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Case Report

The Problem of Empyematous Pleural Effusion in Rheumatoid Arthritis: Report of Two Cases and Review of the Literature

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Abstract: Two patients with rheumatoid arthritis and empyematous pleural effusion were treated with repeated drainage and intrapleural corticosteroids. One patient with active joint disease improved within 3 months without sequelae, probably because of the systemic therapy. The other patient, with non-active joint disease, had persistent pleural effusion which resulted in pleural thickening and symptomatic restrictive disturbance. It appears that early intervention intended to prevent the accumulation of empyematous pleural effusion could also prevent pleural thickening and fibrosis. Therapeutic options are discussed.

Keywords: Pleural effusion; Rheumatoid arthritis; Sterile empyema

Introduction

Pleural effusion in rheumatoid arthritis (RA) represents an inflammatory process in the pleural cavity [1,2]. This fluid, characterised by low glucose and low pH levels, is also known as 'sterile empyema' or 'empyematous effusion'. Left untreated, this condition can lead to the development of pleural thickening and fibrothorax. Management is aimed at preventing this course of events [3,4].

As pleural effusion in RA does not correlate with joint exacerbation or other extra-articular manifestations, treatment strategies vary from local procedures, such as repeated punctures and fluid removal, to systemic anti-inflammatory treatment, although success is far from guaranteed. Persistent effusion despite these means has led some authors to administer intrapleural injections of corticosteroids, with inconsistent results [5–8].

We report the management of two patients with RA and empyematous pleural effusion.

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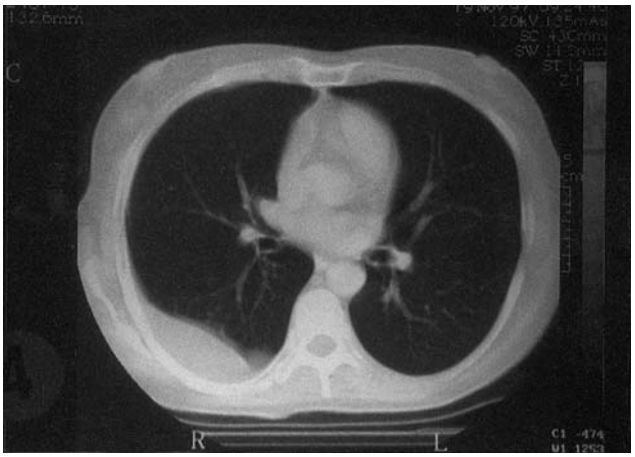
Case Reports

Patient 1

A 46-year-old woman was diagnosed with RA, based on the presence of morning stiffness, symmetrical polyarthritis involving the small joints of the hands and feet for 3 months, and a positive test for rheumatoid factor in the synovial fluid. Tests for antinuclear factor and anti-DNA antibodies were negative. She was put on non-steroidal anti-inflammatory drugs, without improvement. One month before admission, intramuscular methotrexate (7.5 mg/week) was started. She had no history of smoking, comorbid conditions or the regular use of medications.

On admission, physical examination revealed normal vital signs with no signs of respiratory distress. Decreased breathing sounds were noted in the lower portion of the right lung. Symmetrical polyarthritis of the metacarpophalangeal and proximal interphalangeal joints, wrists, right elbow and right shoulder was noted. Radiography and computed tomography (CT) of the chest showed a moderate amount of right-sided pleural effusion (Fig. 1a).

Thoracocentesis revealed 1500 ml of cloudy fluid (pH 7.09). Laboratory test results were as follows: glucose 3 mg/dl; total protein 5.3 g/dl; complete blood count 4100 leukocytes/mm^3 (80% lymphocytes); lactic dehydrogen-



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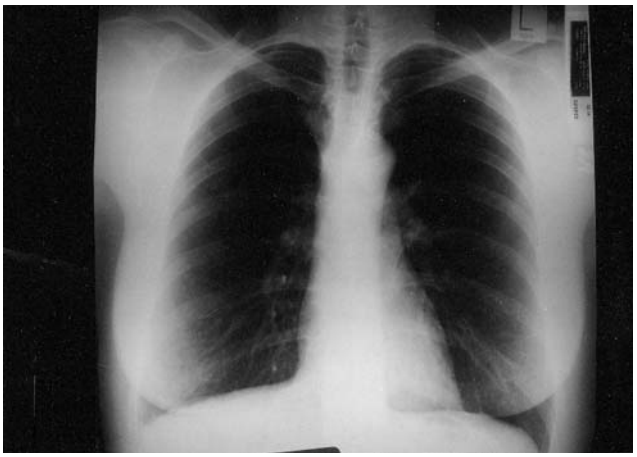

B

Fig. 1.A Chest CT scan at the level of the intermediate bronchus, showing small to moderate amounts of loculated right-sided pleural effusion. **B** Chest X-ray, same patient, 2 years later: no evidence of pleural effusion. Note the blunted right costophrenic sinus.

ase 1745 IU. Direct smear and culture for aerobic and anaerobic bacteria and for tuberculosis were negative. Cytology examination showed leukocytes and mesothelial cells. Closed pleural biopsy showed proliferative mesothelial cells without malignancy. The data were consistent with a diagnosis of an RA-associated empyematous pleural effusion. The absence of pulmonary symptoms led us to follow the patient without intervention.

Oral prednisolone (7.5 mg/day) was added to the methotrexate, with gradual improvement in the joint symptoms but not in the amount of fluid. One month later, 1400 ml of pleural effusion were evacuated and found to have similar characteristics; 160 mg depomethylprednisolone was injected into the pleural space, as previously described [5–8]. Nevertheless, the fluid accumulated again, and a month later the patient required further drainage. Following this episode, the amount of fluid decreased gradually, resolving completely 4 months later. In the following months she received reducing doses of prednisone and methotrexate, with disappearance of the joint symptoms. At her last follow-up visit 2 years from presentation there were no

Table 1. Characteristics of two patients with rheumatoid pleural effusion

	Patient 1	Patient 2
Age (sex)	46 (F)	47 (F)
Disease duration*	3 months	18 years
Fluid location	Right	Left + right
PH	7.09	7.13
Glucose (mg%)	3	7
LDH (IU)	1745	4529
WBC (/mm^3)	4100	1480
Cholesterol mg/dl	122	104
Cholesterol crystals	No	No
Outcome	Resolution (9 months)	Pleural thickening (12 months)

*To onset of pleural effusion.

respiratory symptoms; a pulmonary function test was normal and X-rays showed only an obscured right costophrenic sinus (Fig. 1b).

Patient 2

A 47-year-old woman with nodular seropositive erosive RA of 18 years' duration had been controlled for the last 8 years with weekly intramuscular injections of methotrexate (7.5 mg/week) and non-steroidal anti-inflammatory drugs. In 1994 extremely large subcutaneous nodules were noted, requiring surgical excision. She had limiting joint deformations and a history of smoking (20 pack/years). In the last 5 years the patient had suffered from mild obstructive airway disease, controlled with inhaled corticosteroids and bronchodilators.

In January 1997 the patient was admitted to hospital because of fever, cough and dyspnoea. Physical examination and chest radiography revealed a large amount of right-sided pleural effusion. A total of 1000 ml of sterile exudative fluid, considered to be parapneumonic, was evacuated via a chest tube and an intravenous antibiotic was administered, with complete resolution of the symptoms and of the fluid. One month later she was readmitted because of a large amount of left-sided pleural effusion and a small amount of loculated pleural effusion (Fig. 2a). Thoracocentesis revealed exudative fluid with a pH of 7.13. Laboratory test results were: glucose 7 mg/dl; complete blood count 1480 leukocytes/mm^3 (lymphocytes 77%); lactic dehydrogenase 4529 IU. Cytologic examination revealed leukocytes, hystiocytes, mononuclear cells and a few mesothelial cells. Closed pleural biopsy demonstrated fibrotic and non-specific inflammatory changes. A diagnosis of RA-associated empyematous pleural effusion was made, and the patient was followed conservatively in view of the favourable outcome of the previous contralateral episode.

A small amount of residual pleural fluid was noted in the first months, but it reaccumulated again 6 months later, resulting in progressive dyspnoea. A total of 1800

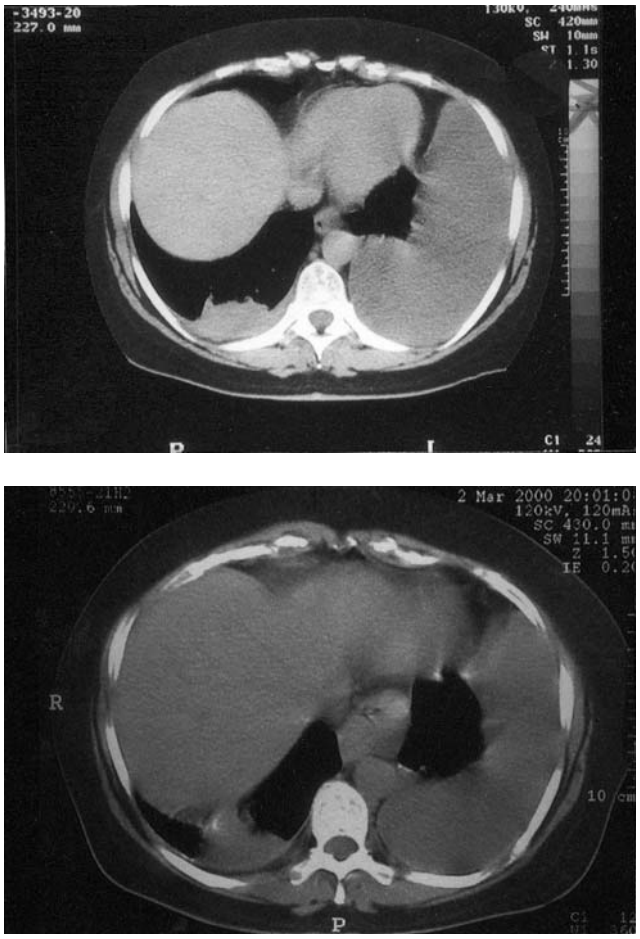

Fig. 2.A Chest CT scan, showing a large amount of left-sided pleural effusion and a small amount of loculated, right-sided pleural effusion with parenchymatic changes. **B** Chest CT, same patient, same level, 3 years later: amount and appearance of the bilateral pleural effusion remain almost unchanged.

ml of fluid was evacuated, and 160 mg of depomethylprednisolone was injected into the pleural cavity. In spite of the steroid injection, the fluid reaccumulated a month later, and during the following months several episodes of thoracocentesis were required.

Chest CT from early 2000 showed that the amount and the appearance of the pleural effusion on both sides had remained almost unchanged compared to 1997 (Fig. 2b). There was an accompanying symptomatic restrictive pattern in the patient's pulmonary function test, with lung volumes reduced to 65% of predicted values. Several attempts to evacuate the pleural fluid failed and, owing to multiple adhesions, only partial drainage was achieved.

Discussion

Some 3%–5% of RA patients suffer from pleural effusion in the course of their disease [1,2]. The pleural effusion of RA is an exudate, rich in immunoglobulin and other proteins. This fluid is thought to be secondary to non-specific pleural inflammation, sometimes in association with the classic rheumatoid nodule. Glucose levels in the fluid are low, apparently owing to impaired glucose transport. Cholesterol effusion levels originating from the breakdown of cells within the pleural space might be increased. For unknown reasons some patients with this 'chyliform effusion' form cholesterol crystals and others do not. Uncomplicated effusion (normal glucose and pH) has also been reported [4,8–10].

This extra-articular manifestation of RA classically occurs in males older than 35 years, with highly positive rheumatoid factor activity, subcutaneous nodules and long-standing disease [1–4]. Mean duration from disease onset to diagnosis of pleural effusion is 10–13 years, but this complication might precede the arthritis [3]. Most patients have a small amount of effusion that resolves spontaneously, after 24 months at the most, without sequelae, comprising a diagnostic rather than a therapeutic problem [4]. Rheumatoid pleural effusions are liable to become infected, sometimes resulting in empyema. Only rarely does a large amount of pleural effusion cause respiratory symptoms that require chest tube drainage.

This report describes the management and course of 'empyematous effusion' in two female patients with RA in the fifth decade of life. The complication was noted concomitant with disease onset in patient 1 and after 18 years of illness in patient 2. Extensive work-up, including thoracocentesis and pleural biopsy, excluded other aetiologies for these effusions. Patients 1 and 2 were managed with repeated drainage and one course of intrapleural corticosteroids, as previously described [5–8], with short-term relief in the amount of fluid. The fluid resolved completely in the first patient after 4 months, concomitant with improvement in her joint symptoms, probably owing to the favourable effect of the antirheumatic medications. The possibility that the pleural effusion resolved because of intrapleural corticosteroid therapy, or represents the natural history of this condition, appears to be less reasonable. The second patient, on the other hand, had persistent pleural effusion despite appropriate antirheumatic therapy and controlled joint disease. The fact that the fluid became loculated prevented its complete evacuation, which causes current symptomatic restrictive disturbances. Although no nodules were found on high-resolution CT or on pleural biopsy, it cannot be totally excluded that local RA (methotrexate induced?) nodules were the trigger for the pleural effusion. Hence, the methotrexate that controlled her arthritis in small doses was neither stopped nor was the dose increased, in the absence of any other sign of extra-articular RA activity and the lack of response to injected local deposteroids balanced against systemic steroid therapy.

Few studies relating to the natural history of pleural effusion in RA were found. In Russel's experience [7], no damage ensued as a result of long-standing large effusion, and it can be managed safely without any specific treatment other than observation and the measures taken for the control of the disease. Shan

[11], on the other hand, found that 50% of patients with this condition had a protracted course of years, occasionally progressing to marked pleural thickening and trapped lung. Our experience has shown that normal pH and normal glucose effusion tends to resolve spontaneously, whereas 'sterile empyema' tends to become complicated with loculations, pleural thickening, fibrothorax, trapped lung and symptomatic restrictive disturbance, sometimes requiring decortication of the pleura to enable re-expansion of the lung [4,8–10].

There are no clear guidelines concerning the management of empyematous pleural effusion in RA. It appears that early intervention intended to eliminate current fluid and to prevent further fluid accumulation would reduce the risk of developing loculations, pleural thickening and fibrosis. The effusion in some patients with uncontrolled joint symptoms would respond to anti-inflammatory treatment, like our first patient [9]. Experience with cytotoxic medications, such as methotrexate and cyclophosphamide, an effective intervention in other extra-articular manifestations of RA in this condition, is scanty. As the degree of inflammation in the pleura does not necessarily correlate with that in the joints [4], local therapy to patients in remission seems reasonable. Intrapleural corticosteroids (depomethylprednisolone 120 mg) were administered to five patients with RA and pleural effusion, with a variable outcome [5–8]: one patient responded [8], two did not [5,6], and two others gained only a temporary decrease in the amount of fluid [7]. Favourable response to this intervention is attributed to local effect or the systemic effects of steroids absorbed from the pleural cavity. There is no experience with repeated courses of intrapleural corticosteroids in refractory effusion.

Pleurodesis is an effective means of controlling persistent pleural effusion of various aetiologies. An extensive literature search revealed only one report suggesting pleurodesis as an optional intervention in long-standing RA pleural effusion [2]. The rationale for this therapy is that pleural obliteration by instillation of tetracycline or talc could interfere with the cascade of persistent fluid, loculations, pleural thickening and fibrosis.

In summary, a large amount of long-standing empyematous pleural effusion in RA is relatively rare. Its management, especially in the absence of active arthritis or other extra-articular manifestations, is not defined. Some patients with persistent effusion develop fibrothorax and symptomatic restriction. We feel that pleurodesis should be considered for patients not responding to other interventions.

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