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Pleural-fluid myeloperoxidase in complicated and noncomplicated parapneumonic pleural effusions

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ABSTRACT: The diagnostic accuracy of myeloperoxidase (MPO) in pleural fluid, for differentiating between complicated and noncomplicated parapneumonic pleural effusions (PPE) evaluated prospectively.

Seventy patients aged >18 yrs with PPE (36 complicated and 34 noncomplicated) were studied after admission to a tertiary referral teaching hospital. MPO concentration was measured in plasma and pleural fluid using a double-antibody competitive radioimmunoassay.

The concentrations of MPO in complicated and noncomplicated PPE were compared using a Mann-Whitney U-test and multiple logistic regression models were used to predict the odds that an effusion was complicated. MPO pleural-fluid concentrations were significantly higher in complicated than in noncomplicated PPE. After excluding purulent effusions, pleural-fluid MPO was the marker that best differentiated between the two types of PPE: the area under the receiver operating characteristic curve was 0.912, the sensitivity was 87.5% and the specificity was 85.1% at a cut-point limit of 3.000 $\mu g \cdot L^{-1}$.

The authors concluded that the concentration of pleural-fluid myeloperoxidase helps to differentiate between nonpurulent complicated and noncomplicated parapneumonic pleural effusions.

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Parapneumonic pleural effusions (PPE) are found in 20–75% of patients hospitalized with moderate-to-severe community-acquired pneumonia [1]. The formation of a PPE consists of three stages: exudative, fibrinopurulent and fibrous [2]. The clinical consequences of this evolution allow PPE to be divided into complicated and noncomplicated types. Therefore, PPE is not a single entity, but represents a progression in which purulent, complicated PPE is the final stage [3]. These parapneumonic effusions are a challenge to clinicians attempting to determine whether the effusion will respond to antibiotic therapy alone or whether the patient requires pleural drainage to manage an established empyema or prevent an empyema from forming. Proper assessment is vital because failure to initiate prompt and effective drainage when indicated increases the morbidity rates associated with pulmonary infection [4]. It is important, therefore, to discriminate as accurately and as early as possible between patients with parapneumonic effusions who are likely to respond to antibiotics alone and those who require pleural-fluid drainage [5].

It is widely accepted that polymorphonuclear cells play a key role in the acute inflammatory response to bacterial infection. Neutrophils participate in the inflammatory response through the release of peptides and proteases [6]. Polymorphonuclear elastase (PMN-E), a protease that originates from azurophil granules of the polymorphonuclear leukocytes (neutrophils) in response to the release of inflammatory mediators, stands out among these [7]. The value of pleural-fluid PMN-E in the differentiation between infective and noninfective effusions has recently been established [8]. Myeloperoxidase (MPO) is a protein responsible for the peroxidase activity characteristic of the azurophilic granules and is essential for the oxidative mechanism of the phagocytes. MPO and reduced nicotinamide-adenine dinucleotide phosphate (NADP-H) oxidase are the main proteins that participate in oxidative-type microbicidal activity [9]. Increased concentrations of MPO have been reported in various inflammatory processes [10–12]. The authors previously detected higher levels of pleural-fluid MPO in complicated bacterial effusions than in noninfective effusions [13].

The criteria currently used for pleural drainage in the treatment of PPE are based on findings such as acid pH and purulent-appearing fluid, signs of an already advanced phase of infection [14, 15]. Measurements of pH are, however, dependant on the mode of sample carriage and delay in measurement [16]. A fluid glucose value <40 $mg \cdot dL^{-1}$ or a located hydogenase (LDH) value >1,000 $IU \cdot L^{-1}$ has also been

used in the early diagnosis of complicated PPE [3], although the development of pleural thickening in the evolution of complicated PPE is not unusual [17, 18]. In view of the persistence of local complications a prospective study, to evaluate whether pleural-fluid MPO concentration might be useful for early differentiation between complicated and noncomplicated PPE, was performed.

Patients and methods

Study population and diagnostic criteria

The study included patients aged >18 yrs with PPE admitted consecutively to a general teaching hospital. Patients were divided into two groups. 1) Complicated parapneumonic, according to at least one of the following criteria: macroscopic pus, presence of organisms on Gram-stain or culture, fluid pH <7.2 with normal peripheral blood pH, or fluid glucose concentrations <40 $mg \cdot dL^{-1}$. 2) Noncomplicated parapneumonic, according to at least one of the following criteria: pleural effusion associated with a nonpurulent pleural fluid; negative fluid microbiological studies; fluid pH>7.2 with normal peripheral blood pH; or fluid glucose >40 $mg \cdot dL^{-1}$.

Seventy patients with PPE were enrolled in the study. Thirty-six had complicated PPE (51.5%) and the remaining 34 had noncomplicated PPE (48.5%). Of the patients with complicated PPE (mean age 56 yrs, 89% males), 21 (58%) had positive cultures and 20 (55%) purulent pleural effusion. Sixty-seven per cent had other illnesses (chronic bronchitis, diabetes mellitus or chronic hepatic disease) and 28% had received antibiotics previously. The most frequently used antibiotic during hospitalization was co-amoxyclavulanic acid. All the patients with complicated PPE were treated by pleural drainage, six received intrapleural urokinase and three had pleural decortication. Complications consisting of pleural thickening and pleural loculation were recorded in 31 patients (86%).

The 34 patients with noncomplicated PPE had a mean age of 54 yrs and 70.5% were males. In 59%, other illnesses were present (chronic bronchitis, diabetes mellitus, chronic hepatic disease) and 35% had received antibiotics previously. During hospitalization, the most frequently used antibiotic combinations (88%) were cephalosporins plus macrolides. Complications, including loculations and pleural thickening, were present in 35% of patients. None of the patients were taking either corticosteroids or nonsteroidal anti-inflammatory drugs.

Biochemical, cytological and bacteriological methods

Biochemical measurements were carried out using a Hitachi 919 automatic analyser (Boehriger Mannheim, GMbH, Mannheim, Germany), using the method of Biuret for proteins, hexokinase for glucose, and pyruvate-to-lactate reduction at 37° for LDH.

For determination, pH pleural fluid was collected directly into a heparinized blood-gas syringe and was maintained anaerobically. The syringe containing the pleural fluid was immediately placed on ice and transferred to the laboratory. Pleural-fluid pH was measured within 20 min after thoracocentesis using a selective pH electrode (Chiron Diagnostics 860; Ciba Corning Diagnostics Corp., Medfield, MA, USA).

For PMN-E and MPO determinations, samples were collected in ethylene diamine tetra-acetic acid and plasma or pleural-fluid supernatants were separated within the first hour. PMN-E was determined by an immunoactivation method (IMAC, Merck kGaA, Darmstad, Germany) that measures free and α_1 proteinase inhibitor-bound PMN-E[19]. The between-run imprecision for a mean value of 134 $\mu g \cdot L^{-1}$ was 8.9% (n=20). MPO was measured by double-antibody competitive radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). The between-run imprecision for a mean value of 450 $mg \cdot L^{-1}$ was 4.8% (n=20). Lysozyme was measured by means of a turbidimetric method.

Total white blood cell counts were carried out with a Coulter®-s-Plus IV Counter Izasa, Spain. To differentiate between leukocytes, the sample was centrifuged (Cytospin® 2, Shandon Southern Products Ltd, UK) at 2,000 revolutions per minute for 8 min, and the preparation obtained was stained with May-Grunwald-Giemsa.

For microbiological studies, pleural-fluid samples were extracted by thoracocentesis under aseptic conditions and sent to the bacteriology laboratory in a sterile tube and an anaerobic blood culture vial (Bactec NR 660 system; Becton Dickinson, USA). Gram and Ziehl-Neelsen stains were carried out and cultures were performed in conventional media for aerobic and anaerobic micro-organisms, fungi, legionella and mycobacteria. Pneumococcal antigen was detected by means of the coagglutination technique (Phedebact Pneumococcus test; Boule Diagnostics, Huddinge, Sweden).

Statistical analysis

Because of the presence of extreme values among the pleural-fluid biochemical variables, the Mann-Whitney U-test was used to compare their distribution in complicated and noncomplicated PPE. Multiple logistic regression models were used to predict the odds that an effusion was complicated.

The validity of the predictions derived from the multiple logistic regression models was assessed. Each type of misclassification was evaluated according to its cost (weights were -2 for misclassifying a complicated PPE as noncomplicated, -1 for misclassifying a noncomplicated PPE as complicated, and 0 for correct predictions). The cut-point with the highest global value was selected according to this evaluation. The binomial distribution was used to estimate the 95% confidence intervals (CI) for sensitivity and specificity. To assess the diagnostic accuracy of MPO as an early marker in the diagnosis of complicated PPE, the statistical analysis was repeated after excluding purulent effusions.

The agreement between pleural pH<7.2, pleural glucose <40 mg·dL^{-1}, pleural LDH>1,000 IU·L^{-1} and a pleural MPO value greater than the suggested cut-point was assessed. The kappa statistic was used to adjust the observed agreement for chance; its standard error was used to test the hypothesis that the underlying value of kappa was zero [20]. This study evaluated whether a difference of 0.3 between plasma and pleural pH differentiated between complicated and noncomplicated PPE. The Mann-Whitney U-test was used to evaluate the associations between pH, glucose, LDH, MPO or polymorphonuclear leukocyte count in pleural fluid and later loculation of PPE. The study was approved by the Clinical Assay Committee.

Results

Table 1 shows the medians, 25th and 75th percentiles and ranges for pH, glucose, proteins, LDH, neutrophil count and MPO in peripheral blood in the patients. There were no statistically significant differences between the two groups.

Table 2 summarizes the distribution of the same biochemical variables in pleural fluid. As expected, fluid pH and glucose values were lower in complicated than in noncomplicated PPE (p<0.001). Median pleural-fluid MPO values were 98.7 μg·L^{-1} in complicated and 1.7 μg·L^{-1} in noncomplicated PPE (p< 0.001). LDH pleural-fluid concentrations were also higher in complicated PPE.

Figure 1 shows the logarithm of pleural MPO concentrations in the two types of parapneumonic effusions. The highest MPO values were seen in complicated PPE. When forward stepwise modelling was used to identify the main predictors of complicated PPE among the pleural-fluid variables (proteins, log LDH, log neutrophil count, and log MPO), the logarithm of MPO concentration was included first (log-likelihood ratio Chi-squared test was equal to 65.656; p<0.001) and was followed by log LDH (log-likelihood ratio Chi-squared test equal to 4.570; p=0.033).

With use of a logistic regression model incorporating the log MPO concentration in pleural fluid, the odds that a PPE was complicated increased with its value (odds ratio (OR): 4.43; 95% CI: 2.18–8.97). When the log MPO in serum was added to this model, the log-likelihood ratio Chi-squared test was not significant (Chi-squared equal to 1.53; p=0.217). The area under the receiver operating characteristics (ROC) curve for the log pleural-fluid MPO was 0.9690 (fig. 2).

The MPO cut-point for the diagnosis of complicated PPE was 3.000 μg·L^{-1}. Sensitivity at this level was 94.1% (95% CI: 80.3–99.3) and specificity was 85.1% (68.9–95). A specificity of 91.2% (75.2–97.7) had a sensitivity of 75% (47.4–91.7) and a specificity of 97.1% (82.9–99.8) had a sensitivity of 56% (30.6–79.2). After excluding purulent PPE from the analysis, the sensitivity of pleural-fluid MPO values equal to or greater than this cut-point was 87.5% (61.7–98.5) and specificity was 85.1% (68.9–95). The area under the ROC curve for the logarithm of pleural-fluid MPO was 0.912. (fig. 3). A difference of 0.3 between plasma and pleural pH had a sensitivity of 77.4% and a specificity of 100% in the differentiation between complicated and noncomplicated PPE.

Thirty-eight patients with complicated PPE or pleural LDH >1,000 IU·L^{-1} had pleural-fluid MPO concentrations >3.000 μg·L^{-1}, while 29 patients with noncomplicated PPE and pleural LDH <1,000 IU·L^{-1} had an MPO concentration <3.000 μg·L^{-1}. The observed agreement between the combination of pleural pH, glucose and LDH with pleural MPO in the diagnosis of complicated PPE was 95.7%, the kappa statistic was 0.913 (SE=0.049; p<0.0001). After excluding purulent effusions, the concordance between pleural MPO and the combination of

Table 1. – Biochemical and bacteriological variables in peripheral blood

	Minimum	P25	Median	P75	Maximum
pH					
Complicated	7.30	7.35	7.38	7.42	7.5
Noncomplicated	7.30	7.37	7.39	7.42	7.5
Glucose mg·dL^{-1}					
Complicated	64	90	115	117	388
Noncomplicated	74	93	120	124	274
Protein g·dL^{-1}					
Complicated	4.8	5.4	6.05	6.5	8.1
Noncomplicated	5.0	5.4	6.18	6.7	7.6
LDH IU·L^{-1}					
Complicated	157	227	312	375	570
Noncomplicated	207	297	450	591	1.17
Myeloperoxidase μg·L^{-1}					
Complicated	172	390	641	798	2.61
Noncomplicated	82	360	604	749	1.45
Neutrophils 10^3·μL^{-1}					
Complicated	4.80	5.34	10.8	14.2	36.1
Noncomplicated	4.50	5.24	8.33	10.1	23.1

Complicated: complicated paraneumonic effusion n=36; Noncomplicated: Noncomplicated paraneumonic effusion n=34; LDH: lactate dehydrogenase; P25: 25th percentile; P75: 75th percentile; No significant differences between types of effusion.

Table 2. – Biochemical and bacteriological variables in pleural fluid

	Minimum	P25	Median	P75	Maximum	p-value
pH						
Complicated	5.5	6.53	6.70	7.07	7.39	
Noncomplicated	7.30	7.37	7.43	7.50	7.61	<0.001
Glucose mg·dL^{-1}						
Complicated	1	5	36.5	65	147	
Noncomplicated	57	97	127	135	374	<0.001
Protein g·dL^{-1}						
Complicated	3	3.3	4.4	5.6	7.3	
Noncomplicated	3	3.2	3.8	4.7	6	0.026
LDH IU·L^{-1}						
Complicated	159	1.37	8.22	6.91	50.0	
Noncomplicated	153	323	539	708	1.74	<0.001
Myeloperoxidase μg·L^{-1}						
Complicated	745	15.0	99.0	5.50	625	
Noncomplicted	21	226	1.70	1.94	12.2	<0.001
Neutrophils 10^3·μL^{-1}						
Complicated	4.05	7.82	65.8	90.0	725	
Noncomplicated	4.02	4.13	3.00	6.78	14.2	<0.001

Complicated: complicated paraneumonic pleural fluid n=36; Noncomplicated: noncomplicated paraneumonic pleural fluid n=34; LDH: lactate dehydrogenase; P25: 25th percentile; P75: 75th percentile.

biochemical markers (pH<7.2 or glucose <40 mg·dL^{-1} or LDH >1,000 IU·L^{-1}) was 94%, with a kappa value of 0.874 (SE was 0.070; p<0.0001).

Among the 36 PPE classified as complicated by the conventional biochemical criteria, 34 (94%) had pleural pH<7.20 or pleural glucose<40 mg·dL^{-1} or pleural LDH>1,000 IU·L^{-1} and MPO>3.000 μg·L^{-1} and none had pH<7.20 and MPO<3.000 μg·L^{-1}. The other two complicated PPE were classified as such by positive pleural-fluid culture, with pleural pH>7.20 and pleural MPO<3.000 μg·L^{-1}. *Serratia marcescens* and *Crytococcus neoformans* were isolated from pleural fluid in these patients.

In the 34 noncomplicated PPE, 28 (82%) had a pH>7.20 or glucose>40 mg·dL^{-1} or LDH< 1,000 IU·L^{-1} and MPO<3.000 μg·L^{-1}. On the basis of biochemical criteria for classifying complicated PPE (pleural pH<7.20 or pleural glucose<40 mg·dL^{-1}), pleural MPO identified five more PPE as being complicated and four of these had pleural LDH> 1,000 IU·L^{-1}. Follow-up radiography on three of these five patients showed the presence of pleural thickening.

Associations between polymorphonuclear count and biochemical markers in pleural fluid and later loculation or pleural thickening were statistically significant for pH (p=0.001), glucose (p=0.048), MPO (p=0.026) and polymorphonuclear leukocyte count (p=0.013).

Discussion

Several pleural-fluid measurements have been used to assess the severity and predict the course of

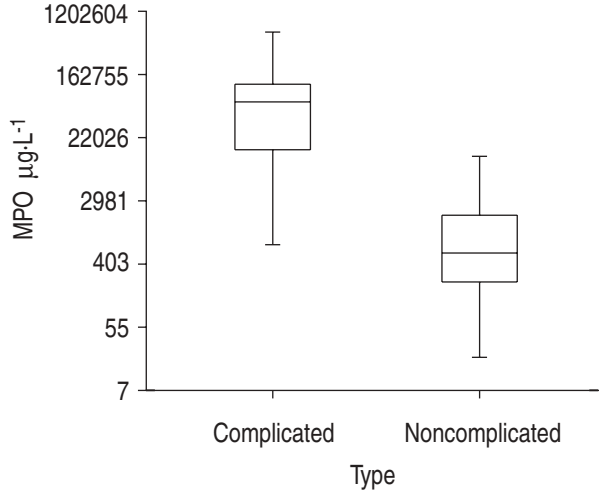

Fig. 1. – Pleural-fluid myeloperoxidase (MPO) distribution in the two types of pleural effusion (complicated and noncomplicated). The box and whisker represent median, interquartile range and complete range.

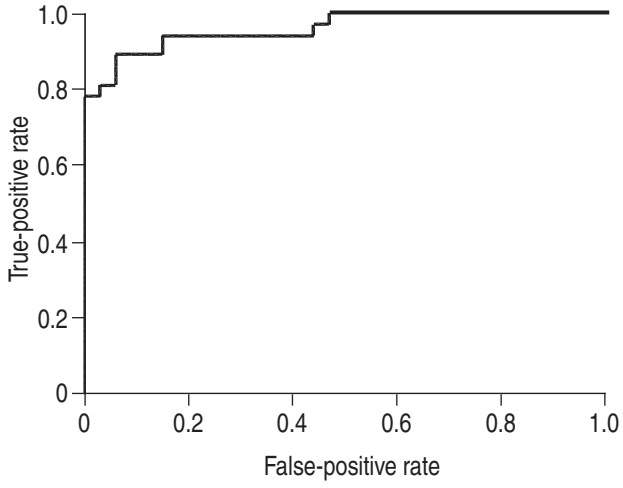

Fig. 2. – Receiver operating characteristic curve for predicting that a parapneumonic pleural effusion is or is not complicated, from a regression model with log pleural-fluid myeloperoxidase (area under the curve 0.969). Cut-off 3.000 μg·L^{-1}.

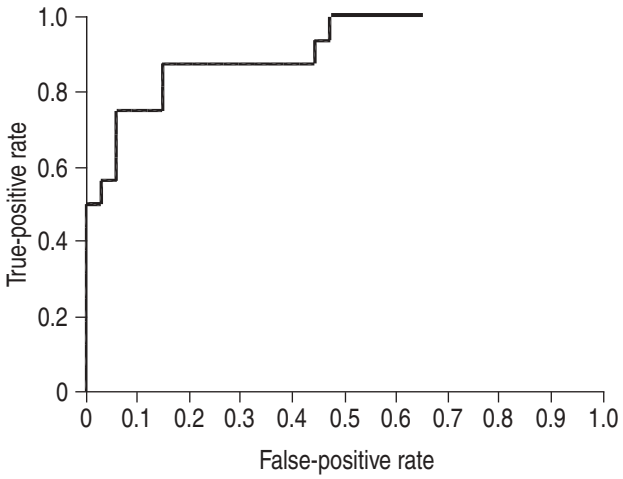

Fig. 3. – Receiver operating characteristic curve for predicting, after excluding purulent effusions, that a parapneumonic effusion is or is not complicated, from a regresion model with log pleural-fluid myeloperoxidase (area under the curve 0.912). Cut-off 3.000 $\mu g \cdot L^{-1}$.

a parapneumonic effusion [21]. The duration and severity of pleural infection and the associated inflammatory response induce metabolic changes that alter pleural-fluid chemistry. Extensive intrapleural infections decrease pH, lower glucose, and raise LDH values in pleural fluid [17]. Case series of patients with parapneumonic effusions suggest that these tests can discriminate between nonpurulent parapneumonic effusions that require drainage and those that will most likely respond to antibiotic therapy alone [17, 22, 23].

The biochemical characteristics of pleural fluid are the indices most often used to identify complicated PPE, and pH is one of the most widely used guides to indicate the need for pleural drainage in this condition [1, 14, 24, 25]. The importance of the combination of biochemical indices (pH<7.2, glucose<40 $mg \cdot dL^{-1}$, LDH>1,000 $IU \cdot L^{-1}$) in the diagnosis of PPE has been stressed previously [3].

It is well recognized that accurate pH determination requires strict anaerobic extraction and rapid transport and analytical techniques. These conditions, however, are not always fulfilled [16]. Physicians handle samples for pleural-fluid pH determination in a variety of ways [26], such as collection in a large syringe and transfer to a heparinized syringe for pH assessment [27], and with varying use of local anaesthesia [28].

In a recently published meta-analysis investigating the ability of the commonly used markers to identify complicated PPE requiring drainage, the results for fluid pH showed an area under the ROC curve of 0.92 and, after excluding purulent effusions from the analysis, 0.89. Pleural-fluid pH had a relatively high diagnostic accuracy, greater than that of pleural-fluid glucose and LDH, for discriminating between complicated and noncomplicated parapneumonic effusions [21].

The present study identified pleural-fluid MPO, with a sensitivity of 94.1% and a specificity of 85.1% at the 3.000 $\mu g \cdot L^{-1}$ cut-point, as the best index for discriminating between complicated and noncomplicated PPE. After excluding purulent effusions, pleural-fluid MPO was still the marker that best differentiated between the two types of PPE, with a sensitivity of 87.5% and a specificity of 85.1% at a cut-point limit of 3.000 $\mu g \cdot L^{-1}$. The differences in mean levels of MPO between a previous report [13] and this study, are due to the inclusion of four additional cases in each subgroup of PPE. The aim of the previous report was to study whether interleukin (IL)-8 was produced in the pleural space and its relation to the neutrophil activation state in infected pleural fluid.

It is recognized that during the inflammatory process, leukocytes release intracellular constituents, such as bactericidal permeability-increasing protein, defensins, lysozyme, cationic proteins, lactoferrin and zinc-binding proteins [9]. MPO is the most abundant protein of the neutrophils and catalyzes the conversion of hydrogen peroxide and chloride into hypochloride [29], an essential component of the oxygen-dependant microbicidal system, with NADPH oxidase of neutrophils and monocytes [30]. An increased MPO concentration is an indirect, but clear indication of MPO release by an inflammatory process. MPO, as a marker of inflammation, has been measured to distinguish otitis media, chronic sinusitis, chronic bronchitis and peritonitis of bacterial origin [10–12], in which excellent correlations have been observed with levels of IL-8, a cytokine involved not only in chemotaxis, but also in neutrophil activation.

The demonstration of the discriminatory role of pleural MPO, after excluding purulent PPE, together with the significant relations between pleural MPO and standard biochemical markers and between pleural levels of neutrophilic markers and pleural complications of PPE, suggest that MPO may be a useful tool for the management of patients with PPE. Correct differentiation between a complicated and noncomplicated PPE is associated with better prognosis [5]. Late pleural drainage can result in complications, leading to decreased pulmonary function. Moreover, there may be a greater need for pleural thrombolytic agents and pleural decortication [4, 5, 15], implying increased hospital stay and healthcare costs [5].

Significant pleural complications still occur when using classical criteria to indicate pleural drainage, *i.e.* the presence of purulent pleural fluid, microorganisms on Gram-stain and/or positive culture andpleural pH<7.20 and/or pleural glucose<40 $mg \cdot 100\ mL^{-1}$ in the context of a clinical and radiological process [17, 18]. There are three situations in which the usefulness of pH is subject to controversy: 1) in cases where pH is between 7–7.2, there is no consensus as to the ideal approach to take and opinions range from the use of conservative treatment, *i.e.* empirical therapy with broad-spectrum antibiotics, to early thoracic drainage; 2) in cases involving technical difficulties in the extraction, transport or processing of the samples; and 3) when the value of pH results is questionable because patients received antibiotic treatment before thoracocentesis. Determination of pleural-fluid MPO

concentration could be particularly useful in these borderline or difficult cases. In the present study, measurement ofpleural MPO permitted early detection of five patients with complicated PPE, four of whom had pleural LDH>1,000 $IU \cdot L^{-1}$. Subsequently, complications consisting of pleural thickening were detected inthree of these patients and two of them also had pleural LDH>1,000 $IU \cdot L^{-1}$. In addition, itwas found that the handling of samples was comparatively simple and did not require the strict conditions required for accurate pH determination [16, 26, 27].

The present results indicate that pleural-fluid myeloperoxidase concentration is a good discriminant between nonpurulent complicated and noncomplicated parapneumonic pleural fluid. Myeloperoxidase measurement could help in the management of this condition, since it is less affected by technical variation than pH determination. Pleural-fluid myeloperoxidase concentrations >3.000 $\mu g \cdot L^{-1}$ are highly suggestive of complicated parapneumonic pleural effusion.

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