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Rapidly progressive fatal interstitial lung disease in a patient with an overlap syndrome of systemic lupus erythematosus and systemic sclerosis

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A B S T R A C T

A 31-year-old woman with a prior history of an overlap syndrome of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) developed fever, pericarditis with pericardial effusion and a rapidly progressive fatal interstitial lung disease. Diagnostic test and procedures, differential diagnosis and therapeutic approach are discussed.

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Enfermedad pulmonar intersticial rápidamente progresiva y fatal en una paciente con síndrome de superposición de lupus eritematoso sistémico y esclerosis sistémica

R E S U M E N

Paciente de 31 años, con historia de síndrome de superposición de lupus eritematoso sistémico y esclerosis sistémica que desarrolla un cuadro caracterizado por fiebre, pericarditis con derrame pericárdico y enfermedad pulmonar rápidamente progresiva y fatal. Se discuten aspectos diagnósticos e indicaciones terapéuticas.

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Case presentation. Dr. Mónica P. Sacnun

Thirty-one-year-old female with no prior history of importance. Risk factors: obesity and sedentary lifestyle. History of disease: cholecystectomy and oophorectomy due to ovarian cyst. In 2003, at the age of 25, the patient began with butterfly-wing malar erythema, photosensitivity, and triphasic Raynaud's phenomenon. Symmetrical, bilateral polyarthritis (affecting hands, feet, and knees) subsequently ensued. She was admitted that same year due to anaemia and pericardial effusion. At the onset of illness, she presented the following laboratory immunological features: antinuclear antibody (ANA) (+) 1/5,120, speckled nucleolar pattern, normal anti-double stranded DNA (dsDNA) (−), extractable nuclear antigens (−), rheumatoid factor (−), and complements (C3 and C4). The simple chest x-rays and osteoarticular x-rays were normal. A 2D echocardiogram revealed moderate to severe pericardial effusion and mild tricuspid insufficiency. With a diagnosis of systemic lupus erythematosus (SLE), she was treated with prednisone (50 mg/day), hydroxychloroquine (400 mg/day), ranitidine (300 mg/day), calcium, vitamin D, and ibuprofen (1,200 mg/day), with improvement of the clinical picture. Later, the steroid dosage was gradually decreased.

By the end of 2003, she began to have intermittent, low-level dysphagia with solid foods and the Raynaud's phenomenon worsened. A calcium channel blocker was added: nifedipine (20 mg/day), with a partial response. Complementary testing included: oesophagogram with sliding hiatus hernia, chest X-ray with images consistent with incipient bibasal interstitial disease, and spirometry manifesting mild restrictive breathing incapacity. Intercostal herpes zoster then began on the left side for which she received specific local treatment.

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In January 2004, the patient was asymptomatic, albeit with mild anaemia. She continued with the same medication, except for prednisone (5 mg/day). The immunological laboratory tests revealed VDRL (+) 2 dils, fluorescent treponemal antibody absorption test (−), anti-neutrophil cytoplasmic antibodies (−), low titre anticardiolipin antibodies (aCL) IgG (+) and IgM (−) and low lupus anticoagulant activity. The patient had no prior history of thrombosis or recurrent miscarriage. The Doppler echocardiogram showed tricuspid regurgitation, pulmonary hypertension (PHT), and mild pericardial effusion. The nifedipine was discontinued and diltiazem (120 mg/day) added. Likewise, low-dose aspirin was added: 100 mg/day.

In September 2004, the patient continued to be clinically stable. She presented patchy ANA (+) 1/5,120, nucleolar (Hep2), VDRL (+) 8 dils, high titre aCL IgG (+), and low titre IgM (+). The routine laboratory workup continued to be within normal limits, except for the anaemia that was compatible with chronic illness.

In November 2004, she presented low grade fever, myalgias, symmetrical, bilateral polyarthritis (hands, knees, feet), and dysuria. The urine culture demonstrated a urine infection due to *Escherichia coli*. Treatment was begun with ciprofloxacin and the dose of prednisone was upped to 20 mg/day, with clear improvement and disappearance of her myalgias and arthritis.

In January 2005 (summer), the patient began to have stress dyspnoea, the Raynaud's phenomenon became worse, and two necrotic ulcers appeared on the third finger of her left hand and on the back of her left leg with persistent cyanosis in her fingers and toes. A high resolution computed tomography (CT) of the chest was performed, revealing alveolytic compromise in both basal zones with incipient pulmonary fibrosis without any other vascular or mediastinal alterations. Treatment was initiated with pulses of cyclophosphamide (CP) at a dose of 1 g monthly. The biopsy of the ulcer of the leg did not show any signs of vasculitis, malignity, or small vessel obstruction. The ulcers gradually healed with local treatment. The dosage of prednisone was lowered to 10/5 mg every other day. The patient only had the first pulse of CP and then quit the treatment, as she was asymptomatic. In October 2005, she consulted due to cyanosis in her fingers and toes, as well as bilateral acrosclerosis. The immunological laboratory findings included speckled nucleolar ANA (+) 1/5,120, extractable nuclear antigens (−), anti-dsDNA (−), VDRL reactive 1 dil, normal C3, and slightly decreased C4 and CH50. The lupus anticoagulant was (−), although aCL could not be performed at that time. She continued her medication, with a prednisone dose of 7.5 mg/day, and she resumed diltiazem (120 mg/day).

In April 2006, she consulted due to pain, swelling and erythema on the palmar aspect of her right forearm and wrist. A simple X-ray showed the presence of subcutaneous calcinosis. Furthermore, she presented several skin lesions in the gluteal region and lower limbs with the appearance of nodes and painful deep infiltrative, inflammatory plaques compatible with lupus panniculitis, which could not be biopsied. The studies showed no variants on the oesophagogram and spirometry, Doppler echocardiogram with minimal pericardial effusion, mild tricuspid regurgitation, and systolic pressure of the pulmonary artery (PSAP) of 28 mmHg. The X-ray of the hands showed diffuse juxta-articular osteopenia and gross amorphous calcifications in the first finger of the right hand and a smaller one on the right ulnar styloid process. The high resolution CT of the thorax evidenced bilateral alveolitis with an increase of the fibrosis in the base of both lungs and spreading to the vertices, far more advanced in comparison with the previous study. CP pulses were resumed, but the patient stopped consulting at the Rosario Provincial Hospital.

In March 2009, at 31 years of age, she was admitted due to fatigue, nausea and vomiting, generalized myalgias, and 39 ºC fever for 10 days. At the time of admission, she was taking prednisone (10 mg/day), omeprazole (20 mg/day), aspirin (100 mg/day), diltiazem (60 mg/day), methoprolol (5 mg/day), methotrexate (15 mg/week), diclofenac and paracetamol. The physical examination showed a heart rate of 100 beats/min, respiratory rate of 18/min, blood pressure 120/80 mmHg, temperature 38 ºC, and weight of 80 kg. The examination of the head and neck displayed jugular ingurgitation, without carotid murmurs. The cardiovascular examination failed to reveal any pathological beats; an apex beat was found in the 5th intercostal space on the left, without thrills. Cardiac sounds were normal, without murmurs or abnormal sounds. The examination of the lungs highlighted fine, bibasal crepitant rales. The abdomen was unremarkable and fist percussion was negative. The patient reported generalized muscle tenderness in the limbs. The skin exhibited livedo reticularis and several nodular inflammatory lesions, and deep infiltrative plaques that were compatible with lupus panniculitis.

The laboratory analyses at the time of admission revealed glucose, creatinine, ionogram, and muscle enzymes all within normal limits. The haemogram yielded the following information: haematocrit 27%, haemoglobin 7.9 g/dL, white blood count 4,600/ml, with normal leukocyte formula and platelets. Globular sedimentation rate and C-reactive protein were 89 mm/h and 6.3 mg/dL, respectively. The urine sediment exhibited proteins (++) and red blood cells (++). The urine culture and serial blood culture were negative. The simple chest X-ray revealed an enlarged cardiac silhouette, compatible with pericardial effusion, discreet prolapse in the left medio-mediastinal arch, intensification of bibasal pulmonary markings and clear costophrenic sinuses. Electrocardiogram with heart rate of 110/min, PR of 160 ms, QRS of 80 ms, a QRS of 0º, negative T waves in D III, V1-V2 with isolated ventricular extrasystoles. The Doppler echocardiogram revealed normal dimensions and motility of the left ventricle, as well as systolic parietal thickening, without any segmental alterations. The systolic fraction of the left ventricle was conserved. The left atrium, right cavities, and aortic, pulmonary, and tricuspid valves were normal. Moderate to severe pericardial effusion was observed with partial collapse of the right atrium without respiratory variability of transmitral flow greater than 10%. The root of the aorta presented a normal diameter. It was difficult to estimate the PSAP. The ejection fraction was 66%. The Doppler echocardiogram was repeated on day 7 of the patient's hospital stay, revealing progression of the pericardial effusion with PSAP of 43 mm; in light of this, the patient was referred to the intensive care unit. She continued to have fever higher than 38 C every day and bibasal pulmonary crepitant rales. Serial blood cultures were repeated, as were urine cultures, all of which were negative. The analyses yielded a haematocrit value of 21%, haemoglobin of 6 mg/dl, ferraemia of 16 mg/dl, white blood count of 2,800/ml with normal formula. Glycaemia, uraemia, and creatininaemia values were normal. A Coombs test was positive. The current picture was considered to represent an exacerbation of the underlying illness and betamethyl-prednisolone pulses were administered at a dose of 1 g/day for 3 consecutive days. In addition, she was given a packed red blood cell transfusion. Over the following days, she became afebrile, without signs of heart failure. Iron and leucovorin were indicated. On day 10 of her hospital stay, the patient presented dyspnoea at rest. The simple chest X-ray exhibited progressive increase of the cardiac silhouette, broadening mediastinal vascularity, disappearance of costophrenic angles, and bilateral and bibasal reticulonodular perihilar radioopacities, with predominance on the right side (Figure 1). The high-resolution chest CT scan showed mild cardiomegaly, pericardial effusion, mild bilateral pleural effusion with predominance on the right side; patchy distribution of segmental, bilateral ground glass opacities, more prominent in the lower pulmonary fields; areas of subpleural, bilateral air trapping, predominating in the upper

Figure 1. Chest X-ray: increased cardiac silhouette, broadening of mediastinal vascularity, disappearance of the costophrenic angles, and bilateral and bibasal perihilar reticulonodular radioopacities, with predominance on the right side.

Figure 2. High resolution computed tomography of the thorax: cardiomegaly, pericardial effusion, bilateral pleural effusion, segmental, bilateral, patchy distribution of ground glass, predominantly in the lower pulmonary fields, areas of subpleural, bilateral air trapping, and bibasal reticulonodular opacities.

pulmonary fields; bibasal opacities reticulonodular opacities, and fluid in the minor fissure (Figure 2).

Treatment with tazonam (4.5 g/6 h) and vancomycin (1 g every 12 h) was initiated. On day 13 of hospitalization, her dyspnoea at rest increased, coinciding with the chest X-ray showing progression of the pulmonary infiltrates and signs of venocapillary hypertension. Oxygen therapy was initially indicated and later, assisted ventilation. After five days of antibiotic therapy, she began to record fever (37.5-38 °C); consequently, treatment with tazonam was discontinued and imipenem (2 g/day) was started. Hydrocortisone (300 mg/day) and amphotericin B (20 mg/day) were added to her treatment. The rate of diuresis decreased and furosemide (60 mg) in continuous perfusion was indicated. Samples for urine culture, serial blood cultures, pericardial fluid (pericardiectomy), as well as the Ziehl-Nielsen staining were all negative. On day 17, a Doppler echocardiogram revealed an ejection fraction of 60%, moderate pericardial effusion, partial collapse of the right atrium, mitral flow with alteration of relaxation, and mild mitral valve

insufficiency. The PSAP was estimated to be 63 mm. On day 20, the patient presented tachypnea, with poor respiratory mechanics, and desaturation. She was put on assisted mechanical respiration in volume-controlled mode. Pneumology was consulted and a biopsy of the lung was carried out. On day 23, the patient coursed with sustained hypotension with no response to fluid infusion. She presented asystole; cardiopulmonary resuscitation manoeuvres were initiated and adrenaline was infused without success. She was pronounced dead on April 11th, 2009.

Differential diagnosis. Dr. Bernardo A. Pons-Estel

The case presented is of a 31-year-old female patient, with a diagnosis of overlapping syndromes of SLE and SSc, hospitalized due to suffering from fever for the preceding 10 days and presenting pericarditis with pericardial effusion, evolving into rapidly progressive interstitial lung disease with hypoventilation, requiring assisted mechanical respiration and determining her demise.

SLE is an autoimmune disease (AID) that can exhibit a very broad spectrum of clinical and immunological manifestations. Moreover, it can overlap with other AIDs, in particular with SSc. On the other hand, SSc is often diagnosed as lupus in its early stages. There is a body of evidence that several AIDs share common susceptibility genes. Such is the case of the *TNFSF4 (OX40L)* gene that codes for the OX40 ligand of the T lymphocyte co-stimulation molecule and the polymorphisms of association have been identified as susceptibility genes for the development of both SLE, as well as SSc.[1] Other genes/loci that are common to several AIDs are *IRF5*, *STAT4*, *PTPN22,* and *BANK1*, which all reveal the shared genetic history of these illnesses, in particular, between SLE and SSc.[2-4]

Inflammation of the pericardium with or without effusion is a common finding in patients who are carriers of AIDs. Generally speaking, immune activity is reflected by the presence of LE, ANA, anti-dsDNA, and FR cells or complement consumption in the fluid obtained by means of pericardiocentesis. In general, pericarditis is expressed as left, retrosternal, precordial pain spreading to the back and to the edge of the trapezium. Clinically, there is pericardial rubbing and tachycardia. If it is of acute onset, it can cause cardiac tamponade in a very short period of time, in which case, further manifestations are added, such as jugular ingurgitation, hypophonetic heart sounds, hepatomegaly, and paradoxical pulse. The differential diagnosis of cardiomegaly on a simple chest X-ray can be difficult, the most common finding being cardiomegaly. The diagnosis must be established by means of a bidimensional echocardiogram. Pericardial effusion (usually exudate) may be the expression of the underlying illness; nevertheless, it may also correspond to an infectious process with which differential diagnosis must be made. Patients with these diseases are known to be more predisposed to infection due to the dysfunction of the immune system added to the usual treatments, such as steroids and immunosuppressants. When considering infectious processes, viral, bacterial, microbacterial, and fungal illnesses should be contemplated. All cultures were negative in the patient currently analyzed.

Raynaud's phenomenon is important in the patient we are dealing with. Its presence at the beginning of the illness is an indicator of the onset of the AID and, in all likelihood, of its evolution toward an overlap syndrome. Raynaud's phenomenon is characterized by the presence of altered microcirculation with triphasic paroxystic vasospasm of the fingers and toes (paleness), followed by vasodilatation (cyanosis), and the return to normal colouring or redness. The imbalance between the secretion of thromboxane A2 (a vasoconstrictor) and prostacyclin (a potent vasodilator) from the vascular endothelium is involved in its pathogenesis. Raynaud's phenomenon may be primary, in the absence of associated illnesses, or secondary, in which case collagen-vascular disorders should be considered as it is a valuable sign, generally occurring early and prior to the development of other

manifestations, such as cutaneous sclerosis or visceral compromise. It is often present in patients with PHT. Videocapillaroscopy of the ungueal bed has been useful in distinguishing between primary and secondary Raynaud's phenomenon.[5] Other methods, such as laser Doppler perfusion imaging are being evaluated.[6] In cases associated with SSc, giant capillaries and microhaemorrhages are found, determining an active pattern when there is a loss of capillaries followed by neoangiogenesis, fibrosis, and "desertification" in subsequent periods. This pattern also differs from the one found in other AIDs such as SLE, dermatomyositis, or antiphospholipid syndrome.[5]

One of the most important challenges for the rheumatologist is to establish the aetiological diagnosis of pulmonary compromise in patients with AIDs.[7] Infections are very commonly the result of alterations to the immune system, such as complement deficit or altered opsonization and neutrophil chemotaxis that predispose to infections due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *E. coli*, or *Klebsiella pneumoniae*; neutropenia gives rise to infections due to *Serratia* or *Pseudomonas aeruginosa*; T cell dysfunctions determine infections due to bacteria *(Listeria monocytogenes, Nocardia, Salmonella)*, fungi *(Cryptococcus, Candida, Aspergillus, Histoplasma capsulatum)*, viruses (cytomegalovirus, smallpox, herpes), and/or parasites *(Pneumocystis jiroveci, Toxoplasma gondii)*. Hyposplenia may also be present, determining infections due to germs such as *Pneumococcus*, *Neisseria meningitides* or *Haemophilus influenzae.*

The infectious pulmonary compromise in these patients demands the maximum effort to identify the microorganism(s) involved, since they will constrain prognosis and treatment.[8] Therefore, invasive study techniques must sometimes be used to obtain samples for culture, immunofluorescence, or electronic microscopy.

When it comes to deciding on treatment, rheumatologists must bear in mind, among others, differential diagnoses such as pneumonitis, lymphocytic pneumonia, pulmonary haemorrhage, pulmonary thromboembolism (PTE), pulmonary reaction to drugs, and infections, given that one area of activity of the illness may call for immunosuppression, which can be fatal in an infected patient.[8] It must be remembered that simultaneous treatment with antibiotics and immunosuppressants may often be indicated.

The clinical picture of pulmonary compromise is similar in most cases. It may begin with coughing, pleuritic pain, expectoration, dyspnoea, hypoxaemia and fever varying between 37.5-40 ºC. Furthermore, pulmonary haemorrhage may present haemoptysis and a sudden fall in haematocrit. The range of progression of the pulmonary infiltrates can, on occasion, be used as a guide to predict aetiology. An acute process evolving over less than 24 h suggests acute bacterial pneumonia, pneumonitis, haemorrhage or PTE. A subacute process lasting several days to a week is more suggestive of viral pneumonia, *P. jiroveci*, *Legionella pneumophila*, mycobacteria, or *Nocardia*. Symptoms coursing over several weeks always points toward tuberculosis, fungal infections (*Histoplasma* or *Coccidioides*), chronic pneumonitis or pulmonary reaction to drugs. In lymphocytic pneumonia, perihilar opacities on the simple chest X-ray leads to a differential diagnosis with cancer. The presence of lobular, segmental, or patchy condensations suggests bacterial or fungal pneumonia, PTE or pulmonary haemorrhage, whereas bilateral alveolar filling is suggestive of pneumonitis, drugs or bacteriaemic pneumonia. Diffuse bilateral interstitial infiltrate speaks to tuberculosis, *P. jiroveci*, cytomegalovirus, *Aspergillus*, drugs or chronic pneumonitis. The presence of mediastinal masses suggests histoplasmosis. The existence of cardiomegaly or pericardial effusion points more in the direction of an underlying autoimmune compromise.

PTE may present in patients with AID.[9] The appearance of thrombotic or thromboembolic phenomena should lead to the suspicion of the presence of an antiphospholipid syndrome. Patients with livedo reticularis, skin ulcers, neurovascular or cardiovascular alterations (particularly in young individuals), recurrent miscarriage, or a false positive blood test for syphilis should cause the physician to be alert to this diagnosis; this is the situation of the patient currently under discussion. In cases of PTE, the ventilation/perfusion scan is used to establish the diagnosis.

PHT is a common complication of SSc and overlap syndromes.[10] It is less prevalent in patients with SLE, which means that it may be an unrecognized manifestation in this disease.[11] In the case of our patient, PHT was another of the findings in the clinical picture. Secondary PHT is similar to the primary form, but more often associated with Raynaud's phenomenon. The clinical manifestations consist mainly of dyspnoea, fatigue, and decreased tolerance to exercise. However, many patients are asymptomatic and the diagnosis is revealed by performing routine studies of their underlying disease. From a pathophysiological perspective, there is vascular hyper-reactivity in addition to a state of hypercoagulability and multiple, recurrent micro-thromboembolisms causing PHT. All of the aforementioned is found in close association with the presence of antiphospholipid antibodies. A Doppler ultrasound cardiogram should be performed in order to establish the diagnosis and, if necessary, cardiopulmonary catheterization.

Interstitial lung disease (ILD) is a heterogeneous group of pathologies characterized by inflammation and/or fibrosis of the pulmonary interstitium. The new ILD classification introduced the term "diffuse parenchymal lung disease", with idiopathic interstitial pneumonia comprising a subgroup of this diffuse disease.[12] In turn, this idiopathic interstitial pneumonia encompasses several subgroups, including *common interstitial pneumonia* (CIP). From a clinical perspective, this refers to patients carrying AIDs (SLE, SSc, dermatomyositis) who present scantly productive cough, progressive dyspnoea on exertion, and bibasal crepitant rales. Since all are late symptoms or signs of interstitial fibrosis, the diagnosis must necessarily be made much earlier in order to initiate appropriate treatment.[13,14]

In patients with SSc, ILD may occur in either the diffuse form or the limited form of the disease.[15] Although the alterations seen on a simple chest X-ray may be present in between 25% and 60% of cases, a high resolution CT of the thorax must be performed as it enhances the possibility of making the correct diagnosis[16] (positive predictive value: 70%-100%), entailing less of a need to carry out a lung biopsy.

In CIP, the CT scan of the chest may exhibit a predominantly basal, peripheral reticular pattern, which tends to be patchy, as well as traction bronchiectasis. In more advanced stages, it is not unusual to see honeycomb images. Ground-glass opacities may be present in both the early stages of ILD (early alveolitis) as well as the late stages of fibrosis.[17] The distortion of the pulmonary architecture becomes prominent when the process moves forward towards fibrosis. Pulmonary function tests such as spirometry reveal a restrictive type of pattern with decreased total lung capacity and forced vital capacity. Because there are cases in which the patients have normal pulmonary function tests, the gold standard for evaluating the extent of pulmonary compromise is the diffusing capacity of the lung for carbon monoxide (DLCO).[18] Blood-gas determination reveals arterial hypoxaemia with normocapnia or hypocapnia, in addition to reduced DLCO. Anti-topoisomerase antibodies (anti-Scl70) correlate more closely with the development of ILD and diffuse cutaneous compromise, whereas anti-centromere antibodies associate more with limited cutaneous compromise and vascular lung disease.[19]

At some point in the course of SLE, most patients display signs of pulmonary, vascular, pleural or diaphragmatic compromise.[20] Pulmonary compromise is classified as secondary, when there are different aetiologies (infections, atypias), or primary; among the latter we find ILD (already described), acute lupus pneumonitis,

diffuse alveolar haemorrhage, PHT, and "shrinking lung syndrome".[21]

Acute lupus pneumonitis is an uncommon manifestation in SLE (1%-14%) and is the result of injury to the alveolopulmonary unit. The hallmarks of its clinical manifestations include fever, cough (sometimes with haemoptysis), pleuritic chest pain, dyspnoea, hypoxia, bibasal rales, pleural effusion, anti-dsDNA antibodies, in the absence of any apparent infection. Lupus pneumonitis may evolve toward severe hypoxaemia over the course of a few hours or days. The simple chest X-ray exhibits patchy unilateral or bilateral areas of parenchymal consolidation, predominantly in the base of both lungs, associated or not with pleural effusion and atelectasias. The bronchoscopy with bronchoalveolar lavage aids in diagnosis and pulmonary biopsy is the cornerstone of the definitive diagnosis. Given that it may course very rapidly towards respiratory insufficiency, it is an emergency requiring aggressive immunosuppressant treatment. For this reason, based on published experience, treatment is empirical and consists of using broad-spectrum antibiotics to cover the likely infectious aetiologies, the use of pulse therapies with high-dose steroids and immunosuppressants, IV immunoglobulin and/or plasmaphoresis.

Acute pulmonary haemorrhage is one of the most devastating complications of lupus, with a prevalence of between 1% and 5%, depending on the series consulted.[22,23] The symptoms, which develop in a matter of hours or days, include dyspnoea, cough, fever, and bloody sputum or frank haemoptysis. This diagnosis must be suspected when confronting the onset of the symptoms cited accompanied by rapidly evolving radiographic changes and a fall in haematocrit. DLCO is typically increased, in correlation with the high levels of haemoglobin inside the alveolus. Bronchoscopy with bronchoalveolar lavage may be performed to rule out other causes, such as infections, and to verify the presence of fluids with a high content of blood on aspiration. Microscopically, an extremely high proportion of red blood cells and alveolar macrophages loaded with haemosiderin can be seen, in many cases with evidence of alveolar capillaritis. Mortality may be high, as much as 50% of patients. On the other hand, a high incidence of infections has been demonstrated in lupus patients with pulmonary haemorrhage, with the most commonly involved pathogens being *Pseudomonas* and *Aspergillus*, thereby complicating even further both prognosis and treatment.[24]

Clinical diagnosis. Dr. Bernardo A. Pons-Estel

A 31-year-old female patient presented with an initial diagnosis of SLE that evolved into an overlap syndrome with SSc; she was hospitalized because of a rapidly evolving pulmonary compromise that worsened over the course of a few days, causing her death. What is most noteworthy of all the previous discussion is the large spectrum of differential diagnoses that must be taken into account in patients with AID and pulmonary compromise.

We must begin by remembering all the usual infectious processes that can affect immunocompromised patients. Therefore, when faced with doubt or the impossibility of establishing an accurate diagnosis before receiving the definitive results of cultures and other complementary studies, broad antibiotic coverage must be administered.

In AID patients (particularly those with SLE and SSc) in whom pulmonary compromise occurs quickly, in addition to infections, all gravely serious syndromes typical of the underlying disease or associated with it must necessarily be considered such as PTE, acute pneumonitis, and pulmonary haemorrhage, all of which develop very rapidly and entail a serious prognosis. Clinical pictures that include pericarditis, with or without pericardial tamponade must always be taken into consideration in these patients.

In the case of the patient that concerns us, after ruling out added infectious disease, but having administered the appropriate anti-infective treatment, the diagnosis was considered to be acute pneumonitis and UIP that evolved rapidly into organ failure that was the cause of death.

Pathology remarks. Dr. Jaime Ferrer and Marisol Ferrer

The surgical biopsy of the lung, representative of the lesion, revealed thickening of the interalveolar walls with a predominance of proliferation of fibroblasts and collagen and minimal lymphoplasmocytic reaction, alternating dilated and collapsed alveolar cavities (Figures 3-5).

No granulomatous inflammatory changes, specific infiltrates, signs of haemorrhagic lesions or signs of colonization by *P. jiroveci* or fungal forms were recognized. There are no signs of neoplasic lesions.

In conclusion, the pathological lesion of the lung parenchyma corresponds to UIP.

Comments and definitive result. Dr. Bernardo A. Pons-Estel

Between 15% and 25% of patients with systemic manifestations of rheumatic disease present as an overlap syndrome of 2 or more specific disease entities or as diffuse, undifferentiated connective tissue diseases,[25] the classification of which is presented in Table. This heterogeneous group of pathologies poses difficulties in establishing a definitive diagnosis, while providing indirect evidence of the fact that common aetiological and pathogenic processes may be underlying these illnesses.

The case of a female patient is presented with an initial diagnosis of SLE that evolves into an overlap syndrome with SSc, developing rapidly progressive pulmonary compromise years later that causes her demise. In addition to the effects of the final course of illness, it is important to extract from her initial history the presence of Raynaud's phenomenon, digit ulcers, ANA (+) with a speckled nucleolar pattern, bibasal interstitial lung compromise, and PHT.

To summarize what has already been said, we must draw attention to the tremendous number of differential diagnoses that must be contemplated when a patient with a diagnosis of prior collagen
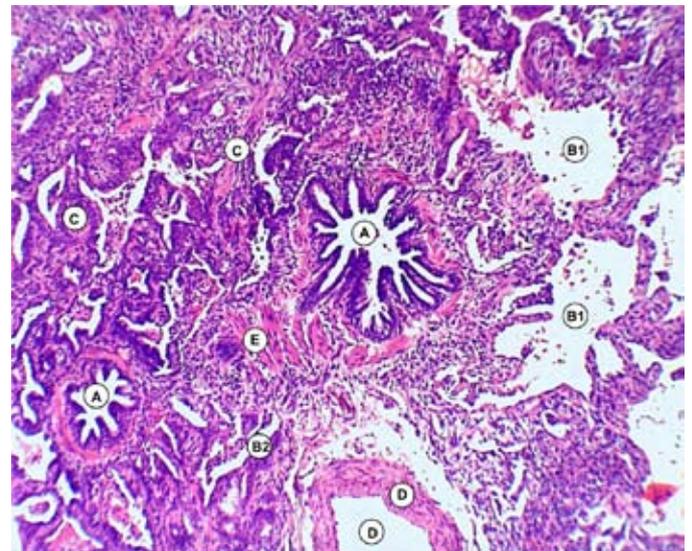

Figure 3. Lung biopsy: haematoxylin-eosin stain. A) Bronchioles. B1) Emphysematous alveolar spaces. B2) Collapsed alveoli. C) Fibrous interalveolar walls. D) Arteriole. E) Muscle hyperplasia.
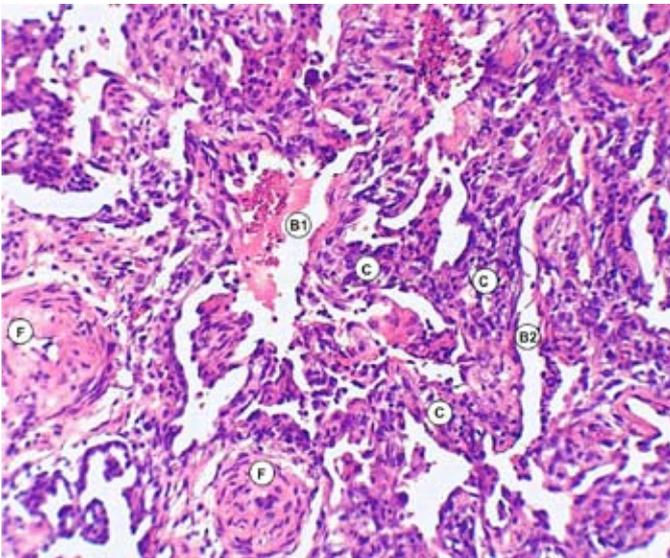
Figure 4. Lung biopsy: haematoxylin-eosin. B1) Emphysematous alveolar spaces. B2) Collapsed alveoli. C) Fibrous interalveolar walls. F) Arteriolosclerosis.
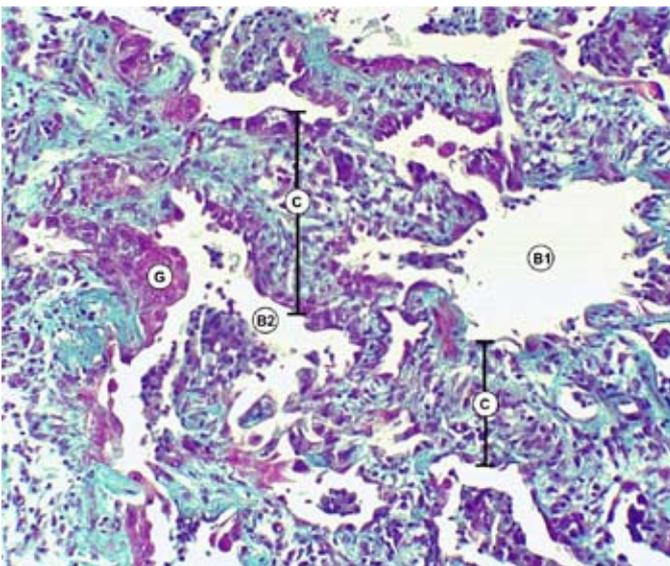

Figure 5. Lung biopsy: Masson's trichrome stain. B1) Emphysematous alveolar spaces. B2) Collapsed alveoli. C) Fibrous interalveolar walls. G) Metaplasia of the alveolar space.

Table
Overlap syndromes and undifferentiated rheumatic diseases

Mixed connective tissue disease
    Lupus-scleroderma-myositis-rheumatoid arthritis

Undifferentiated systemic rheumatic diseases

Overlap syndromes
    Rheumatoid arthritis-lupus (rupus)
    Scleroderma-dermatomyositis/polymyositis
    Scleroderma-lupus
    Scleroderma-rheumatoid arthritis
    Overlap with polymyositis
    Chronic juvenile polyarthritis-lupus
    Overlap with Sjögren's syndrome

Others
    Undifferentiated polyarthritis syndrome
    Undifferentiated spondyloarthritis

Conflict of interest

The authors state that there is no conflict of interests.

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disease presents a pulmonary complication. Highly varied factors must be taken into account, such as respiratory infection, pulmonary haemorrhage, complications associated with vascular compromise such as PTE or PHT, all the way to true immune pneumonitis.

The wide spectrum of such diagnoses obliges the attending physician to perform all diagnostic test techniques called for very quickly, so as to establish suitable treatment which, if initiated early, improves survival. Nevertheless, we must not lose sight of the fact that most immunocompromised patients will have a fatal prognosis, as indicated in most of the series in the literature.[8,13,24] In the case under discussion, it was necessary to perform a lung biopsy by means of a minimal thoracotomy in order to reach the diagnosis, since within just a few days, both the clinical situation as well as the radiological compromise evolved very quickly. The definitive result was in the hands of the pathology study that established the diagnosis of UIP.

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