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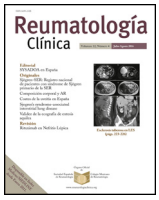

Review Article

Pulmonary Manifestations in Systemic Lupus Erythematosus: Pleural Involvement, Acute Pneumonitis, Chronic Interstitial Lung Disease and Diffuse Alveolar Hemorrhage☆

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ABSTRACT

Systemic lupus erythematosus is the diffuse autoimmune connective tissue disease that most frequently involves pulmonary involvement, affecting 20% of 90% of the patients. The percentage varies depending on the defining criteria (symptoms, pulmonary tests or histopathological studies). At least once during the disease course, 50% of those affected have pleural and/or pulmonary manifestations, which are associated with higher morbidity and mortality. Pulmonary involvement has no correlation with lupus activity biomarkers, and it is necessary to rule out infectious processes in the initial approach. Bacterial infection is most frequently the cause of lung involvement in lupus and is one of the most important causes of death. Pulmonary involvement is considered to be primary when it is associated with disease activity, and secondary when other causes participate. Drugs have been reported to be associated with pulmonary damage, including interstitial disease. The incidence of malignant lung diseases is increased in systemic lupus erythematosus. Treatment depends on the type and severity of pulmonary involvement.

Manifestaciones pulmonares en lupus eritematoso sistémico: afección pleural, neumonitis aguda, enfermedad intersticial crónica y hemorragia alveolar difusa

Palabras clave:
Lupus eritematoso sistémico
Afección pulmonar
Afección pleuropulmonar
Neumonitis lúpica
Hemorragia alveolar

RESUMEN

El lupus eritematoso sistémico (LES) es la enfermedad autoinmune difusa del tejido conectivo que con mayor frecuencia afecta al pulmón, la cual oscila del 20 al 90%, porcentaje variable en función de los criterios empleados en las cohortes estudiadas (sintomatología hasta histopatología). Más del 50% de los pacientes presentan manifestaciones pleuropulmonares por lo menos una vez durante el curso de su enfermedad y tal afección se asocia a mayor mortalidad. Las anomalías pulmonares no correlacionan con marcadores séricos de actividad lúpica. Es prioritario descartar infección pulmonar en la evaluación inicial, ya que la afección parenquimatosa más frecuente es la infección bacteriana y constituye una de las principales causas de muerte. También se han descrito participación de agentes atípicos, que incluyen los que condicionan enfermedades granulomatosas y otros oportunistas. La afección pleuropulmonar en LES puede estar directamente asociada a LES o ser secundaria. Fármacos pueden ocasionar neumonitis e incluso progresión a enfermedad intersticial. Hay un incremento discreto en el riesgo de neoplasias pulmonares.

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Systemic lupus erythematosus (SLE) is the autoimmune disease with the highest prevalence of pulmonary involvement, which ranges from 20% to 90% of the patients, depending on the criteria employed in the cohorts being studied (symptomatology or histopathology).[1,2] More than 50% of the patients develop pleuropulmonary manifestations at least once during the course of the disease; likewise, pleuropulmonary involvement has been associated with a higher rate of mortality.[3] Symptoms such as pleuritic pain, cough and/or dyspnea are usually the first signs of SLE-related pulmonary involvement, or can be the first manifestation of SLE. Up to 60%[4] of the patients have reported dyspnea at least once throughout the disease and abnormal respiratory function tests have been documented in 30%–40%,[5–7] as well as anomalies on computed tomographic scans in 55%–70%.[7] In the Latin American GLADEL (Grupo Latino Americano de Estudio del Lupus) cohort, at least one pleuropulmonary manifestation was observed in 421 of the 1480 patients included (28.4%).[8]

Lung anomalies do not correlate with serum markers of lupus activity. It is essential to rule out pulmonary infection in the initial evaluation, as bacterial infection (67%) has been reported to be the most frequent parenchymatous involvement[1] and is one of the major causes of death.[9] In 2007, Kinder et al.[10] reviewed cases of pneumonia in a cohort of SLE patients and identified the etiology to be bacterial in 75%, mycobacterial in 12%, mycotic in 7% and viral in 5%. The participation of atypical agents and/or opportunist pathogens has also been described.[11]

The risk factors reported for pleuropulmonary involvement in SLE include age at diagnosis of generalized lupus erythematosus (GLE) ≥30 years (odds ratio [OR] 1.42; 95% confidence interval [CI]: 1.10–1.83), presence of lower respiratory tract infections (OR 3.19; 95% CI: 2.05–4.96), nonischemic heart disease (OR 3.17; 95% CI: 2.41–4.18), ischemic heart disease (OR 3.39: 95% CI: 2.08–5.54), systemic (OR 2.00; 95% CI: 1.37–2.91), ophthalmic (OR 1.58; 95% CI: 1.16–2.14) and renal manifestations (OR 1.44; 95% CI: 1.09–1.83),[8] hypocomplementemia (relative risk [RR] 3.38; 95% CI: 2.17–5.24) and high titers of anti-double-stranded (ds) DNA antibodies (RR 1.30; 95% CI: 0.78–2.24).[12]

The conditions that constitute pleuropulmonary involvement in SLE are considered primary when they are directly attributed to SLE or secondary when they are attributable to other causes. Among the latter, infections have a prevalence of nearly 60% and have been responsible for from 30% to 50% of the deaths of patients with SLE.[9] Acute respiratory distress syndrome (ARDS) has a variable prevalence of 4%–15% with mortality of nearly 70% and it is mostly secondary to sepsis.

Drugs like methotrexate (MTX) and rituximab can result in pneumonitis and even progression to interstitial lung disease. Likewise, a slight increase in the risk of neoplasms in general, pulmonary in particular, has been reported in SLE patients.[2]

The disorders that constitute pleuropulmonary involvement in SLE are grouped according to the structures affected:

- Parenchymal involvement[2]:
  - Lupus pneumonitis: prevalence from 1% to 12%.
  - Chronic interstitial lung disease: prevalence from 3% to 13%.
  - Diffuse alveolar hemorrhage (DAH): prevalence from 2% to 6%, high mortality.
- Pleural involvement: 50%–70%, in the form of pleuritis and/or effusion.[2]
- Vascular involvement:
  - Pulmonary hypertension: prevalence of 0.5%–4.2%.[13]
  - Embolism/pulmonary thromboembolism (PTE): deep venous thrombosis with/without PTE in 9%, related to activity. The presence of antiphospholipid antibodies (in up to 30% of the patients with SLE) increases the risk of thromboembolic events by 35%–40%.[14]
  - Acute reversible hypoxemia: a rare condition that is characterized by unexplained hypoxemia with no evidence of parenchymal involvement. Its pathophysiology is controversial, but leukocyte aggregation and complement activation in the pulmonary vasculature have been proposed. It has a good response to steroids within 72 h.[3]
- Shrinking lung syndrome: prevalence of 0.6%–0.9%, characterized by unexplained dyspnea, elevated diaphragm and reduced lung volumes without interstitial involvement. The etiology is controversial but phrenic neuropathy, inflammatory myopathy and, more recently, pleural disease have been suggested. It responds well to steroids.[14]
- Airways: both lower and upper, with a prevalence that ranges from 0.3% to 30%; its course is predominantly subclinical.[3]

Below we review the epidemiological, clinical, diagnostic and treatment aspects concerning the conditions that the authors considered to be of particular interest due to their high frequency or because of the severity they represent.

Pleural Involvement

Prevalence. Pleuritis constitutes the most widespread thoracic manifestation in SLE. Pleuritic pain is present in 45%–60% of the patients, pleural effusion in up to 50% and, in autopsies, it has been reported to be encountered in up to 93%.[2] The experience documented in the GLADEL cohort is similar; pleural involvement was the most common pleuropulmonary manifestation (24%),[8] and it was observed that ischemic and nonischemic heart disease (OR 2.99; 95% CI: 2.33–3.82 and OR 1.99; 95% CI: 1.28–2.09, respectively) constitute risk factors. Other factors include the presence lupus nephritis, hypocomplementemia (C3 and C4) and high levels of anti-dsDNA antibodies.[12] A recent study that included 119 patients with SLE and pleural involvement demonstrated that, even in regions in which tuberculosis is endemic, the main etiology of pleural effusion in these patients continues to be the underlying disease (52%).[15]

Clinical aspects. The main symptom is pleuritic pain, usually accompanied by fever, cough and dyspnea. On occasion, pleural effusion is asymptomatic and can only be detected by radiography. The effusions are usually small and bilateral, although they can also be unilateral. They tend to be evanescent and recurrent.[16]

Diagnostic aspects. The differential diagnosis should include musculoskeletal pain, pulmonary embolism, infection, heart failure, uremia and neoplasm. Analysis of the pleural fluid is the main diagnostic tool. This typically is an exudate with a slight elevation of leukocytes, predomination of mononuclear cells (there are also polymorphonuclear cells) and normal or slightly low glucose levels. The differential diagnosis should include rheumatoid arthritis (RA), characterized by a higher level of leukocytes and lactate dehydrogenase, as well as a low glucose level.[2] The role of the detection of antinuclear antibodies (ANA) in pleural fluid for the diagnosis of lupus pleuritis is controversial. Two recent studies[17,18] have reported ANA at titers >1:160 with sensitivity of 85%–90% and specificity of 80% for the diagnosis of lupus pleuritis in patients with lupus; however, high titers can also be encountered in other conditions. Fig. 1 shows evidence of pleural effusion in a patient with lupus who reported clinical data associated with pleural involvement.

Pleural biopsy. Rarely performed, usually only when the diagnosis is uncertain. The findings are nonspecific: lymphocytic and plasma cell infiltration, fibrosis and fibrinous pleuritis.