficiency virus infection.

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The lung is the site of a wide spectrum of disorders complicating the clinical course of the human immunodeficiency virus (HIV) infection. Pulmonary function tests were routinely performed in several series of HIV-infected patients with or without pulmonary complications. Normal lung volumes have been observed in HIV-seropositive patients without acquired immune deficiency syndrome (AIDS) [1]. In AIDS patients, decreased transfer factor of the lung for carbon monoxide (TLCO) and decreased forced vital capacity (FVC) were found in association with *Pneumocystis carinii* pneumonia or lung involvement by Kaposi's sarcoma [2–4].

Furthermore, an emphysema-like disease consisting of hyperinflation without airway obstruction has been reported in a small series of HIV-infected patients, without infectious or tumoural complications of HIV infection [5].

However, little information is available on changes in pulmonary function over time in HIV infected patients.

We describe three HIV-seropositive patients with severe obstructive disorder associated with bronchiectasis. These patients were unusual in that the rapidly progressing obstruction developed in the absence of a classical cause of bronchiectasis.

## Methods

### Patients

Patients were evaluated among HIV-seropositive adults treated at two University affiliated Hospitals in the Paris

area of France. The average number of HIV-positive patients treated in the hospitals during the last 3 yrs (1992–1995) was 1,500. Not all adults were evaluated by pulmonary function tests. The selection of the patients was made on the basis of increasing dyspnoea unrelated to opportunistic infection, tumour or cardiac failure and documented by successive pulmonary function tests and radiological examination during a follow-up period of more than 1 yr. Only three patients satisfied these selection conditions. This manuscript is a case study of well documented patients. This does not allow the evaluation of the incidence of obstructive airway disease in HIV infected patients.

### Pulmonary function tests

Lung volume and flow-volume curves were obtained using a spirometer (Masterlab Jaeger, Würzburg, Germany) according to the standards of the American Thoracic Society [6]. Airway obstruction was defined by a decrease in both forced expiratory volume in one second (FEV<sub>1</sub>) and the ratio of forced expiratory volume in one second to forced vital capacity (FEV<sub>1</sub>/FVC). Small calibre bronchi obstruction was evaluated using mean forced expiratory flow at 25–75% of the forced vital capacity (FEF<sub>25–75</sub>). Airway obstruction reversibility was measured by pulmonary testing after (200 µg) inhalation: an increase of at least 20% in FEV<sub>1</sub> defined reversibility.

Total lung capacity and residual volume were determined using the helium dilution technique. Predicted values for lung volume were readjusted according to individual body weight variations with time. The  $TL_{CO}$  value was measured in each patient. All measurements were performed after a period of rest. Each test was performed three times and the best result was recorded. Arterial blood gas pressures were determined using a blood gas analyser (Ciba-Corning 280 blood gas system; Ciba Corning Diagnostic SA, Sudbury, UK).

#### Chest radiological imaging

In the three patients, high-resolution chest computed tomography (HRCT) scans were performed on an Elscint model (Elite+ computed tomography (CT) scan; Elscint, Haifa, Israel). High spatial frequency algorithms were used for reconstruction using a collimation of 1.0 mm. Chest images were obtained from the thoracic inlet to the hemidiaphragms. Standard criteria defined bronchial dilatation (bronchial diameter at least twice that of the adjacent artery). HRCT scans were also examined for nodular opacities, ground glass opacities or abnormal vascularity. Lung hyperinflation was examined on both standard chest radiographs and HRCT scans, and was suggested by chest distension, increased radiolucency, nonuniform distribution of vascular markings, or by an inverted diaphragm.

### Results

#### HIV status

Patient characteristics are summarized in table 1. Two had a CD4 lymphocyte count less than 50 cells·mm<sup>-3</sup> at presentation. Prophylactic treatment of opportunistic infections and anti-retroviral therapy were taken by all three patients. None were receiving inhaled pentamidine. Patient 3 had had prior *P. carinii* pneumonia 3 yrs previously. Patient 2, with a CD4 lymphocyte count >200 cells·mm<sup>-3</sup>, had not previously had any HIV-related complication. No patient had evidence of cutaneous or mucosal Kaposi's sarcoma.

Table 1. – Characteristics of three human immunodeficiency virus (HIV) seropositive patients with obstructive airway disease

Pt No.	Age yrs	Sex M/F	Weight kg	Height m	HIV risk group	CD4 count cells·mm <sup>-3</sup> (%)	Alb/ $\gamma$ -glob g·L <sup>-1</sup>	IgG/IgM/IgA g·L <sup>-1</sup>	Previous diagnosis	Antiretroviral therapy	Prophylaxis
1	33	F	60	1.7	IVDA	45 (5)	25/35	30.0/6.0/5.0	Oral leukoplakia Oral candidiasis Thrombocytopenia CMV retinitis	AZT	TMP-SMZ
2	37	F	44	1.6	IVDA	260 (17)	46/24	30.4/5.2/4.5	None	AZT	TMP-SMZ
3	39	M	53	1.7	Heterosexual	5 (1)	34/14	15.0/0.8/5.0	<i>Pneumocystis carinii</i> pneumonia Oesophageal candidiasis Oral leukoplakia Cutaneous herpes	AZT ddC	TMP-SMZ

Pt: patient; M: male; F: female; IVDA: intravenous drug abuser; CMV: cytomegalovirus; Alb: albumin;  $\gamma$ -glob: gammaglobulin; Ig: immunoglobulin; AZT: 3',Azido-2',3'-dideoxythymidine; ddC: 2',3' dideoxycytidine; TMP-SMZ: trimethoprim/sulphamethoxazole.

#### Clinical findings on presentation

All patients were cigarette smokers. Two had been intravenous drug abusers and had stopped 3–5 yrs before the first respiratory symptoms appeared. None had ever used inhaled drugs. No patient described either a family history of pulmonary disease or a personal history of severe chest illness in childhood. All three patients complained of exertional dyspnoea and chronic productive cough with purulent sputum. All were afebrile. Physical examination was unremarkable, except for coarse crepitation over the lower part of the lungs.

Serum electrophoresis showed polyclonal hypergammaglobulinemia in patients 1 and 2 (table 1). Alpha 1 antitrypsin serum levels were within normal values in all patients. Aspergillus serology and cultures of sputum for mycobacterial and fungal agents were negative in all patients.

#### Pulmonary function

Pulmonary function tests showed airway obstruction. Figure 1 shows the course and follow-up of obstructive parameters (expressed as percentages of the predicted values). A decrease in FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio and FEF<sub>25–75</sub> was observed in all three patients (fig. 1a, b and c respectively). In two cases, values decreased from normal to severe obstruction in less than 1 yr. No obstruction reversibility was measured after salbutamol inhalation in all three patients. An increased residual volume (150% pred) associated with a decreased  $TL_{CO}$  (30% pred) was only present in patient 2. Arterial blood gas analysis on room air showed hypoxaemia (fig. 1d) without hypercapnia in all three patients.

#### Radiological examination

Chest radiographs disclosed distension without parenchymal condensation. HRCT scan identified dilated thick-walled bronchi in all patients (fig. 2). Distribution of these bronchiectasis was bilateral with a predominance for basal lobes. Involvement of centrilobular bronchioles was suggested by acinar lesions with a "tree-in-bud" aspect. Neither pleural effusion, nor hilar or mediastinal lymphadenopathy were seen.

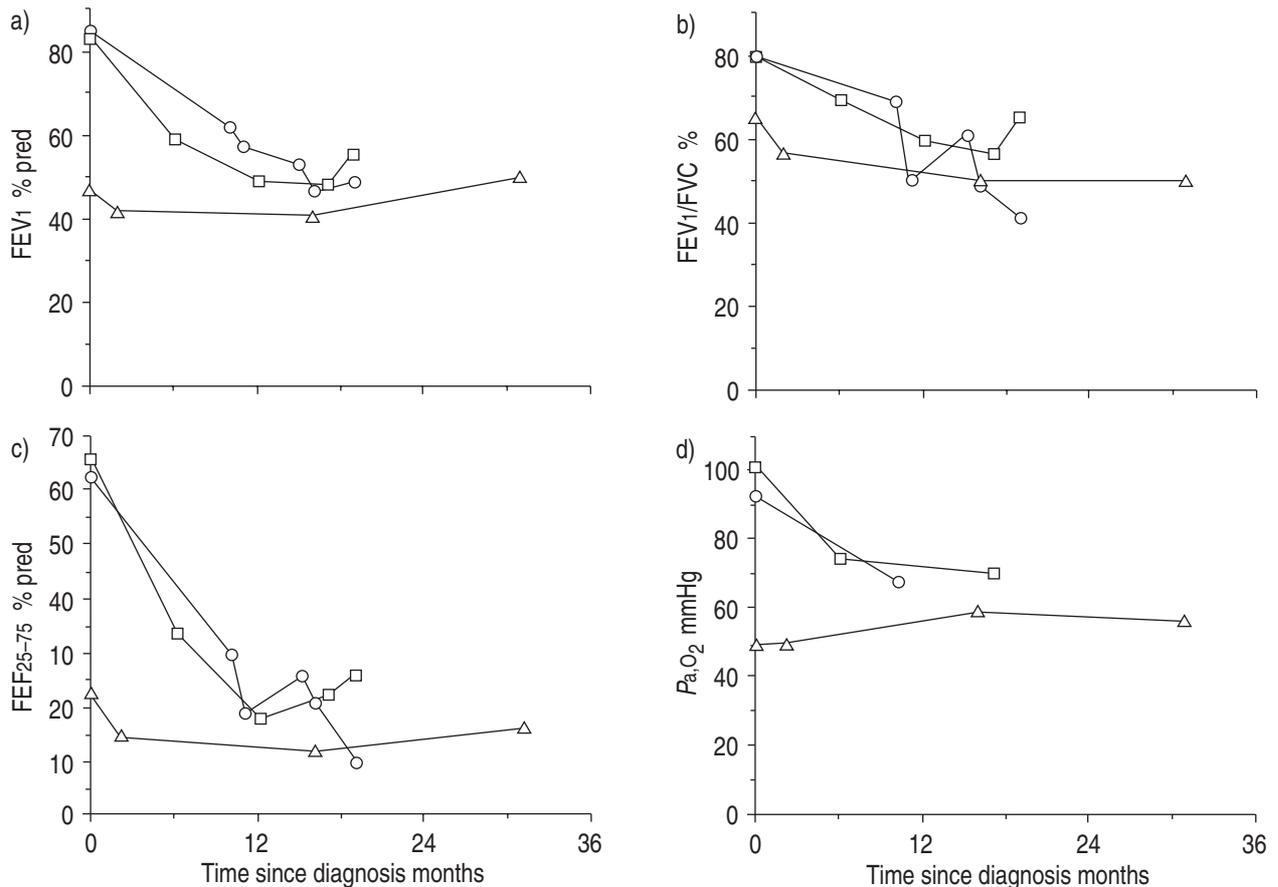


Fig. 1. – Changes in pulmonary function in three human immunodeficiency virus seropositive patients. A severe obstructive pulmonary disorder was observed in all three patients with a decrease in: a) forced expiratory volume in one second (FEV<sub>1</sub>); b) the ratio of FEV<sub>1</sub> to forced vital capacity (FEV<sub>1</sub>/FVC); c) mean forced expiratory flow during 25–75% of FVC (FEF<sub>25-75</sub>); and d) in arterial oxygen tension ( $P_{a,O_2}$ ). Lung volumes are expressed as percentages of predicted values (% pred). □: patient 1; △: patient 2; ○: patient 3. 1 mmHg=0.133 kPa.

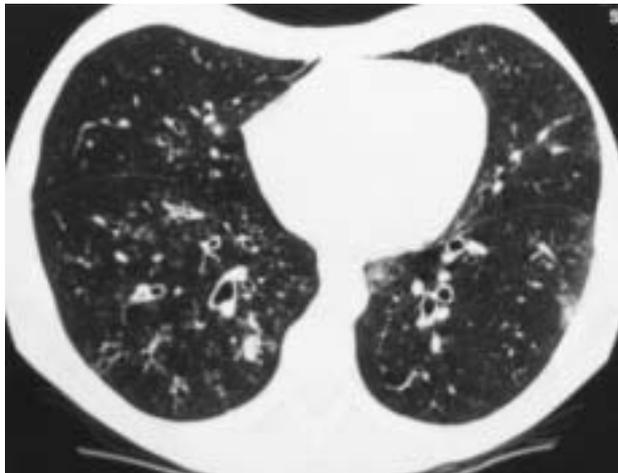


Fig. 2. – High resolution computed chest tomography from patient 3 showing dilated thick-walled bronchi.

#### Outcomes and follow-up

The clinical course of the patients was characterized by rapid worsening of exertional dyspnoea and recurrent episodes of bronchitis. The acute bronchitis episodes was not present at presentation but appeared during the follow-up at a frequency of about three episodes per year. Between

each acute episode, all three patients described a chronic cough with an increase of sputum volume. In patients 2 and 3, fiberoptic examination was performed during febrile acute bronchitis. No endobronchial Kaposi's sarcoma was observed. No evidence of mycobacterial, parasitic or mycotic agents was isolated from sputum, brush and bronchoalveolar samples in our three patients. Bronchoalveolar lavage fluid analysis showed an increased number of neutrophils. Cultures of bronchial brush were positive for *Haemophilus influenzae* (patient 2), *Streptococcus pneumoniae* (patient 3) and *Pseudomonas aeruginosa* (patient 3). In patient 1, sputum culture was positive for *P. aeruginosa*. Acute bronchitis episodes were more often treated with  $\beta$ -lactams variously associated with quinolone or aminosid during a period of about 10 days. No modification in lung function was observed despite the treatment of the bronchitis episodes. Transbronchial lung biopsies were performed in patient 2. Histological examination revealed peribronchial infiltration made up of well-differentiated lymphocytes.

Patient 2 was alive 24 months after diagnosis of airway obstructive disease. Patient 1 developed severe pulmonary hypertension with no known cause other than HIV infection, and died of wasting syndrome and HIV-related encephalopathy 24 months after the onset of obstructive airway disease. Patient 3 died of wasting syndrome 38 months after being diagnosed with airway obstructive disease.

## Discussion

We have described three HIV-infected patients with rapidly increasing afebrile dyspnoea related to airway obstruction. In two patients, the decrease in FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio, and FEF<sub>25-75</sub> developed in less than 1 yr. This accelerated obstructive disorder was associated with bronchiectasis. The outcomes of the three patients was characterized by multiple relapses of bacterial bronchitis.

No classical causes of genetic or acquired bronchiectasis, such as pertussis or measles pneumonia, foreign body inhalation, mycobacterial infection, hypogammaglobinemia, rheumatoid arthritis, or cystic fibrosis history, were identified in the present patients [7]. Although all three patients were smokers, the clinical course was not compatible with smoke-related bronchial disease alone because of the short time over which the patients developed bronchiectasis. It should be noted that patients 1 and 2 were known *i.v.* drug abusers. However, these two patients had not used *i.v.* drugs for more than 3 yrs when they developed dyspnoea. Airway function analysis, chest radiography, and chest CT scan depicted differing pathologies from the panlobular emphysema or foreign particle embolization commonly associated with *i.v.* drug abusers [8, 9]. Moreover, the pathological analysis of lung biopsy in patient 2 did not show panlobular emphysema or pulmonary vascular granulomatosis. None of our patients had a past history of overdose or aspiration pneumonia, both of which are classical causes of bronchiectasis in *i.v.* drug abusers [8, 10]. Other lung diseases related to *i.v.* drug abuse, such as non-cardiogenic oedema, bronchospasm, eosinophilic pneumonia, clearly differ from the manifestations observed in the present patients [11].

Obstructive disorders have been reported previously in HIV-infected patients [2-5]. In these studies, airway obstruction was related to opportunistic pneumonia or Kaposi's sarcoma. No evidence of mycobacterial, parasitic or mycotic agents was isolated from sputum, brush and bronchoalveolar samples in the three patients. No patient showed radiological or endobronchial aspect of Kaposi's sarcoma. Moreover, the survival of more than 2 yrs without specific treatment rules out opportunistic infection in the three patients.

The obstructive disease observed in the present patient was characterized by a worsening airway obstruction affecting both large and small-calibre bronchi. This differs from the emphysema-like syndrome, described in patients with prolonged HIV infection [5], and characterized by hyperinflation with an increase in residual volume but only minimal airway obstruction. The radiological aspect differs from cases of bronchiolitis obliterans with organizing pneumonia previously reported in HIV-infected patients and characterized by pulmonary condensation [12-14].

Airway obstruction was associated with bronchiectasis in the three patients. Diffuse bronchiectasis has been noted previously on chest CT scan studies in HIV-infected patients with severe CD4 lymphopenia [15, 16]. In most cases, bronchiectasis was associated with recurrent bacterial bronchitis, as in these three patients. As previously reported in patients with advanced HIV disease [17], *P. aeruginosa* was isolated in patients 1 and 3. The dramatically altered lung function in the patients may be secondary to an infectious process associated with chronic *P.*

*aeruginosa* colonization, which is known to accelerate deterioration of lung function in non-HIV bronchiectasis [15, 18]. To date, similar accelerated airflow obstruction has only been observed in bone marrow and lung transplant recipients [19, 20] and in patients suffering from primary immunodeficiency [21]. Indeed, microscopic examination of lung TBBs from patient 2 showing peribronchiolar lymphocytic infiltration similar to that sometimes observed in chronic lung transplant rejection [19] suggests an analogy between post-transplant pulmonary disease and HIV-related obstructive airway disease.

Patient 2 presented some differences in terms of immunodepression status and clinical outcome. The lung function tests practised in this patient showed an immediate serious obstructive disorder that remained stable over time. However, the worsening of the bronchial disease has been observed clinically with a rapid increase in exertional dyspnoea. The radiological finding and recurrent bronchial infection history were similar in patients 1, 2 and 3. The less severe CD4 lymphocytopenia and the lack of *P. aeruginosa* in bronchial samples observed in patient 2 differ from patients 1 and 3. However, the analysis of only a limited number of patients does not allow a conclusive assumption to be drawn as to an earlier stage or different clinical course for patient 2.

In conclusion, accelerated airway obstruction associated with bronchiectasis should be added to the wide spectrum of respiratory complications of human immunodeficiency virus infection. The practice of pulmonary function tests in human immunodeficiency virus infected patients displaying exertional dyspnoea or repeated bronchial infections may permit a better characterization of this bronchial disease in the future.

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