Non-infectious lung manifestations of autoimmune diseases in Cameroon

A M Nana, C Ng nie, A Wandji, P Halle, and M Solange

Abstract
Autoimmune (AI) diseases are secondary to lack of tolerance against self antigens. They may have systemic or organ-specific manifestations. All lung structures can be affected. The aim of our study was to determine clues of diagnosis and treatment facilities for non-infectious lung manifestations of AI disease.

A multi-centre retrospective study was performed from January 2006 to July 2009 in Douala, Cameroon. Twenty-nine patients were included (59% female), with an average age of 42±10 (18–58) years. The lung was the discovery mode of AI disease in 79%. Systemic lupus erythematosus (SLE) was the most frequently observed AI disease (48%). Thirty-eight percent have at least one cure against pleural or smear-negative tuberculosis. Clinical anomalies found were: cough 79%, dyspnoea 69%, and crackles 41%. Morphological anomalies were interstitial lesions in 55% of chest X-rays, 50% of ground grass pattern, and 25% of fibrosis on CT scan; chest function test showed restrictive pattern in 41%. Three (10%) patients were HIV positive with a CD4 cell count more than 500/mm³. Two patients underwent talc pleurodesis for recurrent pleural effusion. General steroids were prescribed to all patients, hydroxychloroquine to 31% and azathioprine to 21%. At the time of writing, 18 patients were still being followed up and 3 (10%) had died. AIs exist in many countries. Clues of diagnosis of non-infectious pulmonary involvement are a patient presenting with chronic respiratory symptoms, crackles at physical examination, negative sputum smear, and unusual chest X-ray abnormality for tuberculosis.

Introduction
Autoimmune (AI) diseases are a heterogeneous group of disorders that result from a breakdown in tolerance against self antigens. Their origin is unknown, and many factors (immunogenetics, neuroendocrine, infectious, toxic, or environmental) may lead to their development. Several mechanisms are described to explain this self-reactivity, ranging from direct cross-reactions between infectious or environmental antigens and self antigens to indirect reactions via super antigens, or bystander mechanism. AI diseases are classified as those with systemic manifestations (sub divided by well-defined criteria into lupus, scleroderma, Sjogren syndrome, rheumatoid arthritis, polymyositis), mixed connective tissue disease combining several criteria of well defined diseases, and undifferentiated connective tissue disease. Another group of AI diseases are organ-specific diseases such as thyroiditis and autoimmune hepatitis. Many systemic AI diseases can affect the lung, and all structures from the trachea to the parenchyma and pleura may be involved.

AI diseases exist in all countries of the world. Their diagnosis is easy in developed countries and difficult in poor countries, and mainly confirmed by treatment trial. In Cameroon, lung specialist activity is dedicated to treatment of respiratory infection mainly tuberculosis (TB); non-infectious diseases are poorly evaluated and their prevalence is unknown. Respiratory symptoms related to AI diseases in our settings are associated with infectious diseases. The aim of our study was to determine clues of diagnosis and possible treatment for non-infectious lung manifestations of AI disease in poor countries.

Methods
We carried out a descriptive retrospective study from January 2006 to July 2009 simultaneously in the General Hospital and Laquintinie Hospital in Douala, Cameroon.

We included patients without lung infection with respiratory symptoms in a known or newly diagnosed AI disease. We excluded all patients with AI disease and lung infections; patients aged less than 15 years; and those with no chest X-ray or erythrocytes sedimentation rate (ESR) in their file.

The sex, type of AI disease, respiratory and extrarespiratory symptoms and signs, chest X-ray, computerised tomography (CT) scan, lung function results, and biological tests were recorded for all patients. We also noted duration, frequency, and intensity of respiratory symptoms and physical chest signs, such as rhonchus, crackles, wheezing, and pleural findings. Dyspnoea was classified using the New York Heart Association (NYHA) scale. From chest X-rays, lesions were classified according to interstitial, parenchyma, or pleural localisation and from CT scan images, ground-glass
opacities, honeycomb opacities, bronchial dilatations, and fibrosis were recorded. Restrictive-like syndromes were described as slow vital capacity (SVC) and forced vital capacity (FVC) below 80%, obstructive syndrome when the ratio of forced expiratory volume in 1 second (FEV1)/FVC was below 70%, and finally the mixed syndrome associated with both abnormalities. In our study, no bronchial washing or lung biopsy was performed. Other examinations and analysis carried out were guided by clinical findings such as echocardiogram, renal function test, or dermatological evaluation. To follow up the treatment, liver function test and ionic examinations were performed. Patients’ treatments were noted, as well as underlying events. All these data were analysed by Excel 2005 and Epi Info 2000 software.

Results
Characteristics of patients
Twenty-eight patients were identified as having a non-infectious pulmonary manifestation of AI disease, representing 26% of all patients treated for AI diseases and 0.4% of all newly diagnosed TB cases. Seventeen (59%) were female. Their average age was 42±10 years (18–58). AI disease was known in 6 (21%) and lung manifestation was the discovery mode in 23 (79%) patients. Systemic lupus erythematosus (SLE) was the most frequently found AI disease in 14 (48%) patients. Note that five (17%) patients had an unclassified disease. The average duration of respiratory symptoms before diagnosis was 12.6 months (2 months to 8 years). Eleven (38%) patients had at least one anti-TB cure – five patients for pleural TB and six others for smear-negative pulmonary TB. We found skin lesions in four (14%) SLE patients, and thrombo phlebitis in two (7%) SLE patients, one associated with pericardial effusion. We also found pulmonary hypertension associated to scleroderma; sinusitis in Shurg and Strauss vasculitis; end-stage renal disease requiring dialysis in Wegener’s granulomatosis; and thyroiditis in unclassified AI disease.

Respiratory abnormalities
Dry cough was reported by 23 (79%) patients, with a median duration of 11.5 months; dyspnoea reported by 20 (69%), mainly grade I and II of the NYHA scale, and 17 (59%) reported weight loss. The physical signs were dominated by crackles in 14 (48%) and signs of pleural effusion 5 (17%). Note that 6 (21%) had a normal physical examination.

Table 1 Patients’ data according to specific group of the AI disease found

<table>
<thead>
<tr>
<th></th>
<th>SLE (n=14)</th>
<th>Rheumatoid arthritis (n=3)</th>
<th>Scleroderma (n=2)</th>
<th>Vasculitis† (n=4)</th>
<th>Undifferentiated (n=5)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>10/4</td>
<td>2/1</td>
<td>1/1</td>
<td>1/3</td>
<td>3/2</td>
<td>17/11</td>
</tr>
<tr>
<td>Newly diagnosed AI disease</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Prior anti-TB treatment</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Crackles</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>X-ray findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Pleural</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Alveolar</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Lung function test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictive</td>
<td>n=6</td>
<td>n=3</td>
<td>n=1</td>
<td>n=3</td>
<td>n=4</td>
<td>17</td>
</tr>
<tr>
<td>Obstructive syndrome</td>
<td>1 (65%*)</td>
<td>2 (75%, 55%)</td>
<td>1 (43%)</td>
<td>2 (58%, 74%)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Mix syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: AI: auto immune, SLE: systemic lupus erythematosus, TB: tuberculosis, * percent of vital capacity, †vasculitis: Wegener granulomatosis, Shurg and Strauss vasculitis.
Data of one patient with anti phospholipids syndrome (APL) are not reported in the table.
A lung function test was performed by 17 (59%) patients and showed a restrictive-like syndrome in seven patients; three had obstructive pattern and five had normal lung function.

Biochemical data
Inflammation was present in all patients; median ESR was 59 mm/hour in the first hour and 78 mm/hour in the second hour; median C reactive protein (CRP) was 38 milligram per litre. Auto antibodies were available in only 12 (41%) files, anti-nuclear antibody was positive in 91% of patients tested, ranging from 1/20 to 1/1280, rheumatoid factor was positive in 45%, and native DNA antibodies positive in only 27%. Three (10%) patients were infected with HIV, with an average CD4 T cell count greater than 500/mm³.

Outcome
At the time of writing of this paper, 18 (62%) patients were still being followed up, 8 (28%) were lost to the study, 3 (10%) had died (pulmonary hypertension, brain thrombo phlebitis, infectious pneumonia in an unclassified AI disease). Two (7%) patients underwent talc pleurodesis for recurrent pleural effusion. All patients received steroid treatment, administered daily as bolus (14%). Other drugs prescribed were hydroxychloroquine in 9 patients (31%), azathioprine in 6 (21%), bolus of cyclophosphamide in 4 (14%), and methotrexate in 3 (10%).

Comments
AI disease can be diagnosed and managed in sub-Saharan countries, although infectious diseases are more frequent.4-11 Even in northern countries with diagnosis facilities the incidence is low.12 The course of disease before diagnosis was long associated with alternative diagnosis; this fact was reported in Senegal.9 The most frequent alternative diagnosis found was smear-negative and pleural TB. Isoniazid, a first-line anti-TB drug, can induce auto-antibody production and drug-induced lupus;13,14 some publications point to its role in aggravating pre-existing lupus.15 For 79% of our patients, pulmonary manifestations led to the diagnosis of AI diseases; Bauer et al16 found 41% in the UK. This difference could be due to poor organisation of the health system, lack of training of medical personnel in recognising AI diseases and absence of referral habit when treating a patient. Overall findings on clinical,17 radiological,18,19 respiratory function test,20 and biological manifestations were similar to those found in the literature. We did not find any acute pulmonary manifestations or ‘shrinking lung syndrome’ described in numerous publications.21,22

Human immunodeficiency virus serology was positive in three patients with a high CD4 cell count; the relationship between viral infection and onset of autoimmune disease is well described23 also with HIV infection.23,24 Correctly managed, we have a survival rate similar to that by a Senegalese team,9 in Zimbabwe the rate of death in lupus patients was higher. One restriction that can lead to patient death is the cost of laboratory exams and treatment, particularly as no health insurance was available.

Conclusions
AI diseases are present in our regions but are less common than infectious diseases. They suffer from a delayed diagnosis. Clues of diagnosis of pulmonary involvement are a patient presenting with chronic respiratory symptoms, negative HIV test, negative sputum smear, chest X-ray abnormalities that are unusual for TB. Treatment is available and mortality of the disease is low when correctly managed.

References