Rheumatol Int (2007) 27:919–925
DOI 10.1007/s00296-007-0322-9

ORIGINAL ARTICLE

Pleural effusion associated with rheumatoid arthritis: what cell predominance to anticipate?

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Received: 23 July 2006 / Accepted: 11 January 2007 / Published online: 9 February 2007

Abstract Pleural involvement is the most frequent manifestation of rheumatoid arthritis (RA) in the chest. We report here two patients who presented with large exudative pleural effusions and subsequently developed sero-positive RA. In both cases, the differential cell count of the pleural effusion suggested empyema. A literature review identified that RA-associated pleural effusion afflicts more men than women and 95% of the patients have high titers of rheumatoid factor (RF). In 46% of cases, RA-associated pleural effusion is diagnosed in close temporal relationship with the diagnosis of RA. The effusion is an exudate and is characterized by low pH and glucose level, and high lactic dehydrogenase (LDH) and cell count. At diagnosis there is a tendency for predominant neutrophils to occur consistent with an empyema and 7–11 days later, the cells in the pleural effusion are replaced by lymphocytes. Pleural effusion with predominant eosinophilia is rare. RA patients with acidic effusion and low glucose content with neutrophils predominance should be treated with thoracic drainage and antibiotics until an infection is ruled out. The histo-pathologic findings in pleural fluid of tadpole cells and multinucleated giant cells and the replacement of the mesothelial cells on the parietal pleural surface with a palisade of macrophage derived cells are described as pathognomic for RA. Treatment with systemic steroids and intra-pleural steroids are effective in most cases.

Keywords Pleural effusion · Rheumatoid arthritis · Aseptic empyema · Eosinophilia · Tadpole cells

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Pleural involvement is reported to be the most frequent manifestation of RA in the chest [1]. However, it is not a common condition and clinically significant RA-associated pleural effusion is encountered rarely; of 289 RA patients examined with computerized tomography (CT) of the chest, eleven patients (3.8%) were reported to have pleural effusion, in most cases these were small, asymptomatic and of no clinical significance [2–4]. In addition, among 2,346 patients evaluated for the etiology of exudative pleural effusion, only 14 patients (0.6%) were identified as suffering from RA-associated pleural effusion [5–9]. Very rarely, pleural effusion is the first presentation of RA. Pleural fluid associated with RA is characterized by being aseptic, an exudate, with a low glucose content and reduced pH [1].

In cases of exudative pleural effusion of unknown etiology, the pleural effusion differential cell count is used to construct a differential diagnosis and to guide further evaluation [10]. This statement is based on

studies that are 2–3 decades old but they should be hailed for their timelessness and their sefulness emphasized. A recent exhaustive review of pleural effusion associated with RA omitted purposely to discuss the predominant cell type and simply stated that these effusions are rich in cells [11]. In patients with RA, the cell count of the pleural effusion shows a tendency towards lymphocytic predominance [1, 10].

We report here two patients who presented with large exudative pleural effusions and subsequently developed sero-positive RA. In both cases, the differential cell count of the pleural effusion was important in the management. The features of RA-associated pleural effusion including the cell count are detailed.

Case presentations

Case No. 1

A 65-year-old man was admitted to the internal medicine department for evaluation of left pleural effusion involving half the hemithorax. He noticed shortness of breath and coughing for a month prior to his admission. He had been treated by his general practitioner with cefuroxime and roxithromycin without improvement. He denied fever, chest pain, night-time sweating and weight loss. He suffered from chronic sino-rhinitis and had undergone nasal polypectomy 7 years ago. He has 100 pack years smoking history.

The physical examination was unremarkable except for dullness on percussion. The results of the laboratory work up and pleural tap (Table 1, time 0′) revealed leukocytosis with peripheral eosinophilia and an exudative pleural effusion with predominant lymphocytes and eosinophilia; cultures were sterile and there was no evidence of malignant cells in cytology.

The patient underwent a closed pleural biopsy (Table 1, 3 weeks) which showed no evidence of malignancy or granulomatous inflammation. The pleural fluid persisted despite prednisone 20 mg/day and left thoracoscopic pleural biopsy was performed; a fibrin like material on the surface of the lung and parietal pleura was identified and biopsies were taken from those areas. The initial pathological impression was that the surface of the parietal pleura resembled bronchial epithelium (Fig. 1), however, further staining revealed the presence of characteristic histo-pathological manifestations of RA with the mesothelial layer having been replaced by palisades of macrophages as proven by the cells being strongly positive for CD68 staining, but calretinin staining showing an almost complete lack of mesothelial cells within the palisade; also present in fluid itself were slender elongated macrophages called tadpole cells and multi nucleated giant cells (Fig. 2).

Two weeks later and before receiving the results of the pleural biopsy, the patient was admitted with 3 days of fever accompanied with arthralgia and myalgia. In the chest X-ray there was a new right-sided pleural effusion and there was persistent peripheral blood eosinophilia; a right thoracocentesis revealed an exudate with predominant neutrophils without eosinophilia, and low glucose content with a reduced pH

Table 1 The laboratory work-up of the first patient

Time period	0′	Week 3	Week 10	Week 11	Week 21
Serum					
ERS	40				80
HB (mg%)	13.9		13.3		11.8
HCT (%)	43		40.2		36.3
WBC	12,370		21,440		10,740
Eosinophils (%)	3500 (27.7%)		7260 (34.4%)		1,380 (12.9%)
PLT	279,000		447,000		420,000
Albumin (mg%)	4.2		2.8		2.9
Globulin (mg%)	2.5		2.5		
LDH U/l	429		386		
Effusion from	Pleura left	Pleura left	Pleura right	Pleura right	Pericardium
pH	7.4	7.3	7.0		
Glucose (mg%)	1	4	5		2
LDH U/l	4,352	2,693	3,520		2,800
Total protein (mg%)	5.9	7	4.7		4.6
Cells/μl	4,100		4,580	3,930	9,400
PMN (%)	2		78	17	63
Eosinophils (%)	39		0	0	10
Lymphocytes (%)	59		12	83	27
Mesothelial (%)	0		0	0	0
Culture	Sterile	Sterile	Sterile	Sterile	Sterile

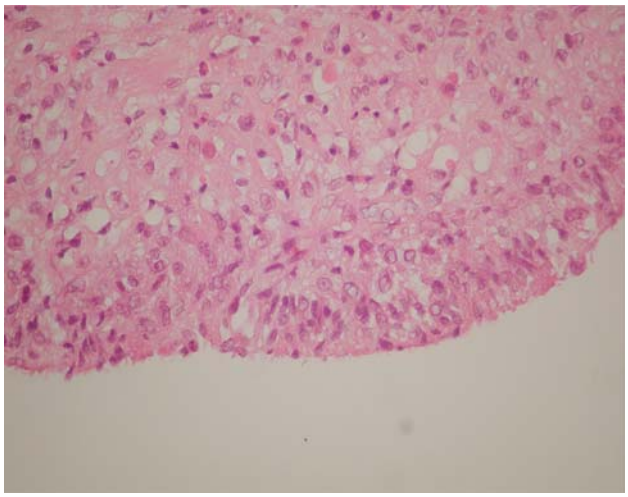

Fig. 1 Thoracoscopic parietal pleural biopsy: "an opened out" rheumatoid nodule surfaced by palisades of pseudo-stratified epitheliod cells of macrophage origin [24, 26]

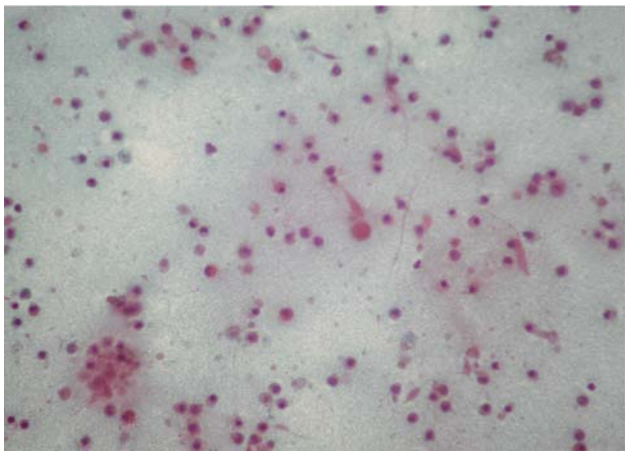

Fig. 2 Pleural effusion showing characteristic tadpole cells (*center*) as well as a multinucleated cell (*lower left corner*) and other inflammatory cells including eosinophils on a background of amorphous material

(Table 1, 10 weeks). A thoracic tube was inserted for a presumed diagnosis of pleural empyema and intravenous clindamycin and ofloxacin initiated; the culture results were negative from the pleural fluid as well as from blood.

Musculoskeletal examination revealed symmetric polyarthritis involving 2nd–4th metacarpophalangeal, proximal interphalangeal, knees, and ankles. Laboratory data included a positive RF: 136 IU/ml (normal 0–20); anti-nuclear antibody, anti-myeloperoxidase and anti-proteinase 3 were all negative. The C-reactive protein was 19.6 mg%. The patient was diagnosed with RA with pleural effusion as initial presentation and methotrexate (MTX) 7.5 mg/week and hydroxy-chloroquine were begun.

Ten weeks later, an ambulatory CT of the chest showed a significant pericardial effusion with echocardiographic evidence of tamponade. Eight hundred milliliters of pericardial effusion was evacuated; shown to be an exudate with predominantly neutrophils. (Table 1, 21 weeks). The pericardial fluid showed many tadpole cells, multinucleated giant cells and other inflammatory cells including eosinophils on a background of amorphous material exactly like the findings in the pleural effusion (Fig. 2).

The patient improved significantly, pericardial and/or pleural effusions have not recurred for 2.5 years of follow-up and he is maintained on oral prednisone, methotrexate and hydroxyl-chloroquine therapy.

Case No. 2

A 62-year-old man presented at the age of 52 years with prolonged fever, fatigue and coughing. Physical examination revealed temperature of 39.5°C, respiratory rate 24 in mild distress. There was dullness to percussion over the left hemithorax to the level of the lower edge of the scapula associated with diffuse rales over both lungs. The heart sounds were normal as were the findings of the abdomen and extremities.

Chest radiograph and CT scan demonstrated bilateral pleural effusion. A left pleural tap revealed a cell count of 15,500 with 80% of the cells being neutrophils and the LDH and total proteins levels were 1,730 U/ml and 5.8 mg%, respectively. A chest tube was inserted into the left pleural effusion and the patient was started on intravenous ciproxine, clindamycin and amikacin; cultures from blood and pleural effusion were all negative. The fever and general wellbeing of the patient improved; however on the 10th hospital day, the temperature increased to 39°C and the white blood cells (WBC) in the peripheral blood increased to 32,800 with 46% of the cells being eosinophils. The pleural effusion was an exudate with glucose level of 2 mg% and pH of 6.4 with WBC count 23,000 and with 100% being neutrophils without eosinophils consistent with an empyema; however all cultures from the pleural fluid and from the blood returned sterile. The cytology of the pleural effusion was negative for malignancy and showed a large amount of neutrophils and a significant number of eosinophils without tadpole cells or multinucleated giant cells.

A CT scan of the chest showed bilaterally diffused interstitial lung disease and transbronchial biopsy revealed severe parenchymal fibrosis and focally severe inflammatory changes, no granulomas and no eosinophils were identified. The patient was started on systemic steroids with improvement in fever,

wellbeing, leukocytosis and peripheral eosinophilia. The pleural effusion persisted as pyo-pneumothorax and after 5 months he underwent left surgical pleurectomy; the findings in the surgical specimen were compatible with a granulomatous reaction of a foreign body reaction type, presumably as a reaction to the thoracic tube which had been in place for 5 months. The patient improved and was discharged with systemic steroids.

One year later, the patient presented with severe arthralgia associated with malaise and morning stiffness; on examination it was found that polyarthritis had affected the joints of the shoulders, elbows, wrists, knees and 2nd and 3rd proximal interphalangeal of both hands. The RF titer was 159 IU/ml. The patient was diagnosed with RA and he was started on gold injections in addition to systemic steroids. MTX was not begun because of elevated liver enzymes. He experienced considerable improvement and has since been followed at the Rheumatology Clinic; gold therapy was stopped in January 2004 and was replaced by hydroxychloroquine.

Literature review

A literature review has identified 20 RA patients with data available to describe the characteristics of their pleural effusions [12–27]. Nine cases have been reported as single case reports, two reports included two cases each [16, 18] and one study included seven cases with incomplete details available of their pleural effusions [21]. Another nine patients were reported to have undergone thoracotomy for RA-associated pleural effusion but no information is available on the characteristics of their pleural effusions but are included because of the extensive description of the pathological findings [27]. Only one report relates to the cell predominance of the pleural effusion in RA [12].

Clinical picture of pleural effusion associated with RA

Among the 29 reported patients and our two patients included in this study, there were 21 (70%) men and 9 (30%) women; the mean age of the patients was 56.2 (range 32–73) years. Twenty-one (95%) patients had high titers of RF. Sixteen patients (53.3%) had longstanding RA (range 2–30 years) before the onset of pleural effusion and in 14 cases, RA and pleural effusion were diagnosed concurrently. Table 2 summarizes the demographics, association between the onset of RA and effusion, course and management of the effusion in patients with new onset of RA and those with longstanding disease.

Table 2 The characteristics of patients with pleural effusion in temporal relation to being diagnosed with RA and patients with long standing RA

	New RA	Long standing RA
Number of patients	14 (46.7%)	16 (53.3%)
Male (%) : female (%)	12 (88.7%) : 2 (14.3%)	9 (56.3%) : 7 (43.8%)
Mean age (SD)	54.4 (11.2) (12 patients)	59.6 (11) (8 patients)
When pleural effusion occurred in relation to diagnosis of RA	Simultaneously: 4 (28.6%) patients Pleural effusion first: 7 (50%) patients (range 2.5 months–2 years) RA first: 3 (21.4%) patients (range 1–3 months).	Mean (SD) period patients suffered from RA before pleural effusion occurred: 13 (10.1) years (range 2–30 years).
Recurrent pleural/ pericardial effusion	3 (21.4%)/1	4 (25%)/1
Evaluation		
Thoracic tube	5 (35.7%)	1 (6.3%)
Closed pleural biopsy	4 (28.6%)	3 (18.8%)
Thoracoscopy	2 (14.3%)	1 (6.3%)
Bronchoscopy	2 (14.3%)	2 (12.5%)
Thoracotomy	3 (21.4%)	8 (50%)

Seven (23.3%) patients had recurrent pleural effusion and two patients developed pericardial effusions with characteristics similar to those of the pleural effusion [Table 1, 16–19]. Chest pain, shortness of breath and coughing were the most common symptoms. Three patients were asymptomatic. Other symptoms included fever (four patients) and weight loss (six patients), respiratory distress requiring mechanical ventilation (one patient) [18]; and hemodynamic instability due to cardiac tamponade (one patient) [20]. Among the patients with longstanding RA, it was reported that subcutaneous nodules appeared together with the pleural effusion. This finding was not noted in our two patients.

Characteristics of pleural effusion

Pleural effusion analyses were available from 30 aspirations, including five effusions from our two patients. The color of the pleural effusion was reported to be straw colored (2), cloudy white (2), and greenish (2)

and macroscopically bloody pleural fluid in one case [17–20, 22, 23, 27]. All effusions were exudates. The mean LDH level was 2,348 IU/ml (range 125–8,520 IU/ml) and the mean total protein level was 5.24 mg% (range 3.5–7.6, SD = 0.93 mg%). The pH level was available for 21 pleural taps. A very low (6.4–7.14) pH was seen in 15 (71.4%) tests and pH above 7.30 was observed only in four samples. Glucose content was less than 20 mg% in 24 of 30 (80%) samples. In three cases, the analyses of the effusion revealed low glucose levels and normal pH. Only in one test the pH and glucose levels were within normal range (12).

In 20 cases (66.7%) the cell count was above 3,000 WBC/ ml. The differential count revealed lymphocytic predominance in ten tests (37%), neutrophils predominance in 15 tests (55.6%) and eosinophilic pleural effusion in four cases including our two patients [21]; all four patients were male, aged 51, 54 and our patients 65 and 52 years of age; RA was diagnosed concurrently, 11 weeks 1, and 2 years after diagnosis of pleural effusion, respectively [21].

One patient was tapped thrice during 11 days [12] and over that period the differential count of the cells changed from neutrophils to lymphocytic predominant cells. Our first patient was tapped twice within a week and he also had the predominant cells changing from neutrophils to lymphocytes (Table 1). Mesothelial cells were not identified in any of the reported pleural effusions.

Further evaluation

Table two outlines the evaluation of pleural effusion associated with RA. Four patients with new onset RA had a chest tube inserted for suspected empyema with predominant neutrophils in the pleural tap [14, 15, 17 Table 1–10 weeks]; among the patients with long standing RA, one patient had a chest tube inserted with pleural fluid showing a glucose of 7 mg% and pH of 7.13, but the cells were predominant lymphocytic [16].

Histopathological findings in RA pleural effusion

The histological findings have been outlined in detail in nine patients who underwent thoracoscopic biopsies [27]. The pleural effusion in RA is thought to be caused by rheumatoid nodules on the parietal pleural surface which increases permeability of the pleural capillaries [12, 13, 25–27]. Mesothelial cells are replaced by a pseudo-stratified epithelioid cell layer that may be multinucleated and of macrophage origin (Fig. 1). This layer is easily detached and leaves a denuded inflamed pleural surface; a pattern described as "an opened out rheumatoid nodule with palisading epithelioid cells" [27; Fig. 1]; also found are multi-nucleated giant cells and characteristic elongated "tadpole" shaped cells on a background of granular necrotic material of decaying leukocytes; the "tadpole" cells have been shown by staining to be of macrophage origin [Fig. 2; 26, 27]. These histo-pathological findings in the pleura are considered by Naylor to be pathognomic for RA-associated pleural effusion and similar to the findings seen in RA synovitis (Figs. 1, 2) [25–27]. Classic rheumatoid nodules on the pleura are seen occasionally if thoracoscopic biopsies are performed [27], however they are rarely detected in small pleural samples obtained by closed pleural biopsy.

The high cellular content seen in RA-associated pleural effusion has been reported to be due to exfoliation of inflammatory cells from the rheumatoid nodules [25 –27].

Patho-physiologic considerations

The very low glucose levels in pleural effusion associated with RA is the result of consumption of glucose by the high content of activated inflammatory cells and by a metabolic block that prevents transfer of glucose into the pleural fluid [12, 21, 27]. The very low pH correlates with the low glucose level and it is due to relative lack of reabsorption into the blood of glucose metabolites including lactate [12, 21]. The acidic milieu in the pleural cavity interferes with repair processes and may contribute to the development of chronic pleural effusion [12, 21].

Treatment of pleural effusion associated with RA

Medical therapy included systemic steroids (eight patients,) intra-pleural and intra-pericardial steroids (six patients), NSAID (one patient). One study suggested that MTX may accelerate the development of pleural effusion and MTX therapy was withheld. [19].

Two patients underwent pleurectomy for non-expanding lung [16, Case 2]. In the majority of patients, the pleural effusion disappears in an average of 14 months (range 1–36 months) [27]. A restrictive ventilatory defect in spite of MTX and intrapleural steroid therapy developed in a single case [16].

Discussion

We report two men with symptomatic pleural effusion: in the first case, the pleural fluid was an exudate with

predominant lymphocytic cells and eosinophilia and the histological features of pleural characteristics of RA-associated pleurisy. The patient then developed sterile empyema on the contra-lateral side and on his pericardium. The second patient presented initially with a sterile empyema and was treated with a chest tube and antibiotics necessitating pleurectomy 5 months later. He was diagnosed with RA 1 year later.

A literature review has found that pleural fluids associated with RA are highly cellular. The WBC differential count in the pleural fluid shows an initial predominance of neutrophils and over a period 7–11 days, this changes to a predominance of lymphocytic cells [12; Table 1]. Eosinophilic pleural effusion associated with RA has also been reported. It is usually associated with a good prognosis [28].

Both of our cases had peripheral eosinophilia. Case 1, had peripheral eosinophilia 10 days after stopping roxithromycin; making drug allergy being unlikely. Furthermore, the eosinophilia persisted in spite of systemic steroids for 17 weeks. Case 2 developed peripheral eosinophilia while being treated for 10 days with ciproxine, clindamycin and amikacin. Eosinophils were seen in his pleural effusion but not in preparations from transbronchial biopsy, or in broncho-alveolar lavage. The patient had also interstitial lung disease. Following systemic steroids, eosinophils in peripheral blood disappeared and the interstitial lung disease resolved suggesting a possibility of an acute eosinophilic pneumonia. Cases of acute and chronic eosinophilic pneumonia as presenting symptom of RA have been reported [29, 30].

The characteristics of the pleural effusion of RA may mimic those of infected para-pneumonic effusion, a condition that is treated optimally with thoracic drainage and antibiotics. In addition, patients with RA have an increased risk of developing major infections [1, 31], therefore, it is mandatory to treat RA patients with acidic effusion and low glucose content with neutrophils predominance with thoracic drainage and antibiotics until an infection can be ruled out.

Tuberculosis was also included in the differential diagnosis of both patients, however, the clinical and radiological picture of our patients are not typical of tuberculosis, tuberculosis was not identified in the biopsies and furthermore our patients received prolonged systemic steroids and improved; this would be highly unlikely if tuberculosis had been present.

The emergence of new biologic therapy for RA makes it imperative also to rule out tuberculosis in patients with RA and a pleural effusion with lymphocytic predominance [31]. We have not found any RA patient with tuberculosis of the pleural cavity from the literature review.

Mesothelial cells usually are not detected in pleural effusions associated with RA and it has been reported that lack of mesothelial cells in pleural effusion associated with RA is a characteristic finding; a finding more commonly associated with tuberculosis pleurisy [15, 25].

The literature testifies to the hesitancy in accepting pleural effusion with predominant lymphocytes as associated with RA. Patients with long standing RA who present with pleural effusion undergo invasive testing although the histo-pathological findings reported by Naylor are pathognomonic. It is stressed, however, that there is little awareness of these pathognomonic findings of this rare condition [25].

Treatment with systemic steroids has been useful in most cases; and is also reported to be effective given intra-pleurally. One report cautions against methotrexate as an agent associated with extra-articular worsening.

In summary, an exudative pleural effusion with lymphocytic predominance (more than 50% of cells) of unknown etiology in usual clinical practice is evaluated with a closed pleural biopsy or thoracoscopic biopsy to determine whether tuberculosis or malignancy is the cause. We suggest that before these invasive tests are performed that RA-associated pleural effusion be actively sought looking for tadpole cells, palisades of epitheliod cells and a lack of mesothelial cells. When an exudate exhibits neutrophilic predominance and is suggestive of empyema, (defined by presence of pus; or any of the following pH >7.20, glucose >40 mg%, presence of bacteria on gram stains or in fluid cultures), evacuation of fluid is indicated until an infection has been ruled out. The differential cell count in pleural effusion is useful to direct the management of patients also in RA.

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