Effects of Coexisting Pneumonia and End-stage Renal Disease on Pleural Fluid Analysis in Patients With Hydrostatic Pleural Effusion

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Background: In individual patients, especially those who are hospitalized, several conditions often coexist that may be responsible for the development of a pleural effusion and may affect the pleural fluid analysis (PFA). The objective of this study was to investigate the effects of end-stage renal disease and pneumonia on PFA in patients with hydrostatic pleural effusion.

Methods: In a retrospective analysis of 1,064 consecutive patients who underwent thoracentesis at a university hospital, cell counts and pleural fluid protein, lactate dehydrogenase, pH, and glucose levels were examined in those ($n = 300$) with clinical evidence of hydrostatic pleural effusion.

Results: The 300 patients (28.1%) with pleural effusions had congestive heart failure (CHF), circulatory overload (CO), or both. Expert consensus was achieved in 66 (22%) for CHF as the sole diagnosis (SCHF), 30 (10%) for CHF and coexisting pneumonia (PCHF), and 26 (8.7%) for end-stage renal disease (ESRD) with coexisting CO or CHF. The remaining 178 patients were excluded because of complicating conditions. There were minor, but statistically significant differences in pleural fluid/serum protein ratios in patients with ESRD with coexisting CO or CHF compared with SCHF. Compared with SCHF, there were statistically significant tendencies for higher protein and lactate dehydrogenase concentrations and lower pH levels in those with PCHF. The total nucleated cell count and the absolute neutrophil count were significantly higher in PCHF.

Conclusions: ESRD in patients with hydrostatic pleural effusions has a minimal effect on the PFA. Coexisting pneumonia most often results in an exudative effusion in patients with CHF.

CHEST 2013; 143(6):1709–1716

Abbreviations: ANC = absolute neutrophil count; CHF = congestive heart failure; CO = circulatory overload; ESRD = end-stage renal disease; ESRDCOCHF = end-stage renal disease with coexisting circulatory overload or congestive heart failure; LDH = lactate dehydrogenase; PCHF = congestive heart failure and coexisting pneumonia; PFA = pleural fluid analysis; SCHF = congestive heart failure as the sole diagnosis; TNC = total nucleated cell count

Pleural effusion may be caused by a myriad of medical conditions. A detailed understanding of the clinical presentation in concert with the pleural fluid analysis (PFA) is of value in differentiating the cause of an effusion. In the individual patient, more than one medical condition may exist and be responsible for the development of pleural effusion. Such coexisting conditions that may influence the results of the PFA often are present in hospitalized patients. Although the findings of an inconclusive PFA may suggest more than one condition, the role an individual condition plays in the accumulation of pleural fluid cannot always

be determined. Ultimately, confirmation that a single condition is responsible for the development of pleural effusion can only be obtained by documenting resolution of the effusion after successful treatment of the single condition while other complicating conditions remain unresolved. These observations were reported in a study of congestive heart failure (CHF)-related effusions by Eid and colleagues¹ in 2002. According to this retrospective study of hospitalized patients who met criteria for a clinical diagnosis of CHF, roughly 50% had an exudative pleural effusion. In the majority of these patients, the cause of the

pleural effusion was attributed to noncardiac etiologies. However, to the best of our knowledge, a systematic investigation to determine the influence of coexisting conditions on the PFA has not been reported.

We attempted to elucidate whether the presence of end-stage renal disease (ESRD) treated with effective hemodialysis or the presence of pneumonia can change the characteristics of the PFA in patients with CHF or circulatory overload (CO). Our reasons for selecting these conditions are twofold: Pleural effusions resulting from CO or CHF in ESRD or from pneumonia (1) are commonly encountered in clinical practice and (2) are represented in sufficient numbers in our existing database to allow for analysis.

The rationale for the investigation of CHF and coexisting pneumonia (PCHF) is that pneumonia may result in inflammation of the pleural membranes and subsequent extravasation of protein and lactate dehydrogenase (LDH) into the pleural effusion. Furthermore, there is increased leukocyte trafficking into the pleural space, resulting in lowering the pleural fluid pH level. The rationale for comparing pleural effusions caused solely by CHF and by CO with coexisting ESRD addresses the question of whether the presence of subclinical uremic pleuritis affects the PFA. This question is of interest because the clinician must know whether deviation from the typical PFA of hydrostatic pleural effusions can be discounted on the basis of the presence of ESRD.

The present investigation treats the PFA in patients with CHF as the sole cause of the pleural effusion as the standard against which the PFA of patients with ESRD with coexisting CO or CHF (ESRD/COCHF) and patients with PCHF are compared. The rationale for these comparisons is that in patients with ESRD, CHF, and pneumonia, the potential for the development of an exudative pleural effusion exists. Alterations of the PFA may occur if subclinical uremic pleuritis or active lower respiratory tract infection is present in patients with CHF. Our investigation focuses on standard tests performed as part of the routine PFA,

such as protein, LDH, pH, and glucose levels and nucleated cell counts.

MATERIALS AND METHODS

We reviewed 1,064 consecutive thoracentesis procedures performed at the Medical University of South Carolina from January 2001 through July 2009. Repeat thoracenteses were excluded.

All patients with CHF or CO recorded in the clinical database were reviewed by an expert panel comprising P. D., J. T. H., and S. A. S. and were excluded either because of the absence of sufficient evidence for the presence of CHF or CO or because of the presence of complicating conditions other than ESRD and pneumonia. The data reviewed for each case included history and physical examination, radiographic images, laboratory values, and echocardiography findings as recorded in inpatient and outpatient charts as well as in hospital discharge summaries.

A clinical diagnosis of pneumonia required the presence of two or more of the systemic inflammatory response syndrome criteria (temperature, WBC count, respiratory rate, heart rate) with productive cough of mucopurulent sputum. Patients were considered to have CHF if they had typical presenting symptoms, such as orthopnea, dyspnea, left ventricular S3 gallop sounds, fine crackles, and supportive chest radiographic findings of pulmonary edema and cardiomegaly. When echocardiography and pro-brain natriuretic peptide levels were known, both supported a diagnosis of CHF.

Patients with ESRD/COCHF receiving long-term hemodialysis were included if there was an absence of symptoms or factors associated with uremic pleuritis (absence of pleuritic chest pain, compliance with hemodialysis, a BUN level < 80 mg/dL prior to thoracentesis). Inclusion of a case in any of the analyzed groups required unanimous agreement among the three expert reviewers.

PFA included the appearance of the fluid; total nucleated cell count (TNC) with differential; pH, glucose, total protein, albumin, LDH, and chylomicron levels; and cytology. The sonographic images and chest radiographs were also reviewed when available.

The cell count was performed using an automated body fluid analyzer (iQ 200 Body Fluids Module; Iris International, Inc). A manual differential cell count was performed. All other components of the PFA were measured using a DXC analyzer (Beckman Coulter, Inc).

Descriptive statistics, including mean $\pm$ SD; median and interquartile range, and fifth and 95th percentiles were calculated for each subpopulation of interest (ie, CHF as the sole diagnosis [SCHF], ESRD/COCHF, PCHF). One-sided Wilcoxon rank sum tests were conducted to determine whether the PFA values were higher or lower (pH, glucose) in patients with ESRD/COCHF than among those with SCHF and whether values were higher or lower (pH, glucose) in patients with PCHF than in those with ESRD/COCHF and SCHF. The study was approved by the Institutional Review Board of the Medical University of South Carolina (Pro00017679).

RESULTS

Three hundred of 1,064 consecutive patients (28.1%) in the database had CHF or ESRD/COCHF. Of these, 66 (22%) met the criteria for SCHF, 30 (10%) for PCHF, and 26 (8.7%) for ESRD/COCHF. The remaining 178 patients were excluded because of the existence of complicating conditions or lack of expert consensus, as follows: Of 225 patients with CHF without ESRD, 129 (57.3%) were excluded, and 49 of

Manuscript received September 12, 2012; revision accepted December 1, 2012.

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Funding/Support: This study was supported by the National Center for Research Resources (award number UL1RR029882).

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DOI: 10.1378/chest.12-2221

75 patients with ESRDCOCHF (65.3%) were excluded (Fig 1).

Diuretic use at the time of thoracentesis was noted in 62 of 66 patients (94%) with SCHF. Six of 66 patients with SCHF had protein-discordant exudates, whereas the remainder had transudates. All six patients with exudates were receiving diuretics at the time of thoracentesis.

The mean pleural fluid pH level in patients with SCHF was 7.46 (range, 7.27-7.57). Seven patients (10.6%) had a pH < 7.40. Concurrent systemic acidemia (defined as an arterial pH < 7.38, serum bicarbonate level < 20 meq/L, or the presence of an anion gap) was noted within 24 h of obtaining the PFA in all seven patients.

The mean serum creatinine level in patients with ESRDCOCHF was 5.5 mg/dL (range, 0.8-10.0 mg/dL), and the mean serum BUN concentration was 43 mg/dL (range, 15-75 mg/dL). Table 1 shows the comparison of PFA results in patients with SCHF, ESRDCOCHF, and PCHF. Table 2 shows the individual PFA results of the eight patients with PCHF transudates.

There was a statistically significant difference in pleural fluid/serum protein ratios and pleural fluid protein concentrations, revealing a minor tendency for a higher protein concentration in patients with ESRDCOCHF and PCHF than in patients with SCHF (Fig 2). In a comparison of the PFA results between SCHF and PCHF, we found statistically significant tendencies, with higher protein concentrations, higher LDH concentrations, and lower pH levels in patients with PCHF. In addition, the TNC and, specifically,

the absolute neutrophil count (ANC) were significantly higher in PCHF and showed the least overlap of percentile ranges (Figs 2-4, Table 1).

DISCUSSION

Pleural effusions from CHF or CO in the setting of ESRD result from a hydrostatic mechanism and typically are transudative by protein and LDH criteria.²⁻⁶ Pleural effusions from pneumonia or uremic pleuritis typically are exudative by both criteria.⁷⁻¹⁵ In addition, transudative effusions as a result of CHF or CO are paucicellular with low neutrophil counts. Pleural effusions resulting from pneumonia or uremic pleuritis have a higher TNC and ANC and higher protein and LDH concentrations. Therefore, the coexistence of a hydrostatic pleural effusion with either pneumonia or uremic pleuritis may influence the PFA. The present investigation attempted to demonstrate the effects of PCHF on the PFA and the effects of ESRDCOCHF on pleural effusion.

CHF as the Sole Diagnosis

There were 66 patients with SCHF identified. The typical PFA was a paucicellular transudate. Sixty of these patients (91%) were found to have transudative effusions. In the remaining 6 (9%), the PFA showed a protein-discordant exudate. All patients with protein-discordant exudates were undergoing treatment with diuretics, but so were 56 of 60 patients with transudative effusions.

FIGURE 1. Flowchart describing the selection of patients (n = 1,064). CHF = congestive heart failure; ESRD = end-stage renal disease; ESRDCOCHF = end-stage renal disease with coexisting circulatory overload or congestive heart failure; PCHF = congestive heart failure and coexisting pneumonia; SCHF = congestive heart failure as the sole diagnosis.

Table 1—Comparison of PFA Characteristics in Patients With SCHF, ESRDCOCHF, and PCHF

Characteristic	SCHF (n = 66)			ESRDCOCHF (n = 26)			PCHF (n = 30)		
	Mean ± SD	Median (IQR)	5th-95th Percentile	Mean ± SD	Median (IQR)	5th-95th Percentile	Mean ± SD	Median (IQR)	5th-95th Percentile
Protein, g/dL	1.95 ± 0.72	1.80 (1.30-2.60)	1.00-3.30	2.36 ± 0.88	2.30 (1.60-2.80) ^a	1.20-3.50	2.97 ± 1.00	3.15 (2.20-3.80) ^a	1.10-4.30
Protein ratio	0.32 ± 0.12	0.31 (0.24-0.44)	0.25-0.55	0.38 ± 0.12	0.36 (0.28-0.44) ^a	0.25-0.55	0.48 ± 0.14	0.52 (0.42-0.58) ^a	0.24-0.63
LDH, IU/L	81 ± 30	82 (56-104)	36-133	93 ± 30	87 (68-122)	50-136	440 ± 929	171 (114-384) ^a	48-1,049
LDH ratio	0.34 ± 0.13	0.34 (0.23-0.43)	0.15-0.55	0.39 ± 0.13	0.36 (0.28-0.51)	0.21-0.57	1.83 ± 3.87	0.71 (0.48-1.60) ^a	0.20-4.37
pH	7.46 ± 0.06	7.47 (7.43-7.50)	7.36-7.56	7.45 ± 0.07	7.46 (7.42-7.49)	7.35-7.56	7.37 ± 0.17	7.42 (7.34-7.47) ^a	7.00-7.53
Glucose, mg/dL	127 ± 44	116 (100-136)	89-204	125 ± 61	103 (87-136)	53-253	107 ± 56	100 (70-131) ^a	37-207
TNC, cells/μL	199 ± 187	157 (80-241)	23-480	281 ± 335	225 (143-330)	32-540	4,791 ± 11,643	1,664 (427-3,414) ^a	171-22,809
Neutrophil Count, cells/μL	29 ± 38	17 (6-40)	0-104	40 ± 54	15 (29-49)	0-165	3,364 ± 9,624	430 (138-1,703) ^a	79-15,054
Percent	15 ± 14	12 (4-21)	0-44	17 ± 20	8 (4-21)	0-56	51 ± 28	52 (27-78) ^a	10-90
Lymphocytes Count, cells/μL	103 ± 148	60 (18-139)	3-305	148 ± 342	92.08 (20-114)	8-210	791 ± 1,353	240 (107-784) ^a	29-3,489
Percent	46 ± 26	49 (25-66)	8-86	44 ± 27	41 (30-63)	4-92	30 ± 22	30 (9-48) ^a	3-78
Macrophages Count, cells/μL	57 ± 64	36 (17-88)	2-149	701 ± 2,209	73 (16-170)	0-6,913	565 ± 1,344	216 (48-645) ^a	3-1,597
Percent	33 ± 23	29 (14-51)	5-75	35 ± 26	33 (15-60)	0-74	15 ± 14	10 (5-18) ^a	2-43

ESRDCOCHF = end-stage renal disease with coexisting circulatory overload or congestive heart failure; IQR = interquartile range; LDH = lactate dehydrogenase; LDH ratio = pleural fluid LDH/upper limits of normal serum (240 at our institution); PCHF = congestive heart failure and coexisting pneumonia; PFA = pleural fluid analysis; protein ratio = pleural fluid protein/serum protein; SCHF = congestive heart failure as the sole diagnosis; TNC = total nucleated cell count.

^aP < .05 by one-sided Wilcoxon rank sum test compared with the SCHF group.

Table 2—Summary of the PFA Characteristics of the Eight Patients With Transudative Pleural Effusions and PCHF

Characteristic	Patient							
	1	2	3	4	5	6	7	8
Protein, g/dL	1.8	0.9	1.7	1.4	2.1	1.1	2.0	2.7
Protein ratio	NA	0.16	0.24	0.24	0.32	NA	0.33	0.43
LDH, IU/L	118	48	62	85	112	33	125	114
LDH ratio	0.49	0.20	0.26	0.35	0.47	0.40	0.52	0.48
pH	NA	7.47	7.43	7.54	7.47	7.34	7.44	7.51
Glucose, mg/dL	NA	116	70	95	207	74	131	NA
TNC, cells/ μ L	1,697	171	792	385	4,055	718	510	950
Neutrophils, %	48	77	13	70	42	16	27	30
ANC, cells/ μ L	815	132	103	270	1,703	115	138	285

ANC = absolute neutrophil count; NA = not available. See Table 1 legend for expansion of other abbreviations.

The effects of diuretic therapy on the PFA were reported in two prior studies with conflicting results. Romero-Candeira and colleagues¹⁶ observed that the concentrations of pleural fluid total protein, LDH, and albumin increased progressively during diuretic therapy. Shinto and Light¹⁷ reported increases in the levels of protein and LDH with diuresis. In their study, the pleural fluid in only one of 12 patients showed values compatible with an exudate. The present results confirm this observation.

The effusions in SCHF were paucicellular with a predominance of mononuclear cells and a mean and median ANC < 30 cells/ μ L. The characteristics of the PFAs in the present sample are consistent with previous reports on PFAs in CHF-related effusions.³⁻⁶ We are confident that this sample can serve as the baseline with which the PFAs of patients with concurrent conditions may be compared.

ESRD With CO or CHF

Hemodialysis patients with ESRD are susceptible to uremic pleuritis, CO, and CHF. In the present study, we isolated a sample of patients with ESRDCOCHF but without clinical evidence of uremic pleuritis. Overt uremic pleuritis may result in a pleural effusion with LDH and protein values higher and pH and glucose values lower than in the typical transudative effusion. Cell counts, especially neutrophil counts, are higher in uremic pleural effusions than in CHF.⁷⁻⁹

To our knowledge, the effect of ESRD on the PFA as a result of CO in the absence of clinical signs of uremic pleuritis has not been reported to date. We found a statistically significant difference in protein concentrations and pleural fluid/serum protein ratios in pleural effusions in ESRDCOCHF compared with SCHF. The difference of the means was small (SCHF, 1.95 g/dL; ESRDCOCHF, 2.36 g/dL), and we speculate that the difference may be due to greater chronicity of the pleural effusion in ESRDCOCHF. It is conceivable that a referral bias exists in ESRDCOCHF

because it is likely that a patient is referred for thoracentesis if a pleural effusion does not resolve quickly with hemodialysis. Although there was a trend for a higher TNC in ESRDCOCHF, this difference was not significant. The LDH, pH, and glucose levels were unaffected by the presence of ESRD in patients with hydrostatic pleural effusions.

The pleural fluid protein concentration was slightly higher in ESRDCOCHF; however, the protein ratios were no more likely to be in the exudative range when compared with SCHF. In fact, the fifth and 95th percentiles for protein ratios were identical for both ESRDCOCHF and SCHF. Overall, the differences in the PFA between SCHF and ESRDCOCHF were minor.

In conclusion, there is some evidence that the PFA of hydrostatic pleural effusions is affected in hemodialysis patients with ESRD, but the effect is small and should not affect the clinical interpretation of the PFA in the individual patient. A question awaiting further study is whether the degree to which the PFA in patients with overt uremic pleuritis is affected by concomitant hydrostatic pleural effusion.

CHF and PCHF

CHF and pneumonia represent the two most common causes of pleural effusions and occur more commonly in elderly and debilitated patients. Thus, it is not surprising that our database contained a substantial number of patients with pleural effusions and PCHF.

A true clinical conundrum occurs when pneumonia and CHF coexist. The treatment of a parapneumonic pleural effusion and a hydrostatic pleural effusion differ fundamentally. The clinician is challenged to interpret the PFA in a patient with PCHF as either supporting the diagnosis of a parapneumonic pleural effusion with evidence of dilution by a hydrostatic mechanism or as a hydrostatic pleural effusion with evidence of alteration of the PFA by a coexisting

FIGURE 2. Comparison of pleural fluid protein/serum protein ratio and LDH in patients with SCHF, ESRD with hydrostatic pleural effusions, and PCHF. The box represents the interquartile range, the line within the box represents the median, bars represent the 5% to 95%, the dots represent outliers, and the dotted line represents the cut point for exudative vs transudative effusions whereby above the dotted line is exudative. **P* value comparing SCHF with ESRDCOCHF; ***P* value comparing SCHF with PCHF. LDH = lactate dehydrogenase. See Figure 1 legend for expansion of other abbreviations.

pneumonia. The PFA in a typical parapneumonic pleural effusion is an exudate by both protein and LDH criteria and is further characterized by elevated nucleated cell counts, particularly neutrophils in the acute phase, and a tendency to lower pH and glucose values than in the typical hydrostatic pleural effusion.¹⁰⁻¹⁵

We found that all PFA parameters were affected by the presence of pneumonia in patients at risk for hydrostatic pleural effusion when looked at as a group. However, in eight of the 30 patients with PCHF, the pleural effusions remained transudates by protein and

LDH criteria, despite the presence of pneumonia. The ANC in all of these transudates was >100 cells/ μL , and in four of eight patients, the ANC was >200 cells/ μL . Of the 22 exudates, 12 were concordant exudates, four were LDH-discordant exudates, and five were protein-discordant exudates. The TNC, and especially the ANC, demonstrated minimal overlap compared with SCHF. These data suggest an elevated ANC in a pleural effusion otherwise attributed to CHF and should raise the suspicion of coexisting pneumonia, even if the effusion is transudative.

FIGURE 3. Comparison of pleural fluid pH and pleural fluid glucose levels in patients with SCHF, ESRD with hydrostatic pleural effusions, and PCHF. The box represents the interquartile range, the line within the box represents the median, bars represent the 5% to 95%, and the dots represent outliers. **P* value comparing SCHF with ESRDCOCHF; ***P* value comparing SCHF with PCHF. See Figure 1 legend for expansion of abbreviations.

FIGURE 4. Comparison of pleural fluid total nucleated cell count (cells/ μ L) and pleural fluid absolute neutrophil count (cells/ μ L) in patients with SCHF, ESRD with hydrostatic pleural effusions, and PCHF. The box represents the interquartile range, the line within the box represents the median, bars represent the 5% to 95%, and the dots represent outliers. *P value comparing SCHF with ESRDCOCHF; **P value comparing SCHF with PCHF. See Figure 1 legend for expansion of abbreviations.

Limitations

A limitation of the present study is that it was retrospective. An effort was made to arrive at the diagnoses by reviewing all available clinical data without considering the results of the PFA. It is possible, however, that the PFA results influenced the clinical judgment of the physicians responsible for the care of the patient, and the patient records may contain information influenced by the PFA. Consequently, this study contains an unquantifiable element of circular reasoning. For this reason, the results should be viewed as preliminary and perhaps as a starting point for future prospective study.

Summary

This study demonstrates that the presence of ESRD in patients with hydrostatic pleural effusions does not affect the PFA in a clinically meaningful way. PFA findings inconsistent with a hydrostatic pleural effusion should not be ascribed to the presence of ESRD and should alert the clinician to consider the presence of concurrent conditions.

The study demonstrates that SCHF-related pleural effusions typically are transudates and paucicellular, with mononuclear cell predominance. Diuretic therapy appears to have a minimal effect on the PFA, but several cases of protein-discordant exudates were noted.

PCHF associated with a pleural effusion commonly affects the PFA. Coexisting pneumonia most commonly results in an exudate by the protein criterion and even more so by the LDH criterion. Glucose and pH values are less affected. The predominant change is seen in the TNC and ANC. An increased ANC in an otherwise transudative effusion may support the

suspected diagnosis of coexisting pneumonia, which is clinically relevant because the differentiation of pulmonary parenchymal opacities on standard chest radiographs in patients in CHF is problematic.

ACKNOWLEDGMENTS

Author contributions: Dr Doelken had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Doelken: contributed to the study design; data collection and analysis; chart review; and preparation, writing, and revision of the manuscript.

Dr Huggins: contributed to the data collection and analysis; chart review; figures; and preparation and revision of the manuscript.

Dr Goldblatt: contributed to the data collection and analysis; figures; and preparation, drafting, and revision of the manuscript.

Dr Nietert: contributed to the statistical and data analysis; tables; and preparation and revision of the manuscript.

Dr Sahn: contributed to the data collection and analysis; study design; chart review; and preparation of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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