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Procalcitonin as a diagnostic marker in differentiating parapneumonic effusion from tuberculous pleurisy or malignant effusion

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ABSTRACT

Objectives: Differential diagnosis of exudative pleural effusions can be difficult, despite the use of several biomarkers. Serum procalcitonin (s-PCT) is a well-known biomarker for systemic bacterial infections. However, the usefulness of pleural fluid procalcitonin (pf-PCT) in clinical practice has not been established. This study evaluated the usefulness of PCT measurements in differentiating parapneumonic effusion (PPE) from tuberculous (TB) pleurisy or malignant effusion.

Design and methods: Ninety eight adult patients diagnosed with exudative pleural effusion were enrolled and allocated into the PPE group ($n = 32$), TB pleurisy group ($n = 40$), or malignant effusion group ($n = 26$). Both s-PCT and pf-PCT concentrations were measured at admission using an immunoluminometric assay.

Results: Both s-PCT and pf-PCT were significantly increased in the PPE group compared with the TB pleurisy or malignant effusion groups ($p < 0.001$). The optimal cut-off value for s-PCT in the diagnosis of PPE was 0.18 ng/mL (sensitivity 83.3%, specificity 81.0%). The pf-PCT cut-off value was 0.16 ng/mL (sensitivity 81.5%, specificity 72.1%). Serum PCT exhibited better diagnostic accuracy than pf-PCT, with areas under the receiver operating characteristic curves of 0.842 for s-PCT and 0.784 for pf-PCT ($p = 0.015$). In addition, s-PCT and pf-PCT showed better diagnostic accuracy than serum C-reactive protein ($p = 0.005$ and $p = 0.023$, respectively).

Conclusions: Measurement of s-PCT and pf-PCT is useful in differentiating PPE from TB pleurisy and malignant effusion. Both s-PCT and pf-PCT may be useful biomarkers in the differential diagnosis of exudative pleural effusions.

Introduction

Parapneumonic effusion (PPE) and malignant effusion are major causes of exudative pleural effusion, although tuberculous (TB) pleurisy is also a common etiology in areas where TB is prevalent [1]. In most cases, these etiologies can be differentiated by radiologic examination and pleural fluid analyses including differential cell counts and cytological examination. However, these methods are sometimes insufficient for exact diagnosis, especially in the early phase of the diseases. Many studies have aimed to identify biomarkers that would be useful for earlier and more accurate diagnoses of exudative pleural effusions. In the case of TB pleurisy, adenosine deaminase (ADA) is the most widely used diagnostic biomarker, having considerable sensitivity and specificity [2]. However, ADA levels remain low in the initial phase of TB pleurisy and can be high in non-TB pleural effusions, such as PPE or empyema [3]. Carcinoembryonic antigen (CEA) is specific to malignant pleural effusion, but its sensitivity varies widely from 29% to 77% [4]. The clinical usefulness of several biomarkers including C-reactive protein (CRP), soluble triggering receptor on myeloid cells (sTREM-1), and lipopolysaccharide-binding protein for PPE appears limited [5,6].

Procalcitonin (PCT) is a prohormone of calcitonin that is secreted by C-cells of the thyroid gland in response to hypercalcemia. Under normal metabolic conditions, PCT is not released into the blood stream, so its levels are undetectable in healthy populations. However, the level of serum PCT (s-PCT) increases in various settings of systemic inflammation [7–9]. Interestingly, s-PCT concentration increases over several hours in some infections, especially bacterial infection [10,11], while only minimally increasing in viral or TB infections [12,13]. In addition, s-PCT has proven useful for early diagnosis of bacterial sepsis

Abbreviations: ADA, adenosine deaminase; AUC, area under the curve; CRP, C-reactive protein; LDH, lactate dehydrogenase; s-PCT, serum procalcitonin; pf-PCT, pleural fluid procalcitonin; ROC, receiver operating characteristic; TB, tuberculous.

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[14] and for estimation of severity and prognosis in patients with sepsis and multiorgan failure [15,16]. In a recent study, s-PCT-guided treatment substantially reduced antibiotic use without compromising clinical outcomes in patients with lower respiratory infections [17].

In contrast to this wealth of knowledge concerning the clinical implications of s-PCT, few studies have evaluated the usefulness of PCT measurements in body fluids other than serum, especially in pleural effusion. Furthermore, the diagnostic value of pleural fluid PCT (pf-PCT) in the diagnosis of pleural effusions is unclear, since prior findings have been inconsistent [5,18].

The aim of this study was to evaluate the levels of s-PCT and pf-PCT in exudative causes of pleural effusions and to investigate the value of those potential biomarkers in differentiating PPE from TB pleurisy or malignant effusion.

Materials and methods

Study population

We prospectively recruited patients with exudative pleural effusion who were referred or admitted to the Division of Respiratory and Critical Care Medicine at Korea University Anam Hospital (Seoul, Korea) from May 2010 to April 2011. All the patients were not treated for their effusion before enrolment. Among the patients with exudative pleural effusion, patients with PPE, TB pleurisy, and malignant effusion were eligible. This study was performed after obtaining written informed consent from all patients and the study protocol was approved by the Clinical Research Ethics Committee of Korea University Anam Hospital.

Diagnostic criteria

Exudate was defined according to Light's criteria [19] as pleural fluid/serum protein level > 0.5, pleural fluid/serum lactate dehydrogenase (LDH) level > 0.6, and pleural fluid LDH level exceeding two-thirds of the upper limit for serum LDH. The determination of the etiology of the pleural effusions for each patient was based on clinical presentation, appropriate diagnostic test results, and response to treatment. Accordingly, effusions were classified into the PPE group, TB pleurisy group, or malignant effusion group defined by the predetermined criteria. PPE was identified by the presence of pulmonary infection in which the patient had newly acquired fever, purulent sputum, pneumonic infiltration on chest radiography, and response to antibiotic treatment. TB pleurisy was diagnosed in cases of lymphocyte dominancy and a high ADA level (> 40 IU/L) in the pleural fluid, pathological confirmation of caseating granuloma in a pleural biopsy specimen, or a positive TB culture of the sputum or pleural fluid. Malignant effusion was defined as the presence of cytologically identifiable malignant cells in the effusion or pleural biopsy specimen.

Serum and pleural fluid analysis

On the day of admission, the serum and pleural effusion was collected from the subjects, and centrifuged at 3000 rpm for 10 min at 4 °C, and the supernatant was stored frozen at −70 °C until analysis. Measurements included complete blood count with differential counts, as well as the concentrations of protein, albumin, glucose, and LDH in both serum and pleural fluid, ADA in pleural fluid, and CRP in serum. Gram staining of the pleural fluid with ordinary culture, acid-fast bacilli (AFB) fluorescent staining with TB culture, and cytological examination were performed. PCT concentrations were consecutively measured in both serum and pleural effusion specimens.

Measurement of PCT

The quantification of PCT was performed using the PCT sensitive LIA® immunoluminometric assay (BRAHMS Diagnostica, Berlin, Germany) [20]. The analytic sensitivity of the assay was 0.01 ng/mL. The test required 20 μL of serum or pleural fluid and required 2–3 h for analysis. The assay used two monoclonal antibodies. The first antibody was directed against part of the katacalcin sequence of PCT (amino acid residues 96–106), and was the capture antibody. The second, recognized part of the calcitonin sequence (residues 70–76), and functioned as the tracer antibody. During incubation, both antibodies reacted with PCT in a sandwich-like manner. After several washing procedures, the amount of tracer remaining in the test tube was measured using a LUMAT LB 9507 luminometer (EG&G Berthold, Calw, Germany). The intensity of the luminescence signal was directly proportional to the PCT concentration of the serum or pleural fluid sample. The PCT concentration was quantified through comparison with a standard curve.

Statistical analyses

Data were expressed as median (interquartile range) because they did not show a normal distribution. The Kruskal–Wallis test or Mann–Whitney *U* test for nonparametric variables was used to compare the differences among groups. All tests were two-tailed, and p-values were corrected for the number of comparisons using the Bonferroni method. Spearman's test was used to assess the correlations between variables. A difference was defined as statistically significant if $p < 0.05$. The receiver operating characteristic (ROC) curves were analyzed to determine the optimal cut-off value and to compare the diagnostic accuracies of biomarkers. Statistical analysis was carried out using SPSS version 13.0 for Windows (SPSS, Chicago, IL, USA) and MedCalc software (MedCalc, Mariakerke, Belgium).

Results

Ninety eight patients (67 males, 31 females; median age 58.6 years) were enrolled and divided into the PPE, TB pleurisy, or malignant

Table 1
Clinical characteristics of the three patient groups.

Characteristic	PPE ($n = 32$)	TB pleurisy ($n = 40$)	Malignant effusion ($n = 26$)	*p* Value
Age, years	65.4 (30–73)	41.3 (25–67)	64.1 (49–73)	0.001
Male sex	20 (62.5)	30 (75.0)	17 (65.3)	0.587
Serum CRP, mg/L	148.0 (82.9–209.6)	82.1 (36.5–93.1)	36.5 (26.8–49.1)	<0.001
Blood WBC count, $\times 10^3/\mu L$	14.7 (8.8–17.9)	7.6 (6.9–7.8)	9.1 (7.0–9.9)	<0.001
Pleural fluid ADA, IU/L	30.5 (23.2–53.5)	88.73 (71.4–101.0)	23.6 (20.8–32.1)	<0.001
Pleural fluid LDH, IU/L	398.4 (251–420)	341.6 (234–383)	367.5 (343–371)	0.418
Serum PCT, ng/mL	0.76 (0.16–2.23)	0.11 (0.06–0.32)	0.10 (0.02–0.11)	<0.001
Pleural fluid PCT, ng/mL	0.54 (0.10–1.32)	0.09 (0.03–0.13)	0.08 (0.03–0.12)	0.002

Data are presented as the median (interquartile range) or no. (%); interquartile range, 25th to 75th percentile; *p* value, Kruskal–Wallis test; ADA, adenosine deaminase; CRP, C-reactive protein; LDH, lactate dehydrogenase; PPE, parapneumonic effusion; PCT, procalcitonin; TB, tuberculous; WBC, white blood cell.