Is pulmonary embolism associated with pleural transudates, exudates, or both?

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Abstract

Introduction and objectives: Whether pleural effusions (PEs) secondary to pulmonary embolism can be exudative or transudative is controversial. This study aims to determine which type of effusion (exudate or transudate) is typically associated with pulmonary embolism, using Light's criteria as the discriminative gold standard. **Methods:** A retrospective analysis of all consecutive patients with pulmonary embolism subjected to a diagnostic thoracentesis over a 25-year period in a University Hospital was performed. Pleural fluid data were described in detail. **Results:** Seventy-one patients with pulmonary embolism-associated PEs comprised the study population. Pleural fluids were bloody in more than half the cases. The pleural fluid differential white blood cell count was variable; the predominant cells (> 50% of the total leukocytes) were lymphocytes in nearly two-thirds of the patients and neutrophils in about 30%. A proportion of eosinophils > 10% was observed in 7% of the cases. All fluids were exudates, meeting either 3 (78.2%), 2 (12.7%), or just 1 (9.1%) of the Light's criteria. **Conclusion:** The pleural fluid that accompanies pulmonary embolism is invariably an exudate.

Key words: Pleural effusion. Pulmonary embolism. Transudate. Exudate.

Introduction

Pulmonary embolism is a relatively infrequent cause of pleural effusions (PEs) but, at the same time, it is a disorder commonly overlooked during the work-up of undiagnosed effusions. In a series of 3077 patients with PEs who underwent thoracentesis, pulmonary embolism accounted for just 1.5% of the cases¹. Paradoxically, PEs are observed in about one-third of patients with pulmonary embolism by chest radiograph, and half the cases when using computed tomography². The fact that most of these PEs are small (and thus not amenable to thoracentesis) or discovered when the diagnosis of

pulmonary embolism is already established (thus making unnecessary a diagnostic aspiration), explains the low prevalence of pulmonary embolism among the etiology of tapped PEs³.

Whether pulmonary embolism may generate transudates or exudates has long been a point of discussion, largely due to the unawareness of the exact pathophysiology of fluid formation in this condition. The aim of the current study was to define the transudative or exudative nature of PEs secondary to pulmonary embolism, using Light's criteria as the reference standard⁴, in the largest series published to date.

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Methods

We performed a retrospective analysis from a prospectively maintained database, which includes all consecutive patients with PEs who have undergone a diagnostic thoracentesis at the Arnau de Vilanova University Hospital (Lleida, Spain) for the past 25 years. Patients with a final diagnosis of PE secondary to pulmonary embolism were the focus of the current investigation. The study protocol was approved by the local ethics committee (CEIC No. 1965).

The diagnosis of pulmonary embolism was made radiographically by computed tomographic pulmonary angiography and, except in two patients with a history of hypersensitivity reaction to iodinated contrast agents who were diagnosed by using lower extremity compression ultrasonography with Doppler in the adequate clinical context. Attributing the PE to pulmonary embolism also required excluding other potential causes of fluid formation based on clinical data and pleural fluid analyses.

We recorded demographics, location, and size of PEs on chest radiographs, biochemistries of serum (i.e., protein, albumin, and lactate dehydrogenase [LDH]) and pleural fluid (i.e., total and differential cell count, protein, LDH, glucose, pH, adenosine deaminase and, if available, C-reactive protein, cholesterol, albumin, carcinoembryonic antigen [CEA], carbohydrate antigen 15-3 [CA 15-3], and natriuretic peptides), time from symptom onset to thoracentesis, and elapsed time between the start of anticoagulation and pleural tapping.

Most thoracenteses were performed under ultrasound assistance. If the patient had been submitted to repeated thoracentesis, only the results of the first one were considered. All biochemical measurements of pleural fluid and serum were performed on selective, discrete multichannel analyzers using standard methodologies. Pleural fluid cell counts were carried out either manually in a Thoma counting chamber or using an automatic hematology analyzer. In our laboratory, the upper normal limit for serum LDH is 375 U/L. Malignancy cutoff points used for pleural fluid CEA and CA 15-3 were 45 ng/mL and 77 IU/mL, respectively⁵. Pleural fluid levels of brain natriuretic peptide (BNP) > 115 pg/mL⁶ and of N-terminal pro-BNP > 1500 pg/mL⁷ are generally associated with heart failure. A serum-pleural fluid albumin gradient (serum albumin minus pleural fluid albumin) > 1.2 g/dL or a serum-pleural fluid protein gradient > 3.1 g/dL has long been proposed to indicate a likely transudate in the setting of

clinically suspected cardiac effusions that meet Light's criteria for exudate⁸.

PEs were categorized as transudates or exudates using the criteria reported by Light et al.⁴, wherein exudative PEs are identified by the presence of one or more of the following findings, whereas a transudate has none: (1) pleural fluid protein divided by serum protein > 0.5, (2) pleural fluid LDH divided by serum LDH > 0.6, and (3) pleural fluid LDH more than two-thirds (67%) of the upper normal limit for serum LDH (which in our study implies a pleural fluid LDH > 250 U/L).

Descriptive statistics were used to summarize patient characteristics and pleural fluid findings. Data are presented as numbers (proportions) or median (interquartile range [IQR]) as appropriate. Between-group comparisons were assessed by means of the Mann-Whitney U-test. $p < 0.05$ was considered statistically significant. Calculations were done using the SPSS version 24.0 statistical software.

Results

By November 2020, our database encompassed 5460 patients with PEs, of whom 71 (1.3%) had pulmonary embolism. Partial data of 26 of these patients were already reported in a previous own study with different primary outcomes².

The current study population comprised 45 (63.4%) men and 26 (36.6%) women, with a median age of 74 years (IQR 52-84 years, range 23-93 years). On chest radiographs, PEs were right sided (34, 48%), left sided (29, 41%), or bilateral (8, 11%), while occupying one-third or less of the hemithorax in 63 (88.7%) cases.

In the subgroup of patients in whom electronic records were available ($n = 31$), the median lag time between symptoms onset and diagnostic thoracentesis was 9 days (IQR 6-12 days). At the time of thoracentesis, 14 (45%) patients were receiving anticoagulant therapy and 12 (38.7%) were on diuretics.

Pleural fluid biochemical data are presented in [table 1](#) and their interpretation, according to widely accepted cutoff values, is shown in [table 2](#). Pleural fluid cultures and cytological examinations were performed in 46 and 59 patients, respectively, with negative results in all cases. The pleural fluid red blood cell count was higher than 10,000/ μ L, which usually corresponds with a bloody appearance, in 55.7% of the cases and surpassed 100,000/ μ L in 6 (8.6%). The differential white blood cell count revealed a predominance of lymphocytes (i.e., > 50% of the total leukocyte count) in about two-thirds of the cases, of neutrophils in nearly 30%, and pleural eosinophilia

Table 1. Pleural fluid findings in pulmonary embolism

Pleural fluid parameter	No. of patients	Value, median (quartiles)
Erythrocyte count, × μ L	70	15,150 (3028-38,800)
Leukocytes, × μ L	71	1639 (900-4000)
Polymorphonuclear cells, %	71	33 (17-59)
Eosinophils, %	71	15 (9-43)
Lymphocytes, %	71	63 (36-83)
Glucose, mg/dL	70	109 (92-129)
pH	65	7.47 (7.40-7.50)
Adenosine deaminase, U/L	70	15 (8-23)
Protein, g/dL	71	4.1 (3.3-4.8)
Pleural fluid to serum protein ratio	65	0.65 (0.59-0.72)
Serum to pleural fluid protein gradient, g/dL	65	2.2 (1.7-2.7)
LDH, U/L	70	428 (287-707)
Pleural fluid to serum LDH ratio	56	1.29 (0.85-2.64)
Cholesterol, mg/dL	29	70 (56-101)
Albumin, g/dL	22	2.3 (1.7-2.6)
Serum to pleural fluid albumin gradient, g/dL	21	1.0 (0.6-1.2)
C-reactive protein, mg/L	30	31 (17-71)
CEA, ng/mL	40	1.4 (0.9-2.2)
CA 15-3, IU/mL	35	14.6 (10.1-20.1)
BNP, pg/mL	12	83 (34-104)
NT-pro-BNP, pg/mL	25	564 (280-1778)

BNP: brain natriuretic peptide; CA 15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; LDH: lactate dehydrogenase; NT-pro-BNP: N-terminal pro-BNP.

(i.e., > 10% of eosinophils) in 7%. The discovery of predominantly neutrophilic or lymphocytic fluids was unrelated to symptom duration until the thoracentesis (median of 9 days when polymorphonuclear leukocytes predominated vs. 8.5 days for lymphocytic effusions, $p = 0.451$). No patient exhibited elevated adenosine deaminase levels, marked pleural fluid acidosis (i.e., $pH < 7.20$), or high concentrations of classical tumor markers. Raised natriuretic peptide levels were observed in some of the few pleural fluids in which they could be measured.

PEs from all 71 patients met Light's criteria for exudates. In particular, of 55 patients for whom all three Light's items were available, one criterion was fulfilled by 5 (9.1%) patients, two criteria by 7 (12.7%), and three criteria by 43 (78.2%). In addition, 85.7% and 92.3% of subjects had serum to pleural fluid albumin and protein gradients which were consistent with exudates, respectively.

Discussion

The present study supports the uniform exudative nature of all PEs secondary to pulmonary embolism. This challenges what has been traditionally taught, namely, that pulmonary embolism-associated PEs may be either an exudate or a transudate. In fact, the concept that pleural fluids in this condition might, although infrequently, have transudative characteristics is still reflected today in time-honored textbooks of Internal Medicine^{9,10}, and even recent reviews in top medical journals¹¹.

Confusion about the precise exudate-transudate classification of these PEs stems from a report dating back to 1976, in which 7 (27%) of 26 pleural fluids associated with pulmonary embolism were labeled as transudates¹². However, the criteria used to define exudates (and therefore

Table 2. Pleural fluid characteristics according to widely accepted cutoff points

Pleural fluid parameter	No. of patients	No. (%)
Erythrocytes $\geq 10,000/\mu\text{L}$	70	39 (55.7)
Neutrophils $> 50\%$	71	21 (29.6)
Eosinophils $> 10\%$	71	5 (7)
Lymphocytes $> 50\%$	71	46 (64.8)
Glucose $\leq 60 \text{ mg/L}$	70	1 (1.4)
pH ≤ 7.20	65	0 (0)
Adenosine deaminase $\geq 35 \text{ U/L}$	70	0 (0)
Protein $\geq 3 \text{ g/dL}$	71	60 (84.5)
Pleural to serum protein ratio > 0.5	65	57 (87.7)
Serum to pleural fluid protein gradient $\leq 3.1 \text{ g/dL}$	65	60 (92.3)
LDH $> 250 \text{ U/L}$	70	58 (82.8)
Pleural fluid to serum LDH ratio > 0.6	56	52 (92.8)
Cholesterol $\geq 45 \text{ mg/dL}$	29	27 (93)
Serum to pleural fluid albumin gradient $\leq 1.2 \text{ g/dL}$	21	18 (85.7)
CEA $> 45 \text{ ng/mL}$	40	0 (0)
CA 15-3 $> 77 \text{ IU/mL}$	35	0 (0)
BNP $> 115 \text{ pg/mL}$	12	1 (8.3)
NT-pro-BNP $> 1500 \text{ pg/mL}$	25	6 (24)

BNP: brain natriuretic peptide; CA 15-3: carbohydrate antigen 15-3; CEA: carcinoembryonic antigen; LDH: lactate dehydrogenase; NT-pro-BNP: N-terminal pro-BNP.

transudates) were not those reported by Light 4 years earlier, which were not yet universally accepted, but rather the pleural fluid concentrations of proteins ($> 3 \text{ g/dL}$) or LDH ($> 200 \text{ U/L}$). Notably, pleural fluid LDH was only measured in 12 (46%) patients¹². It should be stressed that the criteria reported by Light et al. 49 years ago⁴ to separate exudates from transudates still prevail. This is because they are stringent and classifies virtually all exudates correctly (sensitivity 98%); even though they do misclassify about 25% of transudates as exudates, usually by a small margin¹³. Therefore, the application of alternative and less sensitive criteria for the identification of an exudate, as conducted in the study of Bynum and Wilson¹², and two subsequent ones^{14,15}, may miscategorize some cases. In fact, the sum of all studies, including the present one, where Light's criteria were applied demonstrates that all 142 patients with pulmonary embolism who were evaluated had pleural exudates (Table 3).

The terms transudate and exudate reflect the pathophysiological mechanism of pleural fluid formation. Transudates derive from imbalances in hydrostatic and

oncotic forces over a structurally intact pleural surface, whereas exudates accumulate because of local factors affecting the pleura, such as increased capillary permeability and/or impaired lymphatic drainage resulting from many inflammatory and malignant causes. Since all pulmonary embolism associated PEs are exudates, it is presumed that increased permeability of pulmonary capillaries, probably related to the release of inflammatory mediators from the platelet-rich thrombi (e.g., vascular endothelial growth factor), is the most plausible mechanism by which pulmonary embolism produces PEs¹⁹. The right ventricular dysfunction that may accompany acute pulmonary embolism may account for the elevation of natriuretic peptides in the pleural fluid of some of these. Nearly 39% of patients were on diuretics at the time of thoracentesis, as now stated in Results.

This study is limited by its retrospective design and small sample size. However, thoracentesis is rarely attempted in the setting of a confirmed pulmonary embolism unless the PE is increasing in size and it is needed to exclude a hemothorax, or the patient is

Table 3. Studies that have evaluated the categorization of pulmonary embolism-associated effusions as transudates or exudates

Study	No. of patients	Criteria for exudates	No. (%) of exudative effusions
Bynum and Wilson, 1976 ¹²	26	PF protein > 3 g/dL or PF LDH > 200 U/L	19 (73)
Romero-Candeira et al., 2002 ¹⁶	60	Light's criteria	60 (100)
Erkan et al., 2004 ¹⁷	5	Light's criteria	5 (100)
Sandevski et al., 2012 ¹⁴	31	LDH fluid to serum ratio > 0.6	30 (97)
Choi et al., 2017 ¹⁵	13	Not specified	12 (92)
Panjwani et al., 2019 ¹⁸	6	Light's criteria	6 (100)
Current study, 2021*	71	Light's criteria	71 (100)
Total	142	Light's criteria	142 (100)

*This series includes data of 26 patients from a previous own publication².
LDH: lactate dehydrogenase; PF: pleural fluid.

persistently febrile and it is needed to exclude a pleural infection.

Conclusion

In summary, although pulmonary embolism associated PEs were previously sometimes thought to be transudates, the few exudate-transudate studies that have used Light's standard criteria⁴ conclude that all are exudates.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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