



Clinicopathological conference

Dyspnea in a patient with systemic lupus erythematosus

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ABSTRACT

A 33-year-old woman with a previous history of systemic lupus erythematosus complained of exertional dyspnea and pleuritic chest pain accompanied by polyarthritis. Chest-x-rays revealed an elevation of the right hemidiaphragm. We discuss the diagnostic and therapeutic approach.

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Disnea en una paciente con lupus eritematoso sistémico

RESUMEN

Paciente de 33 años, con antecedentes de lupus eritematoso sistémico que consulta por disnea progresiva de moderados esfuerzos acompañada de dolor torácico derecho de características pleuríticas. En la radiografía simple de tórax se evidenció elevación del hemidiafragma derecho. Se discute a continuación el abordaje diagnóstico y terapéutico de la paciente.

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Presentation of the case (Dr D. Taverner)

We present the case of a 33-year-old woman with no known allergies to drugs no any toxic habits. Her history of interest includes a urinary tract infection due to *Escherichia coli* in June 2006, iron deficiency anemia of multifactorial origin and systemic lupus erythematosus (SLE) which was diagnosed in november 2004 after presenting symmetrical polyarthritis of the wrists, proximal interphalangeal (PIP), and knee joints, with sustained leuko and lymphopenia, positive antinuclear antibodies (ANA) with a high titer (1/2560), and anti-double stranded DNA antibodies (dsDNA) >100 U (*Crithidia lucilae*). She had a single positive determination

of anticardiolipin antibodies (aCL) IgM in March 2006, but with no record of prior thrombosis or recurrent abortions. The rest of the autoantibody profile, including anti-Sm, anti-Ro (SSA), anti-La (SSB), anti cyclic citrullinated peptide antibodies (CCP), rheumatoid factor, Coombs test and lupus anticoagulant were negative.

Treatment with hydroxycloquine (200 mg/p.o.) was begun in March 2005 and methotrexate was added afterward (10 mg/week p.o.) in June 2005 until February 2006; the latter was suspended for lack of efficacy, requiring high dose steroids (up to 20 mg/day) for the control of joint pain. Treatment with azathioprine was then installed (150 mg/day p.o.) from February 2006 until September 2006, also suspended for lack of efficacy. She currently continues treatment with hydroxycloquine (400 mg/day) since March 2005, prednisone 15 mg/day and indomethacin 50 mg/8 h.

The patient came in for a control visit in which she referred progressive dyspnea with moderate efforts which had lasted for 5-6 months, accompanied by right thoracic pain of pleuritic

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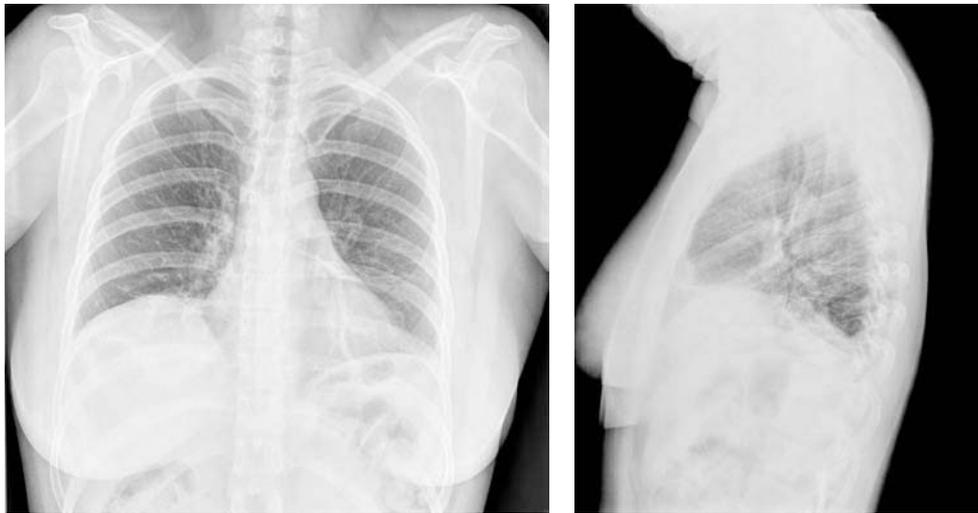


Figure 1. Simple chest x-ray. A: front. B: profile.

characteristics, without cough or sputum. During the past week she had felt the dyspnea increase, presented fever of 38°C and a bout of polyarthritis which affected shoulders, hands, and knees.

Upon examination we found the patient feverish, normotensive, with a baseline oxygen saturation of 98% and a respiratory frequency of 18 beats/min. She had no skin lesions or peripheral adenopathy was seen. Lung examination revealed normal respiratory sounds with right basal hypophonesis and, regarding the joints, arthritis of the right wrist, metacarpophalangeal (second and third on the right hand, third on the left hand), PIP (third on the right hand and fifth on the left hand) as well as limitation in the extension of both elbows and shoulders and pain with an increase in the temperature of the left knee was also seen, with no clear evidence of arthritis. The rest of the examination was normal.

Determinations of glucose, creatinine, serum electrolytes, and muscle enzymes resulted normal. The blood count revealed: hemoglobin 9.6 g/dL (MCV, 82.5 fl; MCH, 25.4 pg) with normal leukocytes and platelets. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were 23 mm/h and 4.1 mg/dL respectively. Coagulation tests were normal, while D dimer was weakly positive (650 ng/mL; normal <500 ng/mL). Urine sediment was normal as were 24 h urine proteins.

Blood cultures were performed, as well as mycobacterial cultures, and serology for hepatitis C, hepatitis B, *Mycobacteria pneumoniae*, *Rickettsia connori*, Epstein-Barr virus, cytomegalovirus, *Legionella pneumoniae*, *Chlamydia pneumoniae*, *Parvovirus B19* and *Aspergillus*, all negative. The antigens for *Legionella* and *neumococcus* in urine and the PPD were negatives.

Chest x-rays showed an elevation of the right diaphragm, laminar atelectasia of the left lung base and impingement of the left costophrenic angle (Figure 1). The electrocardiogram presented sinus rhythm of 80 beats/min, without alterations in repolarization. Abdominal echography showed little diaphragmatic movement, with no evidence of intra-abdominal collections. A thoracic angio-CT was performed where several atelectasias were seen on both lungs, affecting the apical and basal posterior segments of the right inferior lobe, middle lobe, lingual, and left inferior lobe. No signs of vascular affection or pleural effusion were seen. In addition, a transthoracic echocardiogram was performed without finding ventricular dysfunction, valvular affection, pericardial effusion, or signs of pulmonary hypertension.

Spyrometry showed a forced expiratory volume during the first second (FEV₁) of 58%, with a FEV₁/forced vital capacity (FVC)

Table 1

Causes of dyspnea in patients with systemic lupus erythematosus

Primary	
Pleural disease	
	Pleuritis
	Pneumothorax
Parenchymal disease	
	Acute lupus pneumonitis
	Chronic lupus pneumonitis (fibrotic)
	Alveolar hemorrhage
	Airway obstruction
Vascular disease	
	Pulmonary hypertension
	Thromboembolism
	Reversible acute hypoxemia
	Vasculitis
Respiratory muscles disease	
Upper airway disease	
Secondary	
	Infections
	Drug toxicity
Accompanying illness	
	Uremic pulmonary edema
	Postpartum pneumonitis
	Bronchitis/BOOP
	Sarcoidosis
	Interstitial lymphocytic pneumonia
	Lymphoma

Abbreviations: BOOP, bronchiolitis obliterans with organizing pneumonia. Modified from Wallace et al.²

relationship of 86. Carbon dioxide diffusion capacity (DLCO) was moderately reduced. Respiratory muscle function showed moderate intensity muscle dysfunction, with maximal inspiratory pressure (MIP) of 62 cm H₂O (60% of predicted) and maximum expiratory pressure (MEP) of 78 cm H₂O (54% of predicted).

Differential diagnosis (Dr J.A. Gómez-Puerta)

We are faced with a patient with SLE which predominantly affects the joints and who presents activity in the form of polyarthritis and fever with an increase in acute phase reactants (CRP and ESR). Additionally she presents long-standing respiratory difficulty,

without tachypnea or desaturation, and with no evidence of an overlying infectious process (multiple microbiology studies were negative).

SLE is a complex systemic disease in which patients can manifest dyspnea for several causes that include both complications associated to the disease (primary causes) as well as concomitant complications (secondary causes)¹² (Table 1). Taking into account the history of a positive determination of aCL and a positive D dimer, the first option is to rule out pulmonary thromboembolism (PTE). However, we must mention that the pretest probability was a low one because the patient was not tachycardic and did not present desaturation. In this case, angio-CT ruled out PTE or pleural affection.

Once these 2 causes of dyspnea were ruled out, I think we should focus on a restrictive cause that explains dyspnea and the diaphragm elevation seen both on the simple x-ray and the abdominal echography.

Respiratory function tests showed a restrictive ventilator problem (probably extrinsic), accompanied by diaphragm muscle dysfunction. The causes of myopathy in patients with SLE are diverse and include inflammatory myopathies, both related to polymyositis and dermatomyositis (which can accompany SLE in up to 10% of cases) as well as myopathy related to the disease.³ In second place we must mention myopathy secondary to drug toxicity, which includes mainly steroids,⁴ antimalarials,⁵ and statins, among others.⁶ Other less frequent causes of myopathy in SLE are "myastheniform" diseases or concurrent myasthenia gravis and muscle weakness due to vitamin D, which is normally insufficient in patients with SLE due to the lack of sunlight exposure, the use of sunblock and the activity of the disease itself.⁷ Finally, we must mention isolated diaphragm dysfunction.

The present case did not show signs or symptoms of systemic myopathy or muscle weakness of the extremities or other muscle groups. At the same time, muscle enzymes were normal, making an inflammatory myopathy even less likely. In spite of the fact that the patients had received 2 drugs with myotoxic potential (antimalarials and steroids), selective diaphragmatic affection due to this was unlikely. We do not know the concentrations of 25-OH vitamin D in this patient, however hypovitaminosis D is more often related to fatigue and generalized muscle weakness than with the selective affection of certain muscle groups.⁷

Clinical diagnosis (Dr J.A. Gómez-Puerta)

Taking all of the above into account and once we have reasonably discarded the most frequent causes of dyspnea in a patient with SLE, I believe the patient could present *shrinking lung syndrome* (SLS).

SLS was originally described by Hoffbrand et al⁸ in 1965 and is characterized by: a) unexplained dyspnea; b) a small lung with a restrictive pattern; and c) diaphragm elevation. SLS is not present exclusively in patients with SLE and has also been described in other systemic autoimmune processes such as systemic sclerosis⁹ and primary Sjögren's syndrome.¹⁰ The exact prevalence of SLS in patients with SLE is unknown. There are currently 70 reported cases in the literature. Warrington et al¹¹ analyzed 49 cases published since 1965 to 1997. They have recently described 21 additional cases.^{9,12-19}

The pathogenesis of SLS is still unknown. It was initially proposed as the cause of laminal atelectasia as a consequence of loss of surfactant.⁸ A primary diaphragmatic dysfunction has also been described (isolated or in the context of a myopathy) determined through the use of esophageal and gastric pressure balloons.²⁰ Rubin et al²¹ performed postmortem studies and found a diffuse but marked diaphragmatic fibrosis in these patients. Diverse factors that restrict thoracic distension have also been pointed out as potential pathogenic mechanisms.²²

Patients with SLS refer exertional dyspnea that progresses for weeks or months, leading to a marked reduction in tolerance to

exercise and, occasionally, can lead to resting dyspnea. Pleuritic pain is also a frequent symptom in these patients. Upon physical examination there was a marked limitation of the thoracic excursion which, on occasion, led to paradoxical respiratory movement and the use of accessory muscles. Lung auscultation is usually normal, although bibasilar rales can be heard as the result of atelectasia in the base of the lungs. Chest x-ray showed the elevation of a hemidiaphragm, and on occasion, basal atelectasia can be seen, as well as pleural thickening and pleural effusion. Arterial blood gas at rest can be normal or can show discreet hypoxemia which worsens with exercise.¹¹

SLS can be present in any phase of the disease (between 4 months and 24 years after the diagnosis) or can even be its first manifestation.¹² SLS can be related or not to myositis and disease activity. Some patients have a history of recurrent pleuritic pain or a history of pericarditis.¹¹

Functional respiratory tests can show a restrictive pattern with a reduced vital capacity (VC) (52%; interval from 18%–90% of predicted value). Patients with concomitant myositis can present even more reduced lung volumes with a VC around 40%. DLCO is usually reduced, but corrected because the alveolar volume is normal or is slightly decreased (95%; interval, 77%–104%). MIP and MEP that determine general respiratory function are usually reduced in the majority of cases of SLS described.¹¹ However, these tests underestimate the muscle capacity in certain patients because of incomplete activation during the maneuvers.²³ Therefore, Laroche et al²² evaluated pressure during forced nasal inspiration (*sniff*), which provide more precise information on the activation of inspiratory muscles; 9 of 12 patients with SLS in which measurements of transdiaphragmatic pressure were taken had a completely normal study. In 3 patients, the maximum transdiaphragmatic pressure was reduced, but after stimulation of the phrenic nerve it was demonstrated that it was related to an incomplete activation of the diaphragm during a maximum voluntary effort, rather than related to a primary alteration of the diaphragm.²²

Electromyography (EMG) of the phrenic nerve has resulted in disparaging results. Hardy et al¹⁹ and Omdal et al²⁴ found alterations in the form of a phrenic nerve mononeuropathy during EMG. On the other hand, Wilcox et al²⁵ did not find any sign of axonal degeneration in 9 patients studied, and state that it is improbable that SLS is explained by a phrenic nerve neuropathy.

In spite of the different results and taking into account the many limitations of each one of the respiratory muscle tests, I propose to perform a phrenic nerve EMG with the objective of discarding a neuropathy in that territory in our patient.

Results (Dr D. Taverner)

A phrenic nerve electromyogram was performed. She presented partial axonotmesis of the right phrenic nerve with a fall of more than 50% of amplitude with respect to the contralateral nerve and a segregation of the potential. Distal motor latency was symmetrically conserved (Figure 2). Taking all the above into account as well as the radiological studies and the clinical history of the patient, we reached the diagnosis of SLS, related to phrenic nerve neuropathy.

Comments (Dr D. Taverner)

Treatment of SLS is still empirical. In most cases, the dose of steroids is usually increased up to 30–60 mg/day.^{11,15,26} Recently Oud et al¹⁵ described the response to moderate–high doses of steroids (30 and 40 mg/day) in 5 patients with SLS. Two of the patients developed SLS in spite of treatment with methotrexate and hydrochloroquine respectively. The authors pointed out that response was seen after one month of treatment, and up to 4 months after it is begun. However, it must be pointed out that the complete recovery of vital capacity is infrequent.

MNCV curves	MNCV curves	Stimul	
Right phrenic		100 mA	05 mV
Pos. 1 – Rec pos		99.82 mA	5 ms
Pos. 2 – Rec pos			
Left phrenic		96.07 mA	2 mV
Pos. 2 – Rec pos			5 ms

Figure 2. Phrenic nerve electromyogram. MNCV, motor nerve conduction velocity.

Teophyllin has also been shown as useful in SLS, with improvements of up to 31% of lung capacity.²⁷ The use of beta agonists can be beneficial, as mentioned in a case of improvement after treatment with inhaled salbutamol.²⁸ Anecdotal data also supports the use of other immunosuppressants, such as cyclophosphamide or azathioprine in patients with no response to steroids.¹¹

According to data in the literature, the prognosis of patients with SLS is usually favorable. Martens et al²⁹ described a satisfactory progression in 7 patients with SLS followed for a period of 38.5 patients/year. There is only one report in which a patient dies as a consequence of mechanical ventilation dependence with subsequent respiratory failure.²¹

The progression of our patient was favorable; after diagnosis she was treated with monthly intravenous pulse methylprednisolone at a dose of 500 mg for 3 months. She improved progressively with improvement of both the dyspnea and pleuritic pain, and was completely asymptomatic 6 months after the last pulse. A year later she underwent respiratory function tests in which she was observed to be stable with respect to previous testing (total lung capacity, 60%; FEV₁/FVC, 86; moderately reduced DLCO [61%] which was corrected with alveolar volume).

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