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Retrospective Analysis of 240 Cases with Pleural Effusion

Fatma Tokgöz, Nezihe Gökşenoğlu, Yasemin Bodur, Emine Aksoy, Oğuz Aktaş, Tülin Sevim

Department of Pulmonology, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: Pleural effusion (PE) takes an important place in the clinical practice of thoracic diseases because of the difficulties in establishing an etiological diagnosis. The causes of effusion differ depending on the region where the examination is carried out, the clinic and the population involved. In this study, we aimed to evaluate adult patients who were examined due to PE in our clinic at a specific hospital for chest diseases.

Methods: The recordings of 240 patients who were hospitalised between June 2010 and July 2013 in our clinic and examined due to PE were retrospectively evaluated. Their fluid samples were taken and the patients were exposed to advanced invasive procedures when necessary. Demographic features of the patients, fluid analyses, diagnostic methods and diagnoses were reviewed.

Results: Of the cases, 68% were male. The mean age was 58±20 years and the most common complaint for admission was shortness of breath. The amount of pleural fluid was moderate in 56% of the cases. Eighty seven percent of the fluids were exudative. The concentration of glucose was below 60 mg/dL in 40 patients and the concentration of adenosine deaminase was above 40 U/L in 39 patients. The diagnosis of tuberculosis (TB) pleurisy was established to a great extent. Of the invasive procedures, closed pleural biopsy and fiberoptic bronchoscopy contributed to the diagnosis at rates of 47% and 21%, respectively. Of 61 malignancy-induced PEs, 38 were due to primary lung cancer and 8 were due to malignant mesothelioma. Apart from mesothelioma, 66% of these effusions were malignant effusions and contribution of the initial thoracentesis to this diagnosis was found to be 40%.

Conclusion: In our serial study, the most common causes of PE was TB in female patients, and pneumonia in male patients. Invasive procedures except thoracentesis were performed for 160 cases in total in the study. In 10 cases, the etiology of effusion could not be identified.

Keywords: Adenosine deaminase, empyema, exudate, pleurisy, transudate

INTRODUCTION

Pleural effusion is a common clinical condition and its etiology includes many diseases. It takes an important place in the clinical practice of thoracic diseases due to the difficulties encountered in etiological diagnosis. The causal distribution of pleural effusion (PE) varies depending on the features of geographical region, society, hospital and clinic of the study, and the diagnostic methods that are used (1). Its prevalence is estimated to be 400/100,000 in the United States of America (2). There are no reliable data about its prevalence in Turkey. The number of cases diagnosed with pleurisy among the patients hospitalised in the hospitals of chest diseases under the Ministry of Health between 1987 and 1994 ranged from 1912 to 2127 per year (3). However, it is not possible to make an overall evaluation of Turkey based on these data. Since PE can occur during the course of various diseases, many invasive and non-invasive tests are used for establishing diagnosis. In spite of current diagnostic tests, some cases of PE cannot be diagnosed (4).

In this study, the cases hospitalised in our clinic for PE within three years and exposed to advanced invasive procedures when necessary, and whose effusions were sampled were retrospectively evaluated. Demographic features of the patients, remarkable points in the analysis of fluids, diagnostic methods except thoracentesis and their contributions to the final diagnosis, and final diagnoses were assessed.

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Address for correspondence
Fatma Tokgöz, Department of Pulmonology, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
E-mai: fatmatokgoz86@gmail.com

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METHODS

The files of patients hospitalised with the diagnosis of PE in the 34-bed clinic of a chest diseases training and research hospital between June 2010 and July 2013 were examined and 240 adult patients whose effusions were sampled were included in the study. Demographic features, complaints for admission and physical examination findings of all cases were recorded. Posteroanterior (PA) and lateral chest radiographs performed at admission were examined. The amount of pleural fluid according to PA graphy was described as: minimal (fluid involving the costophrenic angle, not covering whole diaphragm), moderate (fluid covering less than 2/3 of the lower hilus) and massive (fluid covering more than 2/3 of the hemithorax). The localisation of pleural fluid was classified as unilateral (right or left hemithorax) or bilateral. Thoracentesis fluid analysis performed at an appropriate site accompanied by physical examination and ultrasonography and concurrent peripheral blood haemogram and biochemistry [glucose, albumin, protein, lactate dehydrogenase (LDH)] results were recorded. Exudates and transudates were categorised based on Light's criteria (5). Pleural fluid culture required due to clinical suspicion and other diagnostic parameters including acid-resistant bacilli (ARB), adenosine deaminase (ADA), cholesterol, triglyceride and rheumatoid factor (RF), and all cytology reports were recorded on the automated system of the hospital. Invasive procedures used for etiological diagnosis, including closed pleural biopsy, fiberoptic bronchoscopy (FOB), transthoracic fine needle aspiration biopsy (TFNAB), peripheral lymphadenopathy (LAP) biopsy, and video-assisted thoracoscopic surgery (VATS), were evaluated. Diagnostic methods were investigated by reviewing the latest diagnoses during the hospitalisation and follow-up periods. The three most common diseases of pneumonia, TB and malignancy-induced effusions were examined more extensively.

Diagnostic criteria

Parapneumonic effusion and empyema

With the findings of pneumonia such as cough, sputum, fever, and side pain, consistency of pleural fluid (alone or with infiltration in pulmonary parenchyma) and fluid analysis with parapneumonic effusion, response given to antibiotic treatment and the absence of any disease that can explain effusion were described as parapneumonic effusion, while collection of pus in the pleural space was described as empyema (6).

Tuberculosis pleurisy

This was described pathologically (presence of granulomatous inflammation with necrosis in tissue samples), microbiologically (sputum ARB positivity) or clinically (younger than 35 years, lymphocyte dominance in pleural fluid and ADA>40, confirmation of diagnosis by medical treatment).

Pleural effusion with a malignant disease

Effusions that were attributed to a malignancy which had been ongoing for a while or in patients diagnosed with malignancy through examinations were evaluated as either malignant (presence of malignant cells in pleural fluid or pleural biopsy) or paramalignant (presence of fluid associated with primary tumour which did not affect the pleura directly) effusions (7).

Pulmonary thromboembolism (PTE)

With consistent clinical findings, the detection of the finding of thrombus on computed tomography (CT) angiography or prediction of moderate or high possibility of PTE on ventilation/perfusion (V/Q) scintigraphy, or detection of deep vein thrombosis (DVT) on lower-extremity venous Doppler ultrasonography (USG) were described as pulmonary thromboembolism.

Rheumatoid pleurisy and systemic lupus erythematosus

This was described in the presence of RF>1 value in fluid/serum, the observation of lupus erythematosus (LE) cell in fluid and confirmation of diagnosis by a rheumatologist.

Drug-induced effusion

Drug-induced effusion was evaluated after the exclusion of other causes of PE, and recovery of fluid after discontinuation of the drug while using a drug proven to cause effusion.

Cyst hydatid

This was considered following indirect haemagglutination test positivity accompanied by consistent clinical and radiological findings.

Sequelae effusion

The fluid attributed to a previous disease and without malignancy during a follow-up period longer than 3 years, following the exclusion of other causes of effusion, and with an unchanged amount of pleural fluid and biochemical parameters during follow-up sessions was described as sequelae effusion (8).

Internal diseases-associated fluid

The fluid was considered to be associated with internal diseases when the findings of systemic diseases such as congestive heart failure (CHF), chronic renal failure (CRF), and hypoalbuminemia were present and clinical and laboratory findings were consistent.

PE with an unknown origin (idiopathic)

This was described in cases of undiagnosed effusion in spite of pleural fluid analysis (cell count, biochemical and microbiological), closed pleural biopsy, CT angiography and VATS being performed.

RESULTS

Of the cases, 76 (32%) were female and 164 (68%) were male. The mean age was 58±20 (15-100) years. The most common complaints for admission were shortness of breath (68%), cough (50%), side pain (25%) and chest pain (25%). Fever, loss of weight, and night sweat were reported in 40 (17%), 18 (8%) and 8 (3%) cases, respectively.

Radiological features

According to posteroanterior graphy, the amount of pleural fluid was classified as moderate in 133 cases (56%), minimal in 70 cases (29%) and massive in 37 cases (15%). Of the effusions, 138 (57%) were in the right hemithorax, 71 (30%) were in the left hemithorax and 31 (13%) were bilateral. The amounts of pleural fluid and locations are presented in Table 1.

Findings of pleural fluid

Pleural fluid was consistent with transudate in 31 patients (13%) and with exudate in 209 patients (87%). The fluid was transudate in 8 female (10%) and 23 male (14%) cases. It appeared as empyema in 3 patients.

Glucose was studied in 234 patients. Of 40 patients with a glucose value lower than 60 mg/dL, 37 were diagnosed with a specific dis-

ease. These diagnoses were as follows: 17 cases (43%) with parapneumonic effusion, 9 cases (23%) with TB, 4 cases (10%) with idiopathic effusion, 4 cases (10%) with malignancy-associated effusion, 2 cases (5%) with sequelae effusion, and 1 case (3%) with rheumatoid arthritis-associated (RA) effusion.

Table 1. Distribution of pleural fluid according to gender

	Female n (%)	Male n (%)	Total n (%)
Amount of fluid			
Minimal	20 (26%)	50 (31%)	70 (30%)
Moderate	45 (60%)	88 (54%)	133 (55%)
Massive	11 (14%)	26 (15%)	37 (15%)
Fluid localisation			
Right	40 (52%)	98 (60%)	138 (57%)
Left	25 (34%)	46 (28%)	71 (30%)
Bilateral	11 (%14)	20 (12%)	31 (13%)

Table 2. Protein concentrations in pleural fluids according to the diagnoses

	< 4g/dL n (%)	≥ 4g/dL n (%)	≥ 5 g/dL n (%)
Tuberculosis	3 (7%)	43 (93%)	39 (85%)
Lung cancer	7 (18%)	31 (82%)	15 (40%)
Malignant mesothelioma	1 (12%)	7 (88%)	1 (13%)
Metastatic cancer	0	11 (100%)	5 (46%)
Parapneumonic effusion	9 (21%)	34 (79%)	20 (47%)

The protein concentration was analysed in 235 patients. It was evaluated as 4 g/dL and above 5 gr/dL. Only in 3 patients with tuberculosis pleurisy was the protein concentration lower than 4 g/dL. It was 4 g/dL in 93% and above 5 g/dL in 85% of the patients with TB pleurisy. Table 2 demonstrates the protein concentrations according to diagnoses.

In our serial study, adenosine deaminase (ADA) in pleural fluid was examined in 216 patients. The mean ADA value was found to be 44 (10-93) U/L. In 39 patients (18%), ADA was over 40 U/L. Of these patients, 24 (62%) were diagnosed with TB, 9 (23%) with parapneumonic effusion, 2 (5%) with idiopathic effusion, 1 with malignant mesothelioma, 1 with lymphoma and 1 with rheumatoid pleurisy. A patient was exitus before his final diagnosis was established.

Diagnostic procedures

As a diagnostic method after thoracentesis, 160 invasive procedures, most commonly FOB and closed pleural biopsy, were performed. Bronchoscopy was conducted in 80 patients and 17 (21%) were diagnosed with a specific disease. Bronchoscopy was diagnostic for primary lung cancer in 54% (14/26) of cases. Closed pleural biopsy was performed in 45 cases and it was diagnostic in 21 of them (47%). Closed pleural biopsy was diagnostic of TB pleurisy in 71% and of malignancies in 54%. A specific diagnosis was established in all 3 patients exposed to lymphadenopathy biopsy and in 1 of the 2 patients exposed to TFNAB. A specific diagnosis was not made in 10 of the 30 patients who underwent video-assisted thoracoscopic surgery. Invasive procedures which were performed and their contributions to the diagnoses are shown in Table 3.

Final diagnoses

The most common causes determined in our study were parapneumonic pleurisy (19%), TB pleurisy (19%) and lung cancer (16%). When all malignancies were considered as a whole, it was seen that one quarter of effusions occurred due to malignant causes (25.4%).

Table 3. Invasive procedures and their contributions to establishing diagnosis

	FOB Diagnostic/total	Closed pleural BX Diagnostic/total	VATS Diagnostic/total	LAP BX Diagnostic/total	TFNAB Diagnostic/total
Tuberculosis	1/7	12/17	5/5	-	-
Lung cancer	14/26	7/11	5/5	1/1	1/2
Mesothelioma	5	2/2	5/5	-	-
Metastatic	2/6	1	3/3	-	-
Pulmonary embolism	3	-	-	-	-
Lymphoma	3	1	1/1	2/2	-
Rheumatoid pleurisy	1	1	-	-	-
Idiopathic	6	3	10	-	-
Other*	11	6	-	-	-
Systemic disease	2	-	-	-	-
Parapneumonic	9	2	-	-	-
Sequelae effusion	1	1	1	-	-
Total	17/80	21/45	-	-	-

BX: Biopsy; FOB: fiberoptic bronchoscopy; LAP: lymphadenopathy; TFNAB: transthoracic fine needle aspiration biopsy; VATS: video-assisted thoracoscopic surgery
*Refused the procedure /exitus

Table 4. Final diagnoses and distribution according to gender

	Female n (% female)	Male n (%male)	Total n (% total)
Parapneumonic	11 (14%)	35 (21%)	46 (19%)
Tuberculosis	23 (30%)	22 (13%)	45 (19%)
Lung cancer	12 (16%)	26 (16%)	38 (16%)
Congestive heart failure	6 (8%)	19 (11%)	25 (10%)
Metastatic cancer	6 (8%)	5 (3%)	11 (5%)
Pulmonary embolism	4 (5%)	6 (4%)	10 (4%)
Malignant mesothelioma	1	7 (4%)	8 (3%)
Lymphoma	-	4 (3%)	4 (2%)
Chronic renal failure	-	4 (3%)	4 (2%)
Rheumatoid pleurisy	2 (3%)	1	3 (1%)
Hypoalbuminemia	1	2	3 (1%)
Sequelae effusion	-	3 (2%)	3 (1%)
Drug-induced	-	2 (1%)	2
Lupus	1	-	1
Hepatic abscess	-	1	1
Cyst hydatid	-	1	1
idiopathic	3 (4%)	7 (4%)	10 (4%)
Refused examinations	5 (7%)	15 (9%)	20 (8%)
Exitus	1 (1%)	4 (2%)	5 (2%)
Total	76	164	240

Etiological causes were TB, malignancies and pneumonia in female patients and malignancies, pneumonia and TB in male patients, respectively. Of the lung cancers, 35 were non-small cell lung cancer, 2 were small cell cancer and 2 were epithelial cancer. The most common cause of transudative effusions was heart failure (68%). Eight of the 10 patients with pulmonary embolism were exudate and 2 were transudate. Diagnostic procedures of 25 patients were not completed due to refusal of further examinations, leaving hospital voluntarily (n=20) or being exitus (n=5). Causes of effusion according to gender are presented in Table 4.

In the patients with parapneumonic effusion, the mean values of the fluid were as follows: glucose, 50 (1-162) mg/dL; protein, 4.6 (2.5- 6.6) g/dL, LDH, 1826 (173-15780, median:685) U/L; ADA, 31 (3-148) U/L. Thirty five patients were followed-up with medical treatment, 11 patients were exposed to chest tube insertion by a thoracic surgeon, and one patient underwent fibrinolytic therapy.

The diagnosis of tuberculosis pleurisy was established pathologically in 18 cases (12 closed pleural biopsy, 5 VATS, 1 bronchoscopy), bacteriologically in one case (sputum ARB positivity) and clinically in 26 cases (increased ADA, younger than 35 years, lymphocyte dominance in pleural fluid and presence of index case).

In our study, 61 patients had malignancy-associated effusion. The rates of these effusions were as follows: Primary lung cancer in 38 (62%) patients, malignant mesothelioma in 8 (13%) patients, lymphoma in 4 (7%) patients, and effusions associated with malignancies of other organs [breast (n=3), mesenchymal tumour (n=2), adenoid cystic carcinoma, thyroid, ovarian, kidney, stomach, colon-associated malignancies] in 11 (18%) patients. Of the effusions, except for malignant mesothelioma, 35 (66%) were malignant and 18 (34%) were paramalignant. Twenty seven of the malignant effusions were revealed by fluid cytology (17 specific tumour cells, 10 atypical cells) and 8 were revealed by biopsy. Thoracentesis was performed twice or three times before biopsy. Atypical or specific tumour cells were observed in 21 of the 53 cases (40%) on the first thoracentesis, in 14 of 47 cases (21%) on the second thoracentesis and in 7 of 25 cases (29%) on the third thoracentesis. Of the specific tumour cells, 6 were reported on the first thoracentesis examination, 5 on the second and 6 on the third thoracentesis examination. In 3 patients diagnosed with a specific disease on the second thoracentesis and in all patients diagnosed with effusions on the third thoracentesis, atypical cell had been detected on previous cytology.

DISCUSSION

Pleural effusion is described as the abnormal collection of fluid in the pleural space resulting from disruption of the balance between fluid production and absorption (9). Pleurisy comprises 4% of all admissions to the outpatient clinic of internal medicine. The most common complaints are shortness of breath, cough, and pleuritic chest pain, which vary depending on the underlying diseases (10). In our study, the most frequent symptoms were shortness of breath and cough, as well as side pain and chest pain.

A detailed anamnesis and physical examination should be conducted initially for patients with effusion. Then, the fluid should be sampled through thoracentesis in the case of fluid collection over 1 cm on lateral decubitus radiography, except for cases with apparent heart failure (10). The first step for a differential diagnosis is to distinguish transudate and exudate, and Light's criteria are used for this aim (5). In our study, the most common cause of transudate fluids was heart failure, while the cause of effusion was heart failure in 4 exudative patients. All of the effusions associated with chronic renal failure and hypoalbuminemia were transudate. These findings suggest that differentiation of transudate and exudate should be supported with clinical findings at the stage of diagnosis.

Concentrations of small molecules like glucose are similar in pleural fluid and plasma. The value of glucose in the fluid can be lower than 60 mg/dL in complicated parapneumonic effusion or in the effusions associated with empyema, TB, malignancy and RA (10). In our serial study, the most common causes of decreased glucose concentration were parapneumonic effusions and tuberculosis pleurisy. In more than 50% of patients with infection, malignancy and RA, the concentration of glucose was over 60 mg/dL. It should be noted that a decreased concentration of glucose in pleural fluid can be helpful for differential diagnosis, but that the evaluation of glucose is not reliable for excluding these differential diagnoses.

The total protein concentration of <4 g/dL in the pleural fluid of TB is rare. In malignancy and parapneumonic effusions, the concentrations of proteins are in a wide range (11). In our study, protein concentration in the fluid was lower than 4 g/dL in only 3 (7%) of the cases diagnosed with TB pleurisy. We believe that fluid containing a high level of protein may be a parameter supporting the diagnosis for the pleural effusions considered to be TB pleurisy.

Adenosine deaminase activity has been used for establishing a diagnosis since 1978 and is an enzyme of the purine degradation pathway, especially reflecting the proliferation and differentiation of lymphocytes. For this marker which has a diagnostic value for tuberculosis, false positivity can be observed in rheumatoid diseases, chronic lymphocytic leukaemia, lymphoma and empyema (12-14). In our study, 15 patients with an adenosine deaminase value higher than 40 U/L were diagnosed with diseases other than tuberculosis. Of the cases with lymphoma and parapneumonic effusion, 2 patients were younger than 35 years. If the diagnosis is established based on the value of adenosine deaminase, non-tuberculosis diseases should be ruled out, particularly in young patients.

Invasive diagnostic methods are used when a diagnosis cannot be made with the biochemical analysis of pleural fluid, cell count and cytological analysis. Closed pleural biopsy conducted with an Abrams needle is diagnostic at the rate of 57% in malignancy and 79% in tuberculosis. The sensitivity of video-assisted thoracoscopic surgery in malignant cases is about 95%. Bronchoscopy is not recommended for routine diagnostic use, but it can be used for cases with haemoptysis and suspected bronchial obstruction considering malignancy (15). In our study, 160 invasive procedures were used in total. The rates of diagnosis were 21% for FOB and 47% for closed pleural biopsy. Thirty three percent of VATS cases were idiopathic. Fiberoptic bronchoscopy (54%) and closed pleural biopsy (71%) were more diagnostic in primary lung cancer and TB pleurisy, respectively. Moreover, peripheral LAP biopsies, determined upon physical examination, were also diagnostic. In conclusion, we suggest that invasive procedures should be planned considering priority diagnoses for each case after extensive clinical evaluation.

The causes of pleurisy differ according to the societies. In the United States of America, the first 3 diseases in PE incidence were CHF, parapneumonic effusion, and malignant effusions (16). In our country, TB is situated close to the top following these diseases (17). In studies of PE etiology which have recently been conducted in our country, the rates of TB and malignancy-induced fluids were higher (18). Bayrak et al. (19) reported malignancy (37%), TB (21%), empyema and parapneumonic effusions (18%) as the most common causes. In the study of Köktürk et al. (20), TB (29%), malignancy (27%) and CHF (13%) associated fluids were the most common causes. In our study, malignancies were the most common cause (25%); the most frequent causes were TB and malignancies in female patients and malignancies and fluids associated with pneumonia in male patients. Since our hospital was a pulmonary diseases hospital and only those cases exposed to thoracentesis were included in the study, the frequency of CHF was lower than in other serial studies. This supports the fact that thoracentesis is not required for those cases having benefited from clinical findings and medical treatment and also shows that the etiological diagnosis frequency can vary depending on the conditions of the clinic in which the study is conducted.

For the final diagnosis of tuberculosis pleurisy, *Mycobacterium tuberculosis* must be isolated in tissue or pleural fluid, or granulomas must be observed in tissue (21). However, diagnosing in this way is not always possible or necessary. It is accepted that in regions where tuberculosis is endemic, other conditions increasing ADA can be excluded and then treatment can be initiated without performing biopsy for cases younger than 35 years with a higher value of ADA (22). In the serial studies about the diagnostic methods for tuberculosis pleurisy, it was reported that the contribution rate to diagnosis was 10-47% for pleural fluid culture and 39-84% for pleural biopsy histology and culture (23-26). In our study, it was determined that only 40% of the TB pleurisy cases were diagnosed histologically and most of these diagnoses were established considering clinical features and laboratory findings. Although the diagnoses of these cases in our study were confirmed by treatment responses, it should be remembered that those cases in which treatment is initiated without histological diagnosis require closer follow-up.

Malignancies are the most common cause of exudative effusions for cases where the patient is aged over 60 years (27). Disruption of lymphatic system integrity between parietal pleura and mediastinal lymph nodes and spread of tumour into the pleura through the neighbourhood or haematogenous ways leads to the formation of pleural fluid (28, 29). Mesothelioma varies depending on the geographical region (30). In a serial study in which 2040 malignant effusions were evaluated, the most common primary causes were reported to be malignancies associated with lung (38%), breast (17%), lymphoma (12%), unknown primary (11%), genitourinary system (9) and gastrointestinal system (7%) (27). In our study, the most common malignancies were lung cancer and mesothelioma.

In malignant effusions, pleural fluid cytology contributes to the diagnosis at a rate of 66% (31). Negative results are associated with type of tumour (like mesothelioma, sarcoma, or lymphoma), tumour margin in the pleural space, and experience of the cytologist (10). In our serial study, the contribution of pleural fluid cytology to diagnosis was at a rate of 53% in malignant effusions.

In the study of Garcia et al. (11) on malignant effusions, they reported that the contributions of first, second and third samples to the diagnosis were 65%, 27% and 5%, respectively. In our study, atypical or specific tumour cells were observed at the rate of 40.2% on the first thoracentesis, 21.3% on the second thoracentesis and 28% on the third thoracentesis. Of the cytologies revealing specific tumour cells, atypical cells were detected in all of the cases diagnosed on the third thoracentesis and in 60% of the cases diagnosed on the second thoracentesis. Although the contributions of these results to the diagnoses are reported to be low in the literature, we believe that a third thoracentesis may be beneficial, especially in cases with atypical cells on the first two thoracentesis.

The effusions which are not diagnosed in spite of biochemical, cytological evaluations and pleural biopsies are described as idiopathic PE. In the studies published, 5-25% of the effusions are reported as idiopathic (15). In our study, 4.7% of the cases, except those refusing further examination and being exitus, were not diagnosed despite VATS and evaluated as idiopathic.

CONCLUSION

In our serial study, the most common diseases identified in the etiological diagnosis of pleural effusion were parapneumonic effusion, TB pleurisy and primary lung cancers. All effusions associated with malignancy comprised 25% of our study group. Tuberculosis was more common in female patients and malignancies were more common in male patients. Closed pleural biopsy, which is used less frequently today, was diagnostic in the rate of 71%. In the patients suspected of having malignant effusion, the third thoracentesis may provide an additional contribution to the diagnosis. Despite all of the invasive procedures, some effusions still cannot be diagnosed.

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