Clinical Implications of Appearance of Pleural Fluid at Thoracentesis

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Abstract

Study objectives : The aims of this study were to describe the different appearances of pleural fluid during thoracentesis and their frequency in relation to diagnosis, and to evaluate the causes and clinical implications of bloody pleural effusions.

Setting : Secondary care, 600 beds Surin hospital.

Subjects and methods : One hundred twenty-four patients with pleural effusion were retrospectively assessed from October 2003 to September 2004.

Results : Pleural effusions developed in 124 hospital admissions. Their sizes were small (27%), moderate (48%), large (20%), and loculated (5%). The associated conditions were infectious: pulmonary tuberculosis (n = 37), bacterial pneumonia (n = 21), empyema (n = 9), parasitic disesas (n=5) and Dengue hemorrhagic fever (n=2); and noninfectious: paramalignancy (n=9), malignancy (n = 6), hepatic cirrhosis (n = 6), pancreatitis (n = 3), congestive heart failure (n = 3), atelectasis (n = 3), hypoalbuminemia (n = 2), renal failure (n = 1). The most common presentations were serous and blood tinged, with 82% of the fluids fitting into one of these categories. The most frequent cause of serous fluid was tuberculosis. There were 18 bloody and 67 nonbloody pleural fluids. The most common cause of bloody pleural effusion (BPE) was malignancy (32%). Nevertheless, only 36% of the neoplastic effusions were BPE. Other common causes of BPE were parapneumonic (21%) or parasitic diseases(16%) pleural effusions. Tuberculosis was the most common causes of pleural effusion. Fluid that was bloody fluid in appearance, increased the probability for neoplasm and parasitic disease(OR, 3.2; 95% CI, 2.02 to 4.42; p = 0.05 and OR, 5.65; 95% CI, 3.79 to 7.51; p = 0.05, respectively).

Conclusions : Serous and blood tinged were the most common presentations of pleural fluid at thoracentesis. Almost half of BPEs were secondary to neoplasms, but only 32% of the neoplastic effusions were BPEs. Other common causes of BPE were parapneumonic and parasitic diseases.

Key Words : bloody appearance • pleural effusion • pleural tuberculosis

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Introduction

In order to determine the etiology of pleural effusions, it has been widely recommended to assess the appearance of pleural fluid at thoracentesis.[1] Pleural effusions that are bloody in appearance have been particularly associated with malignant etiologies.[2] Nevertheless, as far as we know, a systematic approach to pleural fluid presentation at thoracentesis within a large unselected series of patients has not been previously reported. The aims of this study were to describe the different appearances of pleural fluid during thoracentesis and their frequency in relation to diagnosis, and to evaluate the causes and clinical implications of bloody pleural effusion (BPE).

Materials and Methods

Patients

I retrospectively studied 124 consecutive patients with pleural effusion who were assessed in our service from October 2003 to September 2004. Pleural fluid was obtained by thoracentesis with a needle. The macroscopic appearance of the fluid during thoracentesis was assessed. Whenever the pleural fluid became more blood tinged during thoracentesis, the clearer color was contemplated. Fluid appearance was classified into sixed categories: watery (light yellow), serous (yellow), blood tinged (reddish), bloody (dark red, similar to blood), purulent (pus), and turbid (yellow, but viscous or cloudy)

In 85 of the first 124 pleural fluids, interobserver agreement when classifying the pleural fluid into BPE and nonbloody pleural fluid was assessed. All patients were studied according to the same diagnostic algorithm.[3] After completion of clinical evaluation, pleural effusions were classified into diagnostic groups based on explicit previously reported criteria[4] :

Malignant :

Pleural effusions were malignant if there was either a cytologic or histologic diagnosis of neoplasm within the pleural space.

Paramalignant :

Pleural effusions were paramalignant when a histologic diagnosis of malignant tumor in another organ was established, the effusion did not meet the malignant

criteria, and no other cause of pleural effusion was found.

Tuberculosis :

Pleural effusions were tuberculous if a positive Mycobacterium tuberculosis culture finding of pleural fluid or tissue and/or presence of granulomas in the pleural biopsy were found, in the absence of other pleural granulomatous diseases. This group also included 5 patients with positive acid fast bacilli (AFB) smear favorable clinical course after tuberculous treatment, and either microbiological evidence of extrapleural tuberculosis or clinical picture suggestive of pleural tuberculosis.[5]

Parapneumonic :

Pleural effusions were parapneumonic in patients with cough, fever, and a radiographic pulmonary infiltrate that disappeared with antibiotic treatment. Empyema was defined as pus in the pleural space.

Transudate :

Pleural effusions were transudate if defined according to clinical and classic biochemical criteria.[1]

Eosinophilic Pleural effusion :

Eosinophilic pleural effusion (EPE), first described by Harmsen in 1894, is defined as a pleural effusion that contains at least 10% eosinophils.[6]

Other Benign Diseases :

Pleural effusions were other benign diseases if diagnosed on the basis of standard criteria.[1]

Undetermined or Mixed Causes :

Pleural effusions were undetermined or mixed causes whenever the etiology of the effusion was unknown or there were several potential causes of the pleural effusion.

Statistical Analysis :

The strength of the associations has been estimated as odds ratio (OR), and 2 test with the Yates correction or the Fisher exact test were used as appropriate. The Mann-Whitney test or the Student t test were used to compare the differences between continuous variables; $p<0.05$ was considered statistically significant. Interobserver agreement was measured by coefficient.

Results

A total of 124 hospital admissions had pleural effusion on chest radiograph or ultrasonography. The appearance of the pleural fluid was assessed in 85 of 124 patients (68.5%); 78 were male (63%) and 46 were female (37%). Mean age was 63 years (range, 14 to 95 years). Of the 124 effusions, 34 of the effusions were small (27%), 59 were moderate (48%), 25 were large (20%), and 6 were loculated (5%). The conditions associated with the pleural effusions are listed in Table 1. Pleural effusions were present in 46 of 124 hospital admissions (37%) with tuberculosis, 26 of 124 hospital admissions (21%) with bacterial pneumonia, 9 of 124 hospital admissions (7%) with empyema, 5 of 124 hospital admissions (4%) with parasitic disease and 20 of 124 hospital admissions (16%) with non infectious disease.

Table 1. Conditions Associated With Pleural Effusion in Hospitalized Patients

Associated Conditions	No. of Effusions
Infectious	86
- Tuberculosis	46
- Parapneumonic	26
- Empyema	9*
- Parasitic disease	5
- Dengue hemorrhagic fever	2
Noninfectious	20
- Hepatic cirrhosis	6
- Adenocarcinoma	4
- CHF	3
- Pancreatitis	3
- Hypoalbuminemia	2
- Renal failure	1
- Acute lymphoblastic leukemia	1
- Sarcoma	1
Unknown	15

*The pleural fluid from three patients with a tuberculous empyema and one patient with neoplasm were classified as purulent.

Pleural fluid analysis results, available in 85 hospital admissions of 85 different patients, suggested exudate in 79(93%). Positive AFB stain was found from the sputum of five patients.

Presentations of the pleural fluid and their diagnoses are shown in Table 2. The most common appearances were serous and blood tinged, with 82% of the fluids fitting into one of these categories. The most frequent cause of watery fluid was transudate. Tuberculosis and transudates were uncommon causes of BPE. Fluid that was bloody in appearance decreased the probability for both diseases (OR, 0.18; 95% CI, 0.03 to 1.38; P= 0.05, respectively).

Table 2. Appearance of Pleural Fluid and Diagnoses in 85 Patients*

Diagnosis	Watery	Serous	Blood Tinged	Bloody	Purulent	Turbid	Total
Neoplasms	-	8 (57)	4 (29)	1(7)	1(7)	-	14
Tuberculosis	-	29 (76)	3 (8)	-	3(8)	3(8)	38
Parapneumonic	-	5 (38)	3 (23)	1(8)	-	4 (31)	13
Transudates	3 (60)	1 (20)	1 (20)	-	-	-	5
Empyema	-	-	-	-	9**(100)	-	9
Parasitic diseases	-	2(40)	3 (60)	-	-	-	5
Undetermined or mixed causes	-	3 (60)	1(20)	1 (20)	-	7 (8)	5
Total	**3(4)**	**48 (56)**	**15 (18)**	**3(4)**	**9**(10)**	**7 (8)**	**85**

*Data are presented as No. (% within the etiology of the effusion) or No.

**The pleural fluid from three patients with a tuberculous empyema and one patient with neoplasm were classified as purulent.

The etiologies of the BPE are reported in Table 3. There were 18 bloody and 67 nonbloody pleural fluids. The most common cause of BPE was malignancy (32%). Fluid with a bloody appearance slightly increased the probability of malignancy in this series (OR, 3.2; 95% confidence interval [CI], 2.02 to 4.42; p = 0.05). Nevertheless, only 36% of the neoplastic effusions were BPE. Table 4 show the histologic types of the malignant effusions classified according to the bloody nature of the fluid. The most common histologic types were adenocarcinoma. Other common causes of BPE were parasitic diseases (28%) or parapneu- monic (17%) pleural effusions. The relationship between Eosinophilic Pleural Effusion (EPE) and malignancy is controversial. The frequency of malignant etiology among EPEs has varied between 6% and 40% in different studies.[6,7,8,9, 11,12,13] In this series, 3 of 14 cases of EPE (21.4%) found were malignant.

Table 3. Etiologies of the Pleural Effusions According to Fluid Color*

Diagnosis	Bloody Fluids	Nonbloody Fluids	Total
Neoplasms	6 (43)	8 (57)	14
Malignant	2	3	5
Paramalignant	4	5	9
Tuberculosis	3 (8)	35 (92)	38
Parapneumonic/empyema	4 (22)	14 (78)	18
Transudates	1 (20)	4 (80)	5
Parasitic diseases	3 (60)	2 (40)	5
Undetermined or mixed causes	2 (40)	3 (60)	5
Total	**19 (22)**	**66 (78)**	**85**

*Data are presented as No. (% within the etiology of the effusion) or No.

Table 4. Histologic Type of the Tumors According to Pleural Fluid Color*

Histologic Type	Bloody Fluids	Nonbloody Fluids	Total
Adenocarcinoma	3 (50)	3 (50)	6
Squamous carcinoma	0	3 (100)	3
Acute lymphoblastic leukemia	1 (100)	0	1
Hepatoma	0	1 (100)	1
Sarcoma	0	1 (100)	1
Unknown	1 (50)	1 (50)	2
Total	**5 (36)**	**9 (64)**	**14**

*Data are presented as No. (% within the origin of the tumor) or No.

Tuberculosis and transudates were uncommon causes of BPE. There was non statistically significant difference between the mean pleural fluid protein, sugar, LDH level in the pleural tuberculosis and parasitic diseases (5.5 mg/dL vs 5.66 mg/dL, 95.17 mg/dl vs 61.2 mg/dl, 798mg/dl vs 1,368 mg/dl, respectively; p = 0.8650, 0.3843 and 0.1443).

Among 19 patients with pleural fluid red blood cell counts >/=100,000/mm^3 at this institution, only 3 (16%) had pleural fluid eosinophilia. Thoracentesis is thought to be a very common cause of EPE because of the introduction of blood or air into the pleural space. However, this reported that only 3 of 38 patients (7.9%) with non-EPE who underwent a second thoracentesis and 3 of 14 (21.4%) of those who underwent repeated thoracenteses within 2 to 12 weeks had higher numbers of pleural fluid eosinophils in subsequent thoracenteses. There was non statistically significant difference between the mean eosinophil in first and second thoracocentesis (2.5% vs 4%, respectively; p = 0.6130).

Table 5. Appearance of Pleural fluid in Tuberculosis and Parasitic diseases*

Appearance of pleural fluid	Tuberculosis	Parasitic disease	P value
Age (year)	57	46	0.5157
Lehgth of stay (day)	5.4	6	0.8808
Gross (% BPE)	8%	60%	**
Protein level (mg/dl)	5.5	5.7	0.8650
Sugar level (mg/dl)	95.2	61.2	0.3843
LDH level (mg/dl)	797.8	1368	0.1443
Cell coun (/cumm.)	1150	6191	0.0067
% of Neutrophil	11	23	0.5485
% of Lymphocyte	88	23	0.00137
% of Eosinophil	4	50	0.00006
% of Monocyte	1	0	0.0836

* Data are presented as Mean.

**OR,17.5;95%confidence interval[CI],15.36-19.6;P=0.05

The strength of the associations has been estimated as odds ratio (OR), and 2 test with the Yates correction or the Fisher exact test were used as appropriate. The Mann-Whitney test or the Student t test were used to compare the differences between continuous variables; $p<0.05$ was considered statistically significant. Interobserver agreement was measured by coefficient.

Discussion

Pleural fluid appearance has been proposed as a guide for the differential diagnosis of pleural effusions.[1] Nevertheless, to our knowledge, a systematic approach to the causes and clinical implications in a large, unselected series of cases has not been previously reported.

Most effusions from all the diagnostic groups were either serous or blood tinged. A watery appearance was very suggestive of transudate, but most transudates were serous, and these can even look blood tinged, bloody, or turbid.

It has been suggested that the bloody presentation of an effusion increases the probability of malignancy of the pleural effusion. In this series, almost half of the patients with BPE had neoplasms. This ratio agrees with Light's personal experience,1 but would probably be different in a surgical setting, where traumatic etiologies of the pleural effusions would be more likely. Nevertheless, a wide variety of causes can produce BPE, and fluid that is bloody in appearance, even if only slightly, increases the probability of malignancy (OR, 3.32). However, BPE, rather than being a common feature of neoplastic effusions, constituted only 32% of the neoplastic pleural effusions in this series, 33.3% of the malignant effusions, and 67.8% of the pleural effusions due to the other.

Although the color of the fluid is a subjective characteristic, the interobserver agreement in our study was fairly good. The differences with some series might be partially explained by the fact that we assessed pleural fluid color in a transparent tube with 10 mL of pleural fluid; the color is usually darker when several hundred milliliters are accumulated.

BPE can also be due to benign diseases. The most frequent benign causes in our series were parasitic diseases, parapneu- monic and posttraumatic pleural effusions.[1]

Eosinophilic pleural effusion (EPE), first described by Harmsen in 1894, is defined as a pleural effusion that contains at least 10% eosinophils.[6] The relationship between Eosinophilic Pleural Effusion (EPE) and malignancy is controversial. The frequency of malignant etiology among EPEs has varied between 6% and 40% in different studies.[6,7,8,9,11,12,13] In this series, 3 of 14 cases of EPE (21.4%) found were malignant.

EPEs account for 5 to 16% of exudative pleural effusions 6,7,8,9 and can be a manifestation of a great variety of diseases. Most of the information about EPE comes from small series and cases reports. Pleural blood or air does not always cause EPE. Among 250 patients with pleural fluid red blood cell counts >/=100,000/mm^3 at our institution, only 51 (20%) had pleural fluid eosinophilia. Thoracentesis is thought to be a very common cause of EPE because of the introduction of blood or air into the pleural space. However, Rubins and Rubins[8] reported that only 3 of 130 patients (2.9%) with non-EPE who underwent a second thoracentesis and 4 of 36 (11.1%) of those who underwent repeated thoracenteses within 2 to 12 weeks had higher numbers of pleural fluid eosinophils in subsequent thoracenteses. However, this reported that only 3 of 38 patients (7.9%) with non-EPE who underwent a second thoracentesis and 3 of 14 (21.4%) of those who underwent repeated thoracenteses within 2 to 12 weeks had higher numbers of pleural fluid eosinophils in subsequent thoracenteses. There was non statistically significant difference between the mean eosinophil in first and second thoracocentesis (2.5% vs 4%, respectively; p=0.6130).

In conclusion, serous and blood tinged were the most common presentations of pleural fluid at thoracentesis. Almost half of BPEs were secondary to neoplasms, but only 32% of the neoplastic effusions were BPE. Other common causes of BPE were parapneumonic and parasitic diseases. The appearance of the fluid should not be overemphasized as a diagnostic test.

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