Respiratory involvement in systemic lupus erythematosus

D. Carmier, S. Marchand-Adam, P. Diot, E. Diot, Coordinators: A. Bergeron, H. Nunes, E. Marchand

Service de pneumologie, CHRU François-Rabelais de Tours, université François-Rabelais de Tours, 37044 Tours, France
Service de médecine interne B, hôpital Bretonneau, CHRU François-Rabelais de Tours, université François-Rabelais de Tours, 2 bis, boulevard Tonnellé, 37044 Tours cedex, France
Inserm U618, IFR 135, faculté de médecine, université François-Rabelais, Tours, France

Summary  Respiratory involvement in systemic lupus erythematosus (SLE) is not as well-known as the cutaneous, rheumatological and renal manifestations. It occurs frequently but the diagnosis may be difficult because of the heterogeneity of the anatomical and clinical presentations. A precise diagnosis is crucial as new immunosuppressive drugs have considerably improved the prognosis. The pathology involves genetic, endocrine, environmental, pharmacological and immunological factors with a cytotoxic reaction of auto-antibodies against complement, a circulating immune complex reaction and a hyperactivity of B lymphocytes. Respiratory involvement in SLE can be classified in five groups based on the anatomy: pleural involvement, infiltrating pneumonia (lymphoid interstitial pneumonia, bronchiolitis obliterans with organizing pneumonia and acute lupus pneumonitis), airways involvement (upper airways, bronchi), vascular involvement (pulmonary hypertension, acute reversible hypoxaemia, alveolar haemorrhage, and antiphospholipid syndrome), muscular and diaphragmatic involvement (shrinking lung syndrome). Treatment is based, depending upon the type of involvement and its severity, on steroids which may be combined with immunosuppressants and plasmapheresis.

© 2010 Published by Elsevier Masson SAS.
Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the production of autoantibodies directed against antigens, mainly nuclear, and the formation of immune complexes [1]. Respiratory involvement is not as well-known as the cutaneous, rheumatological and renal manifestations, even though it was described by Osler as early as 1904 [2]. It occurs frequently but the diagnosis may be difficult because of the heterogeneity of the anatomical and clinical presentations. A precise diagnosis is crucial as new immunosuppressive drugs have considerably improved the prognosis. SLE as the specific cause of pulmonary manifestations should only be considered after formally ruling out an infectious or iatrogenic disorder in these patients, the most often immunodepressed [3].

Pathogenesis of lupus

Several factors are involved in the onset and persistence of the disease: genetic (C1q, C2 or C4 complement deficit, complement receptor deficit, major histocompatibility complex [MHC] polymorphism with HLA-A1, B8, and DR3), endocrine (female prevalence, role of oestrogen), environmental (exposure to X-ray and ultraviolet radiation, Epstein-Barr virus or viral RNA), drug-related (beta-blockers, isoniazide, penicillamine), and/or immunologic (cytotoxic reaction of autoantibodies against complement, reaction to circulating immune complexes) [1]. Animal models of spontaneous lupus (such as the New Zealand Black [NZB] mouse) have shown intrinsic B cell hyperactivity as their common denominator. This B cell hyperactivity is characterised in vitro by autoantibody and anti-hapten activity. Response to the mitogen or to T lymphocyte stimulation is excessive. However, the primary immune activity of B cells is often faulty.

The origin of B cell hyperactivity is probably mixed with intrinsic hyperactivity and hyperactivity in response to excessive T cell solicitation induced by the antigen. The hyperactive B cells incorporate the autoantigens then present them via the HMC to nuclear autoantigen specific helper T cells (that could result from a lack of thymus regulation, also called lack of immune tolerance). As the B cells are no longer controlled, or are deceived by shared antigen characteristics between autoantigen and extrinsic antigen, overproduction of antibodies directed against the autoantigens is observed. These autoantibodies could play a direct antigenic role (as antibodies against the N-methyl-D-aspartate receptor in lupus with neurologic manifestations, anti-Ro autoantibodies in cutaneous lupus, or antiphospholipid thrombosis) or an indirect role through formation of antigen. The antigen and the antibodies are detected in the alveoli and interstitium by immunofluorescence [9]. Chronic infiltrating and sometimes fibrotic pneumonia is produced in the rabbit after intravenous administration of bovine serum albumin, and is characterised by the presence of deposits in the capillaries, and in the interstitium of antigens, immunoglobulin, and a low level of complement [10]. In other models, the NZB mouse or the NZW (New Zealand white) mouse, the presence of immunoglobulin deposits (but not C3) has been noted in the perivascular and peribronchial zones, associated with interstitial lymphoplasmacytic infiltration [11];

• in humans, specific autoantibodies have been associated with most pulmonary manifestations of SLE. For example, diffuse infiltrating pneumonia has been associated with anti-SSA antibodies [12,13]. CIC with anti-SSA antibodies could be selectively deposited in the lung and cause the initial response. The level of antinuclear antibodies eluted from lung tissue appears to be higher than in the serum, suggesting compartmentation in these sites, possibly related to the presence of autoantigen [14]. The effectiveness of plasmapheresis in patients with acute lupus pneumonia or with alveolar haemorrhage (AH) suggests the importance of autoantibodies in the pathophysiology of this pulmonary damage [15,16];

• the CIC deposits in human SLE prove their implication in the disease. Immunoglobulins with or without complement have been found in the alveolar walls and capillaries of patients with diffuse infiltrating pneumonia [14,17]. This hypothesis is reinforced by the presence of DNA, IgG and C3 on immunofluorescent microscopy of lung tissue in patients with acute lupus [18]. Likewise, CIC deposits in the alveolar septa, as well as the alveolar basal membrane and capillaries, large vessels and bronchi, have been revealed by immunofluorescent and electron microscopy in patients with SLE presenting AH [19,20]. Finally, CIC have been found in pleural effusion [21]. Comparing patients presenting SLE with renal damage and SLE patients with AH showed the same microvascular presence of CIC deposits and induction of proteases at the origin of most of the tissue damage observed.

Even though the aetiology of SLE is not clear, the mechanisms involved in tissue deterioration, in particular the vessels and the kidneys, implicate immune complexes. An elevation in native anti-DNA antibodies often precedes episodes of the disorder [5]. Reductions in these same antibodies and circulating immune complexes are also associated with deposits or the consumption of CIC and autoantibodies in kidney tissue, indicating active renal disease. Native anti-DNA antibodies and CIC are thus detected in the glomeruli of patients. The increase in circulating immune complexes can be linked to impairment of Fc receptor function that could prolong the circulation of CIC and worsen the tissue damage [6—8].

Several facts support the implication of CIC in the pathogenesis of pulmonary manifestations in SLE:

• laboratory models of pulmonary lesions by immune complexes mimic human lupus disease. In the rat, haemorrhagic lesions rich in polymorphonuclear neutrophils (PPN) are generated by the interbronchial administration of heterologous antibodies, and of intravenous administration of antigen. The antigen and the antibodies are detected in the alveoli and interstitium by immunofluorescence [9]. Chronic infiltrating and sometimes fibrotic pneumonia is produced in the rabbit after intravenous administration of bovine serum albumin, and is characterised by the presence of deposits in the capillaries, and in the interstitium of antigens, immunoglobulin, and a low level of complement [10]. In other models, the NZB mouse or the NZW (New Zealand white) mouse, the presence of immunoglobulin deposits (but not C3) has been noted in the perivascular and peribronchial zones, associated with interstitial lymphoplasmacytic infiltration [11];

• in humans, specific autoantibodies have been associated with most pulmonary manifestations of SLE. For example, diffuse infiltrating pneumonia has been associated with anti-SSA antibodies [12,13]. CIC with anti-SSA antibodies could be selectively deposited in the lung and cause the initial response. The level of antinuclear antibodies eluted from lung tissue appears to be higher than in the serum, suggesting compartmentation in these sites, possibly related to the presence of autoantigen [14]. The effectiveness of plasmapheresis in patients with acute lupus pneumonia or with alveolar haemorrhage (AH) suggests the importance of autoantibodies in the pathophysiology of this pulmonary damage [15,16];

• the CIC deposits in human SLE prove their implication in the disease. Immunoglobulins with or without complement have been found in the alveolar walls and capillaries of patients with diffuse infiltrating pneumonia [14,17]. This hypothesis is reinforced by the presence of DNA, IgG and C3 on immunofluorescent microscopy of lung tissue in patients with acute lupus [18]. Likewise, CIC deposits in the alveolar septa, as well as the alveolar basal membrane and capillaries, large vessels and bronchi, have been revealed by immunofluorescent and electron microscopy in patients with SLE presenting AH [19,20]. Finally, CIC have been found in pleural effusion [21]. Comparing patients presenting SLE with renal damage and SLE patients with AH showed the same microvascular presence of CIC deposits and induction of proteases at the origin of most of the tissue damage observed.
apoptosis in the kidney and lung [22]. However, other studies have not succeeded in confirming the presence of these immunoglobulin deposits in the lung [18,23].

- Systemic lupus erythematosus is an autoimmune disorder characterized by B cell hyperactivity.
- The B cell hyperactivity is both intrinsic and secondary to excessive antigen dependent T cell solicitation.
- Overproduction of antibodies directed against autoantigens is noted.
- Complement activation and secretion of cytokines (IL10 and IFNγ) result in the inflammatory reaction and the release of proteases causing most of the tissue damage observed.
- Circulating immune complexes play a role in the pathogenesis of pulmonary manifestations.

Classification and frequency

SLE is the autoimmune disorder where pulmonary damage is found the most frequently. Its prevalence is 20 to 90% depending on the criteria retained for cohorts (ranging from clinical symptoms to histological data) [24–26]. Over half of the patients with SLE have presented pulmonary manifestations at least once during the course of the disease; these manifestations can involve at least one of the respiratory compartments (pleura, pulmonary parenchyma, airways, pulmonary vessels, and respiratory muscles) [3,27]. Respiratory involvement can reveal the disease. Its onset changes the prognosis. It was associated with an increase in risk of mortality by a factor of two in a cohort study of 600 patients [28–30]. The severity of thoracic manifestations varies from asymptomatic pleural involvement to acute respiratory distress. Rapid worsening of respiratory involvement is always possible and often indicates active lupus disease.

The specific thoracic manifestations of lupus can be acute or chronic, and are usually classified in five anatomical groups (Table 1):

• pleural disease;
• infiltrating pulmonary disease;
• airway disease;
• pulmonary vascular disease;
• muscle and diaphragm involvement;
• the prevalence of pulmonary involvement in SLE is 20 to 90%;
• pulmonary involvement increases mortality;
• respiratory involvement varies in severity and can be acute or chronic;
• involvement is classified in five groups: pleural, pulmonary, airway, vascular, and muscle;
• the diagnosis, often difficult, is based on analysis of imaging studies, respiratory function tests, alveolar lavage, and more rarely histology.

Pleural involvement

Pleural disease is seen more often in SLE than in other collagen diseases.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pleuropulmonary manifestations in systemic lupus erythematosus.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td>Acute lupus pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td></td>
</tr>
<tr>
<td>Diffuse alveolar haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td></td>
</tr>
<tr>
<td>Pleuritis with or without effusion</td>
<td></td>
</tr>
<tr>
<td>Reversible acute hypoxaemia</td>
<td></td>
</tr>
<tr>
<td>Pulmonary thrombosis</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td></td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Usual interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td></td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td>Upper airway dysfunction (epiglottitis, laryngitis, crico-arytenoid arthritis)</td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td></td>
</tr>
<tr>
<td>Diaphragmatic dysfunction and shrinking lung syndrome</td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td></td>
</tr>
<tr>
<td>PAH</td>
<td></td>
</tr>
<tr>
<td>Pulmonary thromboembolic disease</td>
<td></td>
</tr>
<tr>
<td>Mediastinal adenopathy</td>
<td></td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension.

Pleural involvement in the most frequent thoracic manifestation in SLE, affecting 45 to 60% of patients in the course of the disease [31] and up to 93% in an autopsy study [32]. It is one of the American College of Rheumatology classification criteria for SLE [30] (Table 2).

It is more frequent in men than women, and in the black population [27].

Pleural involvement in SLE can be asymptomatic, but the most often presents with chest pain, dry cough, fever, and dyspnoea occurring in the context of an exacerbation of SLE, often revealing the disease.

Effusion can be uni- or bilateral, without a predilection for either side, the most often small to moderately in abundance, and can be recurrent. It can sometimes be “dry” pleuritis without effusion, diagnosed on the typical pleural pain. Pericardial involvement is often associated and should be sought.

Before suggesting SLE-associated pleuritis, the priority must be exclusion of other causes of pleural effusion in a patient with SLE (infection, pulmonary embolism, drug-induced, lupus nephritis, heart failure).

Pleural fluid is typically a sterile yellow or serosanguineous exudate with a variable cell count, predominantly polymorphonuclear neutrophils or lymphocytes. Pleural fluid immunological tests have their limits. A high level of antinuclear antibodies (> 1/160) in pleural fluid is strongly indicative of SLE-related pleural involvement but only in the case of known lupus disease; a low level requires investigation of another cause for the effusion. In the absence of any lupus disease, a high antibody level indicates paraneoplastic pleurisy in over half the cases [33]. Data concerning antinu-
Table 2: The 1982 American College of Rheumatology diagnostic criteria for systemic lupus erythematosus, revised in 1997: four or more of the 11 criteria are required for diagnosis.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Malar “butterfly” rash</td>
</tr>
<tr>
<td>2</td>
<td>Discoid rash</td>
</tr>
<tr>
<td>3</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>4</td>
<td>Oral or nasopharyngeal ulceration</td>
</tr>
<tr>
<td>5</td>
<td>Nonerosive arthritis involving 2 or more joints</td>
</tr>
<tr>
<td>6</td>
<td>Pleurisy or pericarditis</td>
</tr>
<tr>
<td>7</td>
<td>Renal disorders: proteinuria &gt; 0.5 g/24 h or cellular casts</td>
</tr>
<tr>
<td>8</td>
<td>Neurologic disorders: seizures or psychosis</td>
</tr>
<tr>
<td>9</td>
<td>Haematologic disorders: haemolytic anaemia or leucopenia &lt; 4000/mm³; or lymphopenia &lt; 4500/mm³ or thrombocytopenia &lt; 100,000/mm³</td>
</tr>
<tr>
<td>10</td>
<td>Immunologic disorders: presence of LE cells or native anti-DNA antibodies or anti-Sm antibodies; false positive serology for syphilis</td>
</tr>
<tr>
<td>11</td>
<td>Abnormal antinuclear antibody titre (in the absence of drugs associated with drug-induced lupus): abnormal antinuclear antibody titre by immunofluorescence, or an equivalent assay at any point in time in the absence of drugs associated with drug-induced lupus</td>
</tr>
</tbody>
</table>

Clear antibody and complement assays are disputed [33,34]. Pleural histology studies finding lymphoplasmacytic infiltration are not specific. Vasculitis elements and CIC deposits are rare. Histology study of the pleura is however indispensible to rule out other causes, in particular tuberculosis and pleural carcinomatosis [35].

Treatment of pleural involvement depends on the severity of thoracic symptoms and the progression of lupus disease. No treatment is proposed for asymptomatic pleural involvement. If pleural involvement is symptomatic but isolated, without evidence of systemic exacerbation of lupus, treatment with non-steroidal anti-inflammatory drugs can be proposed. In the recurrent presentations, corticosteroid therapy is adequate, often long-term. Hydroxychloroquine can sometimes be a cortisone-sparing treatment [31]. When a systemic exacerbation of lupus involves pleurisy, treatment is corticosteroids, sometimes associated with other immunosuppressants. Exceptionally, the abundance and the recurrence of effusion have required surgical treatment with pleurodesis [36].

Infiltrating pulmonary involvement

The diagnosis of SLE-specific infiltrating pulmonary involvement is difficult. On the one hand, the disease can affect different levels and tissues in the respiratory tract, sometimes making the interpretation of imaging studies and pulmonary function tests difficult. On the other hand, the potential pulmonary toxicity of certain treatments should not be forgotten, as well as possible infectious complications in the context of underlying immunosuppression.

The involvement is rarely severe clinically, contrary to that observed in scleroderma and dermatomyositis [31]. The diagnosis is the most often suggested by the onset of dyspnoea. Three forms specifically related to SLE based on anatomic pathology, imaging and clinical criteria have been described:
- chronic interstitial pneumonias, including lymphoid interstitial pneumonia (LIP);
- bronchiolitis obliterans with organizing pneumonia (BOOP);
- acute lupus pneumonitis.

Chronic interstitial pneumonia

Clinically symptomatic chronic interstitial pneumonia is observed in 3 to 13% of patients with SLE, but this is rarely severe [31]. Using only imaging criteria, the frequency is higher, between 6 and 24% on the chest radiograph and can reach 70% on CT scans [37].

A sequential evaluation study of pulmonary function was carried out for a duration of two to seven years in 25 SLE patients aged between 15 and 68 years (35 ± 15 years, mean ± SD), including eight smokers who were clinically free of respiratory symptoms at the initial evaluation [38]. The first evaluation revealed restriction (total lung capacity 76 ± 3%) and deterioration in CO transfer (DLCO 72 ± 4%), both moderate. Follow-up did not reveal any significant deterioration in these values with time. An autopsy study of 18 patients with SLE (17 females and one male aged between 18 and 64 years) has been reported [39]. The supposed cause of death was not indicated, requiring caution with interpretation of the data. Non-infectious (interstitial) pneumonia was found in two cases, described as moderate in one case and severe in the other. Pulmonary fibrosis was found in six cases, but described according to anatomical pathology criteria as mild (four cases) or moderate (two cases). In this old study, the ATS/ERS classification of diffuse infiltrating pneumonias was not used [40].

The severity of the infiltrating pulmonary involvement was not correlated with the lupus disease serological markers. However, an association has been reported between chronic interstitial pneumonia and the presence of anti-Ro (SSA) antibodies [41]. This link could suggest the possible role of Sjögren syndrome secondary to SLE in the onset of pulmonary involvement, and particularly in LIP.

LIP is observed in various immune disorders, with a particularly high frequency in Sjögren syndrome and SLE [42]. It corresponds to infiltration of the interstitium by polyclonal lymphocytes associated with pneumocyte hyperplasia and moderate macrophagic and lymphocytic alveolitis. The clinical signs and pulmonary function values are those of diffuse infiltrating pneumonia (crackles, restriction syndrome) with...
however a low frequency for finger clubbing. Concerning imaging studies, the preponderant pattern is diffuse ground glass opacities that can be associated with small indistinct and thin-walled cysts [41]. Radiological signs of pulmonary fibrosis are rare.

Apart from the specific case of LIP, the histological pattern usually observed in SLE chronic interstitial pneumonia is that of non-specific interstitial pneumonia (NSIP) with, at varying degrees, inflammatory cell infiltrate, peribronchial lymphoid hyperplasia, true homogeneous interstitial fibrosis without alternating healthy and diseased zones, and type II pneumocyte hyperplasia [43]. There are no, or few, foci of fibroblasts and honeycomb architectural remodelling characteristic of usual interstitial pneumonia; the prognosis is better.

Organizing pneumonia

Organizing pneumonia (OP) formerly called BOOP can follow pulmonary insults of various origins: infections, drug-induced, irradiation, inhalation of toxic agents, gastroesophageal reflux, and systemic disorders [44]. OP was reported in a dozen patients with SLE without any radiological or clinical particularities related to other causes [45,46]. OP is thus not specific to SLE and its onset can be considered to be coincidental. However, OP can, as in rheumatoid arthritis, be the initial manifestation and result in the diagnosis of SLE [46]. OP can occur even though the patient does not present any signs of active SLE [45]. As with the other causes of OP, corticosteroid therapy is effective and the prognosis is good.

Acute lupus pneumonitis

Acute lupus pneumonitis has been very widely described, but in reality its frequency does not exceed 4% of cohorts [35,43]. It has probably been overdiagnosed. In a large and old autopsy study of 120 cases, all the cases attributed to acute lupus pneumonitis were, with hindsight, related to an associated cause such as infection or aspiration pneumonia [25]. In the studies including histology examinations, alveolar lesions were sometimes noted, with interstitial oedema and hyalin membrane formation [47]. These lesions corresponded more to AH with capillary involvement [20].

The diagnosis is difficult as the clinical picture is non-specific, both clinically (cough, dyspnoea, chest pain, fever and hypoxia) and radiologically (uni- or bilateral alveolar infiltrates, focal or diffuse and non-specific) [43]. Two factors contribute to the diagnosis: on the one hand, the onset of pneumonia is practically always contemporaneous with exacerbation of the disease with involvement of other organs (kidneys and serous membrane), and on the other hand, the pneumonia occurs in a majority of cases in patients with anti-SSA antibodies (82%); the antibodies have been suspected of playing a role in pathophysiology [13].

The major preoccupation is the formal exclusion of an infectious process. Bronchoalveolar lavage should be performed, if permitted by respiratory status. Pulmonary histology with a surgical biopsy contributes little; the lesions are generally non-specific and moreover the procedure is dangerous in this context.

There is no standard treatment. Corticosteroid therapy is effective in most cases, often started with a bolus of 15 mg/kg for one to three days and switched to the oral route at 1 mg/kg per day. In the case of resistance, immunosuppressants can be used, and even plasmapheresis [3,48]. Immunoglobulins must be administered with caution as they are often associated with renal damage. In all cases, empiric antibiotic therapy is introduced.

Airway involvement

The upper and lower airways can be affected with variable clinical presentations.

The upper airways

Probably rare, prevalence is difficult to estimate with precision because involvement is frequently asymptomatic. It is found in 0.3 to 30% of patients depending on the series [48—50]. Clinically, the symptoms are non-specific (dry cough, laryngeal discomfort, dyspnoea, crowing inspiration) but often accompanied by other general manifestations of lupus disease. Acute epiglottitis, laryngitis, vocal cord oedema, necrotic tracheitis, and early post-intubation stenosis are observed [51,52]. Crico-arytenoid arthritis has been described and responds well to corticosteroid treatment [53,54].

Bronchial diseases

Stenosis of the trachea or main bronchi is rare [38,55,56].

A reduction in FEV1/VC was reported with a frequency of 10% in a study that did not take tobacco smoking into account [57]. The prevalence of these obstructive ventilatory disorders was only 6% against 0% in the control groups in the study by Andonopoulos et al. that excluded smokers [56]. Initial damage to the small airways (defined as MEFV 25—75 below 60% of predicted value) is frequent (24%), with no difference between patients with lupus and the control group (patients free of any respiratory disease and matched for smoking) [56]. However, surveillance of pulmonary function tests for two to seven years revealed a progressive decline in values indicating small airways damage with time, independent of smoking [38,58].

In one of the rare cases where a histology study was available, foci of bronchiolitis with obstruction of the lumen of the bronchioles were identified associated with immunoglobulin deposits (IgG and IgM) and fibrinogen in the alveolar walls [59]. Systemic corticosteroid therapy and cyclophosphamide [60—62] have provided improvement in some cases of bronchiolitis obliterans. The long-term prognosis is unknown.

In the studies based on analysis of thin-slice and high-resolution (HRCT) thoracic CT scans of patients with lupus, a higher frequency of bronchiectasis (13 to 21%) than that suspected by the clinical presentation was reported [37,63,64]. The origin of this bronchiectasis could be involvement specific to lupus, sequelae of bronchopulmonary infection, or the consequence of treatment-induced immunosuppression.
**Vascular involvement**

**Pulmonary artery hypertension (PAH) and pulmonary vascular involvement**

Pulmonary vascular involvement was considered to be rare for some time; the consequence of thromboembolic events. It is in fact a distinct entity with an often multifactorial mechanism [31], progressing spontaneously to pulmonary hypertension, and thus serious.

Since improvements in routine screening for PAH with echocardiography and the creation of registers, we know that SLE is the second cause of PAH in connective tissue diseases, after systemic scleroderma [65,66]. This PAH is as frequently primary as secondary. Concerning secondary PAH, this is cardiac in origin in 50% of cases, either post-capillary (cardiomyopathy, valve disease, systemic hypertension), post-embolic in 13% of cases, related to hypoxia in pulmonary fibrosis in 8% of cases, and association of the three mechanisms in 29% of cases [67,68].

Its prevalence is 2.8 to 14% depending on the series, increasing to 43% on follow-up at five years [65–68]. The discovery of lupus usually precedes the diagnosis of PAH with a mean time to diagnosis of 8.8 months for primary PAH against 43 months for secondary PAH. It rarely reveals lupus disease [65]; its onset is sometimes contributed to by medications, in particular combined oral contraceptives, or pregnancy. It is a slowly progressing condition. The associated factors found are: Raynaud phenomenon (present in 39% of patients with PAH, versus 16% without PAH), presence of a rheumatoid factor, anti-ribonucleoprotein antibodies, a high plasma endothelin-1 level [69,70], and in some patients, active disease.

Though the clinical presentation is not different from that of idiopathic PAH, the prognosis is however poorer (45% survival at five years against 68%), especially if accompanied by Raynaud phenomenon, as death is often due to acute heart failure [71]. Concerning pathophysiology, various mechanisms are implicated.

**Autoimmune and inflammatory factors**

The effectiveness of corticosteroid and immunosuppressive treatments argue in favour of this mechanism:

- anticardiolipin antibodies play a specific pathogenic role; their prevalence is high in PAH, up to 70% of cases depending on the series. The thromboembolic mechanism is however only retained in a minority of patients. The anticardiolipin antibodies induce pulmonary capillary microthrombi, a rarely described authentic veno-occlusive disease. The same antibodies apparently also have a direct action on regulatory T cells, whose protective role is known in vascular remodelling by reducing their activity [27,72];
- anti-endothelial antibodies, by analogy with idiopathic PAH, could possibly induce activation of endothelial cells with release of interleukin (IL6) [73];
- mononuclear inflammatory cells could play a role in endothelial proliferation via activation by cytokines. Whether associated or not with circulating immune complex deposits, they are found in plexiform lesions [74].

**Vasospastic factors**

Though vasospasm secondary to hypoxia is an obvious mechanism in the context of pulmonary fibrosis, the hypothesis of primary pulmonary arterial vasospasm is advanced. It is based on the observation of a greater frequency of Raynaud phenomenon in patients with lupus disease with PAH (60% against 20 to 30% in those who do not present PAH) [75].

**Genetic factors**

A predisposition has been suggested because of the occurrence of PAH in twins with lupus disease [27].

The standard treatment does not differ from that for idiopathic PAH. Anticoagulation is systematic, associated with oxygen therapy in the case of hypoxaemia (< 60 mmHg) and diuretics [76]. The recourse to more specific treatments is usual. Even though there are currently no controlled studies, clinical and haemodynamic improvement has been reported in small series with immunosuppressant therapy with corticosteroids and cyclophosphamide, often used in association [67,77,78]. For this reason, these drugs are usually prescribed as first-line treatment. Administration of the vasodilators used in idiopathic PAH (bosentan, sildenafil, prostacyclin and analogues) is usual, with clinical and haemodynamic benefits reported in small series [79–81]. Associated therapies are in the course of evaluation. Only epoprostenol must be used with particular caution, because of the specific risk of thrombocytopoenia in this condition [67,82].

**Acute reversible hypoxaemia (ARH)**

In 1991, Abramson et al. reported a stereotypic respiratory picture in patients with lupus during an exacerbation of the disease [83]. Since then, several authors have reported similar observations, leading to an estimation of frequency at 25% for this syndrome in SLE [3,27,31]. The clinical picture associates acute dyspnoea, chest pain, and possible pleural involvement. Pulmonary imaging is normal while there are often severe pulmonary function abnormalities associating marked hypoxaemia, and deterioration in vital capacity and carbon monoxide diffusion. The symptoms are remarkably reversible under corticosteroid treatment [3]. Martínez-Taboada et al. however question the reality of this syndrome and consider this picture to be more an "index of disease activity" [84]. It always accompanies a flare-up of the disease, both clinical and serologic, and responds to low doses of corticosteroids, otherwise insufficient for an exacerbation of lupus. The pathophysiology is not clear. By analogy with the description of acute respiratory distress syndrome, the mechanism apparently calls first and foremost on aggregation and activation of neutrophils mediated by complement activation [83]. The role of vascular adhesion cell molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), found at high levels, has also been suggested [85]. Both mechanisms, possibly associated, apparently result in pulmonary vascular disease by endothelial activation and lumen occlusion by leucocyte aggregate, responsible for severe hypoxaemia [31].

Corticosteroid therapy at low doses, associated with high doses of aspirin is sometimes effective [86]. However, the
recourse to higher doses of corticosteroids is usually necessary to halt the disease exacerbation.

**Alveolar haemorrhage (AH)**

AH is an infrequent but potentially serious complication of SLE. Its frequency is estimated at between 2 and 5.4% of patients, found in up to 66% in autopsy series, with a mortality rate of 50 to 95%. However, rapid recognition of this complication permits a considerable improvement in survival with less than 25% deaths [87]. Spontaneous developments can be rapidly unfavourable with death occurring in the 48 hours following onset of the first symptoms. As in acute lupus pneumonitis, AH occurs the most often in patients with an established diagnosis of lupus. Active nephritis is associated in 60 to 93% of cases, and AH could even be precipitated by the high doses of corticosteroids administered for renal involvement [88]. AH however reveals the disease in 20% of cases [89] thus making diagnosis more difficult. The diagnosis should be suggested with the sudden appearance of dyspnoea associated with a cough, fever, and pulmonary infiltrate on the radiographs, identified on the CT scan revealing a “ground glass” appearance (Fig. 1). The association with a fall in haemoglobin level is usual. This picture should however enable the ruling out of other causes, in particular pulmonary infection, pulmonary embolism, left heart failure and coagulopathy, which can also be associated with AH. Carbon monoxide transfer measured at over 130% of the normal contributes to the diagnosis. Its interest is however limited; these modifications are only noted early in the picture and in only one case in three [3]. Bronchoscopy with bronchoalveolar lavage is the key examination providing confirmation of the diagnosis and above all eliminating an infectious cause [43]. A surgical biopsy, a high risk procedure in this context, should only be exceptional.

![CT scan lung parenchymal window image 1 mm in thickness through the cardiac chambers showing bilateral ground glass opacities corresponding to intra-alveolar haemorrhage.](image)

The histology data has characteristics in common with acute lupus pneumonitis, associating interstitial infiltration by mononuclear and polynuclear cells, the presence of hyalin membranes, alveolar necrosis, oedema, microvascular thrombi and intima proliferation with deposits of haemosiderin phagocytizing macrophages [20]. Inflammation of the small pulmonary vessels, arterioles and capillaries has however been found. In the study by Zamora et al., 80% of the patients presented pulmonary capillaritis [89]. Myers and Katzenstein [20] described a clinical picture associating vasculitis and microangiitis of the small pulmonary vessels and small pulmonary muscle arteries. The association of capillaritis and microangiitis is apparently more specific to SLE.

Immunofluorescence studies have revealed, in half the cases, deposits of IgG and C3 in the alveolar cells, capillaries and interstitium, associated with the presence of immune complexes [20,43].

The pathophysiology of AH remains unclear. The mechanism is probably not pathognomonic. Acute lupus pneumonitis and AH, because of certain histological similarities, could be two expressions of the same inflammatory process characterized by involvement of the alveolar-capillary unit. The inflammatory involvement of pulmonary capillaries and arterioles found in AH however suggests the possibility of distinct mechanisms. Infectious agents could act directly on vascular endothelium. In their series, Zamora et al. found a notable number of pulmonary infections associated with AH (Herpes simplex virus -1, cytomegalovirus, *Legionella pneumophila* and *Staphylococcus aureus*) [89]. The role of anticardiolipin antibodies, found at high levels by some authors, does not in the end seem to be worth retaining [87,89].

Concerning treatment, there are no randomized studies to support recommendations. Management takes into account the experience derived from small cohorts [89,90]. Corticosteroids are usually prescribed as first-line treatment. In severe forms, corticosteroid therapy is started with high-dose boluses, readily associated with immunosuppressant treatment with cyclophosphamide. Even though the results with cyclophosphamide are discordant in terms of the effect on survival in small series [89,90], it remains the treatment of choice because of its effectiveness on the other organs involved. Plasmapheresis, whose efficacy is only anecdotally reported, should be reserved for forms resistant to corticosteroids and immunosuppressants [91]. Finally, empiric antibiotic therapy is recommended, even in the absence of obvious respiratory tract infection.

**Thrombosis — antiphospholipid syndrome (APS)**

Antiphospholipid syndrome (APS) is defined as the association of vascular thrombosis (arterial or venous) and/or obstetric complications (early or late fetal death), the presence of lupus type circulating anticoagulant and/or anticardiolipin antibodies and/or anti-ß2GP1 antibodies confirmed at an interval of 12 weeks [92]. Its prevalence in lupus is 30%, and increases with disease progression.

The pulmonary manifestations of APS, constitute “pulmonary antiphospholipid syndrome”. The dominant manifestation is thromboembolic events affecting the pulmonary arteries and their branches. Wahl et al., in their meta-analysis of 2249 patients, emphasized this thromboembolic risk, multiplied by six in patients with lupus...
Respiratory involvement in systemic lupus erythematosus
disease with anticardiolipin antibodies, compared with lupus
disease without anticardiolipin antibodies [93]. The
contradictory results reported in large cohort studies (Cervera
et al.: 1000 patients, Abu-Shakra et al.: 390 patients) have
raised the question of a different pathogenic role depend-
ing on the type of anticardiolipin antibodies [94,28]. A high
level of IgG (and anticardiolipin antibodies directed against
β2GP1) could indeed be associated with a higher risk of
thrombogenesis [95].

Concerning treatment, there are two different situa-
tions:
• secondary prevention (patients who have already pre-
sented thromboembolic events) with long-term anticoag-
ulation with a target INR between 2 and 3. In the case of
a new thrombotic event despite well-managed antico-
agulant treatment, the target INR is increased and the
introduction of low doses of an antplatelet agent dis-
cussed (aspirin, 75 to 100 mg/day) [96];
• primary prevention (discovery of anticardiolipin antibod-
ies in patients without a thromboembolic history); there is
no consensus. Treatment with low doses of aspirin can be
proposed though its efficacy has not been demonstrated
[97]. Some authors advise a higher dose (325 mg/day) [98].

Antiphospholipid antibodies are also implicated in the
pathophysiology of intra-AH, PAH, acute respiratory distress
syndrome, and heart valve lesions [99].

Finally, catastrophic antiphospholipid syndrome is a
specific form of APS resulting from multi-organ failure due
to thrombotic microangiopathy [100]. It must be systemat-
cally considered and sought. This formidable complication
of APS associates massive small vessel thrombosis affecting
at least three organs, preferentially the kidney, the central
nervous system and heart. Pulmonary involvement is
present in 66% of cases [101]. A triggering factor is often
found (infection, neoplasia, surgical procedure). Despite
A link has been reported between chronic interstitial
pneumonia and the presence of anti-Ro antibodies.

Shrinking lung syndrome

Some patients with SLE occasionally present dyspnoea with-
out pleuroparenchymal or vascular involvement. In these
cases, a rare and little-known syndrome should be con-
sidered: shrinking lung syndrome (SLS) corresponding to
respiratory muscle involvement.

SLS was first described during lupus disease, then later
reported in other autoimmune disorders such as Sjögren syn-
drome, rheumatoid arthritis and mixed connective tissue
diseases [103].

It occurs within four months to 24 years after diagnosis of
SLE but can be contemporaneous. The prevalence of SLS is
not known and is difficult to estimate, but a study of trans-
diaphragmatic pressures found diaphragmatic dysfunction in
56% of the patients with lupus [104].

SLS should be considered in a patient presenting dysp-
noea with orthopnoea; pleural type chest pain worsened by
inspiration is often the most important symptom. The clini-
cal examination is non-specific. Pallor in the lower lobes
associated with reduced chest expansion, when present,
should however suggest the diagnosis and lead to imaging
studies.

The chest radiograph shows small lungs and elevated
hemidiaphragms without pleuroparenchymal involvement
apart from possible lines of atelectasis in the lower lobes
[105] (Fig. 2).

The thoracic CT scan confirms the absence of pleuropul-
monary disease apart from the lines of atelectasis in the
lower lobes, resulting from hypoventilation.
The pulmonary function tests show restrictive ventilatory
disorder with reduced inhaled and exhaled lung volumes.
Carbon monoxide transfer is not deteriorated.

Laboratory studies are unremarkable, apart from the
reported association with the presence of anti-SSA antibod-
ies [106].

The diagnosis is difficult because of the need to rule
out other pleuroparenchymal and vascular lupus-related

• Pulmonary vascular involvement is a distinct entity,
with an often multifactorial mechanism, that
progresses towards pulmonary arterial hypertension
with poor prognosis.
• SLE is the second cause of PAH in connective
tissue diseases, after scleroderma. Acute reversible
hypoxaemia is apparently due to aggregation and
activation of neutrophils by complement activation
and the effects of vascular adhesion cell molecule-1
(VCAM-1) and intercellular adhesion molecule-1
(ICAM-1).
• Alveolar haemorrhage reveals the disease in 20% of
cases.
• Early diagnosis and treatment of alveolar
haemorrhage considerably improves the prognosis.
• The prevalence of antiphospholipid syndrome in
lupus is 30%.
• The main manifestations are thromboembolic
events; it can be complicated by formidable multi-
organ failure due to thrombotic microangiopathy.

• Respiratory involvement is rarely clinically severe;
simple dyspnoea is often indicative.
• There are three types of pulmonary involvement:
chronic interstitial pneumonia, bronchiolitis
obliterans with organizing pneumonia, and lupus
pneumonitis.
• A link has been reported between chronic interstitial
pneumonia and the presence of anti-Ro antibodies.
• In lymphoid interstitial pneumonia, the role of
Sjögren syndrome secondary to SLE has been
suggested.
• The frequency of acute lupus pneumonitis has been
greatly overestimated; it does not exceed 4%.
• Diagnosis is based on its association with an
exacerbation of the disease and the presence of anti-
SSA antibodies.
disorders, lupus myopathy and cortisone-induced myopathy, as well as other causes of diaphragmatic and phrenic nerve dysfunction [107].

The pathogenesis of SLS remains controversial. Gibson et al. reported the observation of seven patients with lupus and SLS who presented low maximum inspiratory pressures and abnormal transdiaphragmatic pressures suggesting diaphragm dysfunction. The initial hypothesis was myositis type diaphragmatic involvement [108]. The only anatomical pathology study in the literature found the predominant lesions were diaphragm muscle fibrosis [109]. Laroche et al. advanced the hypothesis of more global involvement associating the accessory respiratory muscles and the diaphragm muscles [104]. More recently, Hardy et al. proposed a neurogenic origin through phrenic nerve involvement based on the observation of a patient with lupus who presented bilateral phrenic nerve paralysis documented by surface electromyogramme (EMG) in response to cervical magnetic stimulation and transcutaneous electrical stimulation [110].

| Table 3 Treatment strategies in SLE depending on the type of respiratory involvement. |
|-----------------------------------------------|-----------------------------------------------|
| Thoracic involvement                          | Treatments                                    |
| Pleural involvement                           | No treatment                                  |
|                                               | NSAIDS                                        |
|                                               | Corticosteroid therapy                        |
|                                               | Hydroxychloroquine                            |
| Chronic pulmonary fibrosis                    | Corticosteroid therapy                        |
| Lymphoid interstitial pneumonia               | Corticosteroid therapy                        |
| Organizing pneumonia                           | Corticosteroid therapy                        |
| Acute lupus pneumonitis                        | Corticosteroid therapy                        |
| PAH                                            | Corticosteroid therapy and cyclophosphamide   |
|                                               | Specific treatments for PAH (bosentan, sildenafil, iloprost aerosol, epoprostenol) |
| APS                                            | Primary prevention: low-dose aspirin?         |
|                                               | Secondary prevention: anticoagulation (INR between 2 and 3) ± low-dose aspirin |
| Alveolar haemorrhage                           | High-dose corticosteroid therapy + cyclophosphamide ± plasmapheresis |
| Reversible acute hypoxaemia syndrome           | Corticosteroid therapy                        |
| Airways                                        | Corticosteroid therapy ± cyclophosphamide     |
| Shrinking lung syndrome                        | Corticosteroid therapy                        |
|                                               | β2-agonists                                   |
|                                               | Theophylline                                  |
|                                               | Immunosuppressant drugs                       |
The measure of maximum respiratory pressure and transdiaphragmatic pressure during maximum voluntary inspiration through the mouth after electrical stimulation lacks reproducibility. It requires the full cooperation of the patient, often made difficult by the chest pain. Only exploration of the diaphragm with bilateral anterolateral magnetic stimulation of the phrenic nerves coupled with EMG detection and evaluation of muscle response by measuring transdiaphragmatic pressure seems to be reproducible and could be useful in investigation of SLS. This painless technique that does not require the cooperation of the patient is more precise than transcutaneous electrical stimulation and cervical magnetic stimulation [111,112]. Its interest has however only been reported in one case and further studies are necessary for validation [113].

No treatment strategies have been validated. Corticosteroids at a daily dose of 30 to 60 mg prednisone equivalent are usually effective providing improvement in clinical status and lung volumes [114]. β2-agonists and theophylline use has been anecdotic, without thorough assessment. Corticosteroid-sparing immunosuppressants such as azathioprine, methotrexate and cyclophosphamide have been proposed by analogy with treatment of myositis, but without proper evaluation [115]. The same is true of respiratory physiotherapy and non-invasive ventilation.

- Shrinking lung syndrome is due to respiratory muscle involvement.
- The symptoms are dyspnoea with orthopnoea and pleural type chest pain worsened by inspiration.
- Its pathogenesis is still debated (muscular or neurogenic).

**Conflict of interest statement**

None.

**References**

[8] Seligman VA, Suarez C, Lum R, Inda SE, Lin D, Li H, et al. The Fcgamma receptor IIIA-158F allele is a major risk factor for...


Respiratory involvement in systemic lupus erythematosus


