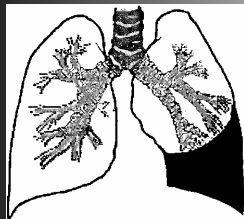


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Pleural Effusion in Rheumatic Diseases

Guest Editor: Dr José M Porcel

Pleural Effusion Associated with Rheumatoid Arthritis

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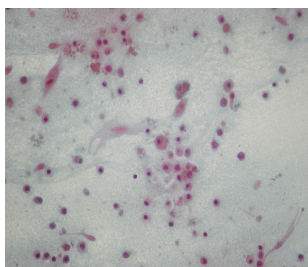
Pleural disease is the most common thoracic manifestation in rheumatoid arthritis (RA). Pleural effusion was identified in 3.8% of asymptomatic RA patients using chest CT. In most cases it is small and without clinical significance^{1,2}. Among patients with exudates, RA was the cause of pleural effusion in 0.6% of 2,346 patients and in 0.75% of 1,200 patients who underwent thoracoscopy^{1,2}. A literature review has identified 30 cases of pleural effusion in patients with RA². The data in this article are based on those cases. Seventy percent were men with a mean age of 56.2 years (range: 32-73)². The effusion was diagnosed subsequent to RA in 16 and concurrently in 14 patients. The mean interval (\pm SD) between the diagnosis of RA and pleural effusion was 13 \pm 10.1 years. In 7 patients the diagnosis of pleural effusion came shortly before that of RA².

The most common pleural effusion-related symptoms are chest pain, shortness of breath and/or coughing. Patients may also present with fever and weight loss and rarely respiratory distress, cardiac tamponade and hemodynamic instability. In most cases, the arthritis was active at the time of diagnosis of pleural effusion. Rheumatoid factor was found in

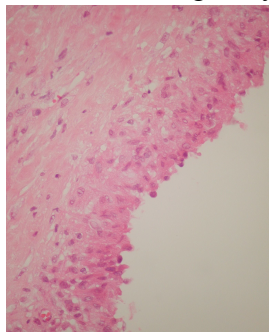
more than 95% of patients and 20% presented with accelerated rheumatoid nodulosis¹⁻³.

The characteristic findings of the RA-associated pleural effusions are a very low pH in the range of 6.4-7.14 in 70% of the patients and a glucose content of <20 mg/dL in 80%¹⁻⁴. The low glucose content is the result of consumption by the activated inflammatory cells and a metabolic block preventing transfer of glucose into the pleural fluid. Low pH correlated to low glucose levels. The effusions were exudates with a mean level of LDH of 2,348 IU/ml and a mean total protein of 5.24 mg/dL. The cell count in the effusions was >3,000 WBC/ μ L in 67% of samples. The differential cell count was found to be of lymphocytic predominance in 37%, neutrophilic in 56% and eosinophilic in 7% of samples. There were no mesothelial cells². In two cases, the differential cell count changed from neutrophilic to lymphocytic predominance² at a repeated tap.

The presence of slender, elongated tadpole cells on a background of many cells, some of which are decaying, on the cytology smears, is considered to be pathognomic³⁻⁵ (left).



Thoracoscopic examination of the parietal pleura shows a "gritty" or frozen appearance, a slightly inflamed and thickened surface with small vesicles and granules of about 0.5 mm³. On the microscopic examination the mesothelial cells are being replaced by palisades of pseudo-stratified epithelioid cells of macrophage origin, representing an erupted rheumatoid nodule (below). Calretinin staining may verify a lack of mesothelial cells. These patterns may not be present on smaller, closed pleural biopsies⁴.



The differential diagnosis of pleural effusion among patients with RA is outlined in Table 1. The presence of the pathognomic cells precludes further investigations and invasive procedures. Treatment modalities include systemic steroids, intra-pleural steroids, methotrexate and/or other immunosuppressive agents¹⁻⁴. Surgical pleurectomy

is rarely indicated. The pleural effusion resolves after an average of 14 months (range 1-36).

Table 1. Causes of pleural effusions in RA patients based on the results of thoracentesis

pH	Glucose (mg/dL)	Predominant cell	Differential diagnosis other than RA
<7.20	<20	Neutrophil	Empyema
<7.20	<20	Lymphocyte	TB, malignancy
<7.20	<20	Eosinophil	Drug reaction, methotrexate
Normal	Normal	Lymphocyte	TB, malignancy, drug reaction

Acknowledgments: Dr N Sion-Vardy kindly provided Figures.

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Prevalence and Outcome of Lupus-Associated Pleural Effusions

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Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that may affect any system of the body. Involvement of the serous membranes is one of the diagnostic criteria in the American College of Rheumatology classification. Serositis of the pleura, pericardium or peritoneum may lead to pain, fluid accumulation, adhesion and/or fibrosis.

The prevalence of lupus-related pleuritis/pleural effusion varies widely depending on the clinical criteria used, patient sampling, diagnostic methods, and whether screening investigations were performed and secondary causes of pleural effusion were included for analysis. In a study of 520 SLE patients conducted in the 1960s, the cumulative incidence of recurrent pleuritic pain was 45% and that of pleural effusion was 30%¹. Pleurisy and pleural effusions were the initial manifestation of SLE in 3% and 1% of patients, respectively. Other studies also documented a high prevalence of pleuritic chest pain, with or without associated pleural effusion, in 41 to 56% of SLE patients during their disease course^{2,3}.

Histologic evidence of pleuritis was present in up to 93% of SLE patients in an autopsy series, but this figure is likely to be a composite of all primary (lupus-related) and secondary causes⁴. Pleural effusion in SLE is often small to moderate, but occasionally massive. Bilateral involvement is present in about half the cases, which may be associated with pericardial effusion and ascites. Pleuritic chest pain has recently been recognized as a common initial manifestation of the rare shrinking lung syndrome in SLE⁵.

In a recent study, we showed that the point prevalence of symptomatic lupus-related serositis was 12% in 310 Chinese patients with a disease duration of 7.2 years⁶. Among the 69 episodes of serositis, 44% were pleuritis/pleural effusion. Bilateral effusions occurred in 36% of patients and the most common presenting features were pleuritic chest pain, non-productive cough and dyspnea. However, the prevalence of pleuritis in this study could have been underestimated as surveillance investigations were not routinely performed.

The exact pathogenesis of serositis in SLE remains elusive. Histologic examination of the serosal membranes reveals inflammation with infiltration by lymphocytes, plasma cells and macrophages, fibrinous exudates, and perivascular fibrinoid necrosis⁴. Immune complexes, complement activation products and immunoglobulins may also be found. However, these immune-mediated mechanisms may not be specific to SLE. Persistent and unresolved inflammation may result in serosal fibrosis and thickening.

Although lupus pleuritis often responds promptly to treatment with non-steroidal anti-inflammatory drugs or short courses of glucocorticoids, a small proportion of patients may present with life-threatening effusion that is refractory to medical treatment.

In our study, 27% of patients with lupus-related pleural effusion required thoracentesis for symptomatic relief⁶. Although all patients responded to treatment within 2 months, 20% of patients had a recurrence of pleuritis and 10% developed localized pleural fibrosis as a sequel. Patients with more serious or recurrent/refractory pleural effusion may require more aggressive immunosuppressive therapies (eg intravenous pulse methylprednisolone, cyclophosphamide, azathioprine, cyclosporin A,

intravenous immunoglobulins), or pleurodesis and pleurectomy for symptomatic alleviation.

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Shrinking Lung Syndrome in SLE

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Shrinking lung syndrome (SLS) is a rare complication of systemic lupus erythematosus (SLE) characterized by unexplained dyspnea, small lung volumes, elevation of the diaphragm, and restrictive physiology.

SLS may complicate SLE at any time over its course, ranging from as early as a few months to 24 years from disease onset¹. Patients with SLS typically present with dyspnea, initially on exertion and later at rest; pleuritic chest pain is present in the majority of patients¹. On physical exam, patients with SLS may have shallow rapid breathing, use of accessory muscles and, occasionally, paradoxical abdominal movements. Elevation of one or both hemidiaphragms is invariably present on chest radiographs. The volitional tests of diaphragmatic strength show that the maximal transdiaphragmatic pressure is diminished, suggesting diaphragmatic dysfunction.

The pathophysiology of diaphragmatic dysfunction in SLS is unclear. The possibility of a myopathic process involving the diaphragm is not supported by the finding of normal diaphragmatic strength in response to magnetic stimulation of the phrenic nerve².

Could pleurisy account for the diaphragmatic dysfunction in SLS? Although it is too premature to firmly attribute diaphragmatic dysfunction to pleurisy, indirect evidence suggests a possible relationship. First, pleurisy is a prominent feature of patients with SLS and a recent literature search found that 65% of all reported SLS patients had pleuritic

chest pain at the time of diagnosis¹. In addition, typical SLS has also been reported in non-SLE patients (e.g. rheumatoid arthritis) who similarly had pleuritic chest pain and improved with anti-inflammatory medications³. The occurrence of SLS in non-SLE patients supports the hypothesis that the association of diaphragmatic dysfunction in the SLS is not unique to SLE but rather reflects the high prevalence of pleurisy in SLE.

The mechanism by which pleurisy and its associated pain may lead to diaphragmatic dysfunction is probably through reflex inhibition of diaphragmatic activation, in a manner similar to that described following abdominal or thoracic procedures. Although the exact neural pathways involved are not entirely clear, experimental data suggest that inflammation of the parietal pleura may lead, through stimulation of the unmyelinated or thin myelinated fibers belonging to the internal intercostal nerves, to suppression of phrenic motor neuron discharge^{4,5}. An additional mechanism may also involve the 'phrenic-to-phrenic' reflex. In animals, inflammation of the diaphragmatic pleura, through stimulation of phrenic nerve afferents, may inhibit activation of the intercostal muscles, *levator costae*, as well as the diaphragm^{5,6}. Given the high prevalence of pleurisy in SLE and the rarity of SLS, one would speculate that only pleurisy in a region near the diaphragm or directly involving the diaphragmatic pleura would be responsible for diaphragmatic dysfunction. Anti-inflammatory therapy, the mainstay therapy for the SLS, is associated with symptom improvement in the majority of patients¹.

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European School of Oncology education course
Approach to Pleural Cancer: State of the Art
 7 - 8 May 2009: Athens, Greece.

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IMAGES OF THE PLEURA

Pleural Lymphatics

Soraya Puente MD

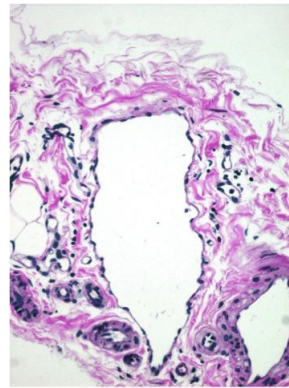
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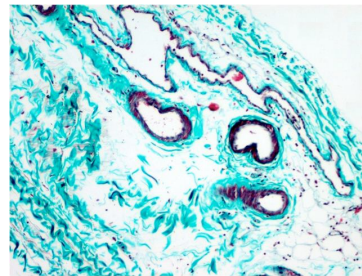
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The lymphatic systems of the visceral and parietal pleura hold roles in pleural fluid turnover. A distinctive feature of the parietal pleura is the presence of lymphatic stomata which open directly

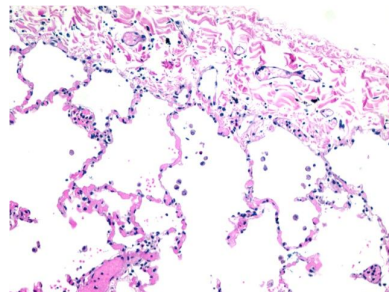
into the pleural space, representing the main route of pleural fluid absorption.



A normal human parietal pleural membrane is shown using H&E stain (x200) (*left*) and Masson trichromic stain (x 200) (*below*).



Note the presence of prominent large lymphatic structures (L) in the subpleural connective tissue.



This contrasts with the appearance of the visceral pleura (*left*; H&E x100).

Treatment of Refractory Pleural Effusion in SLE

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Pleuritis-related pleural effusions in systemic lupus erythematosus (SLE) are usually small or moderate (400-1000mL); massive effusions are uncommon¹. Treatment should be individualized: small asymptomatic effusions may not require treatment; non-steroidal anti-inflammatory drugs are useful for mild pleurisy while corticosteroid therapy is indicated for more severe cases¹. Most patients respond promptly. When the fluid volume is large and causing shortness of breath, aspiration is necessary. Rarely are repeated thoracentesis or other local or systemic therapies required.

The following are data on massive refractory lupus pleurisy from a review of the English-language literature over the past 25 years². Systemic therapy included immunosuppressive drugs, plasmapheresis and intravenous immunoglobulin. Immunosuppressive therapy with azathioprine, cyclophosphamide, cyclosporine, methotrexate or hydroxychloroquine, in addition to corticosteroids, generally did not prevent fluid accumulation. Plasmapheresis was reported in one case, but it failed to achieve resolution of the effusion. Intravenous immunoglobulin (IVIg) therapy was reported in two patients. In one case, the effusion recurred two months after the last dose. In the other patient, IVIg therapy was followed by 4 months of treatment with cyclosporine and no fluid accumulation was observed during a two-year follow-up.

Local therapy included intra-pleural corticosteroid injections, pleurodesis with talc or tetracycline, and pleurectomy. Intra-pleural corticosteroid injections were reported in three SLE patients, with no beneficial response whereas pleurectomy was described in three other patients, with variable responses. Regarding pleurodesis, the use of tetracycline as a sclerosing agent was reported in four patients: two of which had a favorable response, one had a transient response and pleurodesis failed in the other one². The primary problem with this agent is

that the parenteral form was withdrawn from the market several years ago. Talc pleurodesis was reported in six patients, either as a powder (poudrage), or as a suspension in saline (slurry). Five had complete resolution of the fluid without recurrences. Complications were observed in two patients: one developed empyema, and the other (who underwent bilateral pleurodesis) developed a restrictive defect.

The main side effect of pleurodesis is pain, which may last for a few days³. Rarely, debilitating pain may last longer⁴. Mild fever may also be present for a few days. Lung function is not significantly affected in most cases. However, there have been some reports of transient respiratory failure^{3,5}, developing within a day of the procedure. Other uncommon complications of talc pleurodesis include granuloma formation and empyema. Finally, mechanical shunts, either pleuro-peritoneal or pleuro-venous, may be appropriate for some non-malignant cases. However, data on the use of such procedures in refractory SLE-related effusions are limited⁶.

In summary, refractory massive pleural effusion is uncommon in SLE, but the affected patients pose a difficult management problem. Due to the small number of patients reported in the literature, it is difficult to determine the optimum intervention. When refractory pleural effusion is part of an exacerbation of SLE, the treatment of choice would be systemic. Local therapy should be employed if systemic therapy fails, or in cases where pleural effusion is the only manifestation of SLE. Talc pleurodesis seems to be the preferred method of local therapy.

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**If you have any comment on the Newsletter or interesting cases of pleural disease, contact:
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