Etiology of exudative pleural effusions in adults in North Lebanon

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OBJECTIVE: To establish the clinical pattern and etiology of exudative pleural effusions in adults in North Lebanon.
MATERIALS AND METHODS: All patients aged 21 years and older who were admitted with exudative pleural effusions to the Husseini Hospital, Tripoli, North Lebanon, between 1997 and 1999 were studied prospectively.
RESULTS: Of 165 patients with exudative pleural effusions, 114 (69.1%) were men and 51 (30.9%) were women. The most frequent cause of exudative pleural effusions was tuberculosis (43.7%), followed by malignancy (32.1%). The majority (88.7%) of malignant pleural effusions were due to lung cancer. Tuberculous effusions were more frequent in the first five decades of life (66.7%) and were the most common type of pleural effusion, accounting for 68.6% of patients younger than 50 years of age. Malignant effusions were more frequent among the older age groups, with 73.6% of patients with malignant effusions being older than 50 years of age. Most types of exudative pleural effusions showed a preference for the right side of the thorax. Of the diagnostic procedures used in the present study, the most useful were histological examination and culture of pleural biopsies.
CONCLUSIONS: In North Lebanon, the clinical pattern and etiology of exudative pleural effusions are similar to those in the developing countries; the most frequent cause of pleural exudates is tuberculosis, followed by malignancy, particularly malignancy due to lung cancer.

Key Words: *Lebanon; Malignancy; Pleural effusions; Tuberculosis*

Étiologie des épanchements pleuraux exsudatifs chez les adultes au Nord du Liban

OBJECTIF : Établir l'étiologie et le tableau clinique des épanchements pleuraux exsudatifs chez les adultes au Nord du Liban.
PATIENTS ET MÉTHODE : Étude rétrospective de tous les patients âgés de 21 ans et plus, admis à l'hôpital Husseini, à Tripoli, au Nord du Liban, entre 1997 et 1999, pour un épanchement pleural exsudatif.
RÉSULTATS : Des 165 patients admis, 114 (69,1 %) étaient des hommes et 51 (30,9 %), des femmes. La cause la plus fréquente d'épanchement pleural exsudatif était la tuberculose (43,7 %), suivie des tumeurs malignes (32,1 %). La plupart (88,7 %) des épanchements pleuraux malins étaient dus à un cancer du poumon. La tuberculose constituait la principale cause d'épanchement pleural au cours des cinq premières décennies de vie (66,7 %), touchant 68,6 % des patients de moins de 50 ans, tandis que le cancer se rencontrait surtout chez les patients de plus de 50 ans, touchant 73,6 % d'entre eux. Les épanchements pleuraux exsudatifs se situaient de préférence du côté droit du thorax. L'examen histologique et la culture des prélèvements pleuraux par biopsie se sont avérés les interventions diagnostiques les plus utiles dans le cadre de la présente étude.
CONCLUSION : Les épanchements pleuraux exsudatifs au Nord du Liban ont une étiologie et un tableau clinique semblables à ceux des pays en voie de développement, c'est-à-dire qu'ils ont pour principale cause la tuberculose, suivie des tumeurs malignes, notamment du cancer du poumon.

A great variety of disease processes can give rise to exudative pleural effusions, but the principal ones to be considered in a patient with a pleural exudate are tuberculosis and malignancy (1,2). The frequencies of different causes of exudative pleural effusions that are reported in a particular study depend on the patient population used, whether the pa-

TABLE 1
Criteria for diagnosis of tuberculous pleural effusions

Criteria	Number of patients (%)
Presence of epithelioid cell granulomas with or without caseating necrosis, and positive staining for acid-fast bacilli in pleural biopsy specimens	15 (20.8)
Presence of epithelioid cell granulomas with or without caseating necrosis in pleural biopsy specimens plus:	
Positive acid-fast bacilli and/or *Mycobacterium tuberculosis* isolated from respiratory tract specimens	7 (9.7)
Clinical and radiological response to antituberculosis chemotherapy	30 (41.7)
Negative pleural biopsy but tuberculin conversion, lymphocyte predominant exudate, and clinical and radiological response to antituberculosis chemotherapy with:	
Presence of acid-fast bacilli in respiratory specimens	4 (5.6)
Absence of acid-fast bacilli in respiratory specimens	16 (22.2)
Total	72 (100)

TABLE 2
Etiological diversity of exudative pleural effusions in adults in North Lebanon

Cause of pleural effusion	Number of patients (%)	Number of men/women (ratio)	Mean age (years)
Tuberculosis	72 (43.7)	57/15 (3.8:1)	36.5±16.2
Malignancy	53 (32.1)	33/20 (1.6:1)	63.4±11.9
Empyema	22 (13.3)	13/9 (1.4:1)	52.7±15.2
Parapneumonia	18 (10.9)	11/7 (1.6:1)	59.4±16.5
Total	165 (100)	114/51 (2.3:1)	53.6±16.9

tients are investigated and treated in a primary care setting or a tertiary referral centre, and the geographical region where the study is conducted (3,4). In Tripoli, North Lebanon, where the incidence of tuberculosis is relatively high (43 per 100,000 population in 1996), the distinction between tuberculous and nontuberculous causes of exudative pleural effusions is an important clinical problem (5). A prospective study was performed to define the causes of exudative pleural effusions treated in a tertiary medical centre situated in an urban area.

MATERIALS AND METHODS

Data collection: A prospective study was conducted of the medical records and chest radiographs of consecutive cases of exudative pleural effusions referred to the internal medicine service of the Husseini Hospital, Tripoli, Lebanon, during a three-year period from January 1997 to December 1999. All patients aged 21 years and older who presented with pleural effusions routinely underwent tuberculin skin testing, abdominal ultrasound and diagnostic thoracentesis to obtain pleural fluid specimens for cell count, cytology, Gram and Ziehl-Neelsen stain, and bacterial and tuberculosis culture. Total protein and lactate dehydrogenase levels were obtained for both serum and pleural fluid specimens to distinguish exudates from transudates according to Light's criteria (6). Closed percutaneous pleural biopsy was routinely performed with the Abrams needle (7) or Tru-cut needle (8). As a routine, pleural biopsy was performed using the Abrams needle; the Tru-cut needle was used for pleural biopsy only in situations where the Abrams needle biopsy was negative and where computed tomography (CT) of the thorax

showed marked pleural thickening in addition to the pleural effusion. None of the patients underwent more invasive procedures, such as open or thoracoscopic pleural biopsy.

Clinical definitions: Table 1 shows the diagnostic criteria for tuberculous pleural effusions. Malignant or neoplastic pleural effusions were confirmed by positive pleural biopsy and/or positive pleural fluid cytology. Parapneumonic effusions were those that occurred in association with bacterial pneumonia, and empyema was diagnosed when the effusion fluid was purulent or grew a pathogenic organism on culture, or if it was culture-negative on Gram stain (ie, a positive Gram stain) (9,10).

Pleural effusion size: The size of the pleural effusion seen on chest radiograph at presentation was graded as 'small' when the costophrenic angle was obliterated but the hemidiaphragm was not covered, 'medium' when it filled up to half of the hemithorax or 'large' when it filled up more than half of the hemithorax. For patients with bilateral effusions, the size of the larger effusion was recorded.

Statistical analysis: Results are expressed as the mean ± SD. Differences between groups were compared using the two-tailed, unpaired Student's *t* test or one-way ANOVA, with Newman-Keuls' multiple comparisons post hoc test, when appropriate, for continuous variables. The χ^2 test (Yates' corrected, when applicable) was used to analyze categorical data. $P<0.05$ for a two-tailed test was considered statistically significant.

RESULTS

Of the 165 patients between 21 and 80 years of age (54±16.9 years) with exudative pleural effusions during the study period, 114 (69.1%) were men aged 46±15.9 years and 51 (30.9%) were women aged 52±16.4 years. Female patients were significantly older (P=0.05), and the male to female ratio was 2.3:1. The etiological distribution of pleural effusions, with the number of patients in each etiological group and the mean age of the group, are shown in Table 2. The two most common causes of exudative pleural effusions were tuberculosis (43.7%) and malignancy (32.1%). Patients with tuberculous pleural effusions were significantly younger than the rest (P<0.05).

The age distributions of patients with tuberculous and ma-
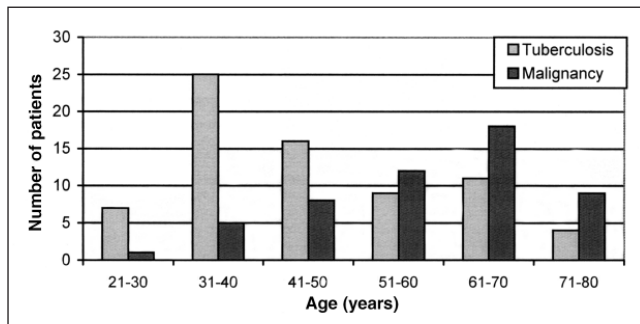
Figure 1) *Age distribution of patients with tuberculous and malignant pleural effusions*

TABLE 3
Neoplasms causing malignant pleural effusions

Type of primary neoplasm	Number of patients (%)
Adenocarcinoma of the lung	31 (58.5)
Squamous cell carcinomas of the lung	8 (15.1)
Small cell lung cancer	5 (9.4)
Mesothelioma	5 (9.4)
Large cell carcinoma of the lung	3 (5.7)
Adenocarcinoma of unknown primary malignancy	1 (1.9)
Total	53 (100)

TABLE 4
Size of pleural effusion according to etiology

	Pleural effusion size			
Etiology	Large (n [%])	Medium (n [%])	Small (n [%])	Total
Tuberculosis	9 (12.5)	42 (58.3)	21 (29.2)	72
Malignancy	28 (52.8)	17 (32.1)	8 (15.1)	53
Empyema	–	16 (72.8)	6 (27.2)	22
Parapneumonia	–	9 (50)	9 (50)	18
Total	37 (22.4)	84 (50.9)	44 (26.7)	165

lignant pleural effusions are shown in Figure 1. Tuberculous effusions were more frequent in the first five decades of life (48 of 72 [66.7%] cases) and were the most common type of pleural effusion, accounting for 48 of 70 (68.6%) patients younger than 50 years of age. Malignant effusions were more frequent among the older age groups – 39 of 53 (73.6%) patients with malignant effusions were older than 50 years of age – and accounted for 41.1% of the 95 cases in this age range. The majority of patients with empyema (18 of 22 [81.8%]) and parapneumonic effusion (14 of 18 [77.8%]) were older than 50 years of age.

In patients with tuberculous pleural effusions, the diagnostic yield of Abrams needle biopsy for the presence of caseous granulomas in pleural biopsy tissue samples was 52 of 72 (72.2%) patients, while that for Tru-cut needle biopsy of seven patients was 100%. In patients with malignant pleural effusions, the diagnostic yield of Abrams needle biopsy was 24 of 53 (45.3%) patients, while that for Tru-cut needle biopsy of two patients was 100%.

Malignant pleural effusions were confirmed by positive pleural biopsy in 16 patients, positive pleural fluid cytology in 27, and positive pleural biopsy and positive pleural fluid cytology in 10. Thus, of 53 patients with malignant effusions, pleural fluid cytology was positive in 37 (69.8%), while pleural biopsy was positive in 26 (49.1%). Table 3 lists the primary neoplasms responsible for malignant effusions. The majority (88.7%) of malignant pleural effusions were due to lung cancer.

Culture of empyema fluid grew *Klesbsiella pneumoniae* in eight patients, *Streptococcus pneumoniae* in four, *Staphylococcus aureus* in two and *Streptococcus* species in two. No bacterial organism was isolated from the empyema fluid of six patients. Of the patients with parapneumonic effusion, *K pneumoniae* was isolated in the sputum of four patients and *Haemophilus influenzae* was isolated in two. The rest of the patients did not have a pathogen isolated. Blood cultures were negative in all patients with parapneumonic effusion. Serological tests for *Mycoplasma*, *Chlamydia* and *Legionella* species were negative in all patients with parapneumonic effusions.

In 106 patients (64.2%), pleural effusions occurred only on the right side of the thorax; in 52 (31.5%), only on the left; and in seven (4.3%), both sides were involved. Most types of pleural effusions showed a preference for the right side. Tuberculous pleural effusions were right sided in 62.2% of patients, while malignant effusions were right sided in 65.5% of patients. Table 4 shows the distribution of size of the pleural effusions according to etiology. Of the 37 large effusions, 28 (75.7%) were caused by malignancy. While 28 of 53 (52.8%) malignant effusions were large in size at the time of presentation, effusions of similar size were only seen in nine of 72 (12.5%) effusions that were tuberculous in etiology (χ^2=24.643, P<0.001).

DISCUSSION

In the present study, the most common etiology of exudative pleural effusions was tuberculosis, which accounted for 44% of all cases. In general, the proportion of pleural effusions due to tuberculosis varies and is likely to reflect the local incidence of the disease, which is high in North Lebanon at 43 cases per 100,000 population. Other authors have reported tuberculosis as the most frequent cause of pleural effusions in areas where the incidence of tuberculosis is high (4,11). Because the incidence of active tuberculous infection in the Eastern Mediterranean region in 1996 was 129 cases per 100,000 persons compared, for example, with 10 cases per 100,000 in the United States and Canada, tuberculosis is likely to be a frequent if not the leading cause of exudative pleural effusions in this part of the world (12).

The greater frequency of tuberculous effusions among our patients was even more pronounced among those aged 50 years or younger, in whom tuberculosis was the cause of about 69% of cases of pleural effusions. The mean age (36.5 years) of patients with tuberculous pleural effusions was much lower than that of patients with most other types of pleural effusion,

in agreement with the findings in other developing countries (13,14) and in contrast to the findings in developed countries, where the age has steadily increased (15-18).

Bacteriological confirmation for *Mycobacterium tuberculosis* in pleural fluid culture is often not obtained because the mycobacterial population in tuberculous pleural effusion is generally small and cultures of pleural fluid specimens are generally positive in only up to about 30% of cases (15,19). The presence of granulomatous inflammation on histological examination of pleural biopsy specimens is frequently used as a diagnostic criterion for pleural tuberculosis (20,21). Acid-fast bacilli were stained positive in granulomas of pleural biopsy specimens from 20.8% of our patients with tuberculous effusions. This is comparable with the range of 20% to 40% described in the literature (20,22,23).

Malignancy was the second most common cause of exudative pleural effusions in our study and the most frequent cause among patients older than 50 years of age. Others have also made the same observation (4). Malignancy was the cause of effusions in 32% of our patients, within the range of prevalence (15% to 48%) reported in other published series (4,24,25). In keeping with reports in the literature (4,26), carcinoma of the lung was the most common neoplasm to cause malignant pleural effusion in our patients. Compared with pleural fluid cytology, needle pleural biopsy has a lower yield for the diagnosis of malignant pleural effusions (27-29). This is borne out by our results, which showed that 70% of patients with malignant effusions had positive pleural fluid cytology, while only 49% had positive pleural biopsy findings. This indicates that cytological evaluation of pleural fluid is more efficacious in the diagnosis of malignant pleural effusion than percutaneous pleural biopsies.

The right-sided dominance of tuberculous pleural effusion in our patients is in agreement with the observations of others (19,20,30,31). The reason for this predilection is not clear. Although other authors have not found a preference of neoplastic effusions for a particular side (4), malignant pleural effusions in our patients occurred much more commonly on the right side than on the left.

The majority of massive pleural effusions are due to malignancy (32). This is also evident from our results, which showed that most of the large pleural effusions were caused by malignancy.

In North Lebanon, the distinction between tuberculous and nontuberculous causes of exudative pleural effusions, especially malignancy, is an important clinical problem. Malignant effusions tended to occur in an older population and were likely to be large at presentation, but the considerable overlap of these characteristics in both types of effusion means that they cannot be used to distinguish one from the other in an individual patient. The diagnosis eventually depends on pleural biopsy findings, pleural fluid cytological and microbiological examinations, and, occasionally, the response to antituberculosis chemotherapy. There is a large literature related to the use of adenosine desaminase level in pleural fluid in diagnosing tuberculous pleural effusions because of its high sensitivity and specificity (33-35).

Effusions with an etiology of parapneumonia or empyema accounted for 24% of all of our cases. It is estimated that about 40% of patients with pneumonia develop a concomitant pleural effusion (10), although some studies show the incidence of this complication of pneumonia to be less than 20% (36). In one series (4), parapneumonic effusion together with empyema accounted for 14% of all cases of pleural effusions, both transudative and exudative. The percentage of positive pleural fluid cultures in our patients with empyema was surprisingly high despite the liberal prescribing of antibiotics by primary care physicians.

During the study period, only five cases of systemic lupus erythematosus (SLE) were registered in our hospital, and none had pleural effusion. This observation agrees with what has been previously published about the clinical expression of SLE in patients in Lebanon (37) and other Arabic countries (38-41). The presence of differences in the symptomatology of SLE in Arabic patients may be influenced by racial and ethnic differences (eg, histocompatibility leukocyte antigen), and geographical and environmental factors (eg, weather, viruses) (41-45).

The etiologies of pleural effusions observed in this study were similar to those found in other Arabic countries (46,47). However, the comparison with experience in a country such as Canada, with a low prevalence of tuberculosis, shows great differences. Among these differences is the higher exposure to asbestos in Canada, with the main causes of effusions being pleural mesothelioma and lung cancer (48,49). Among workers exposed to asbestos, there are two cases of asbestos-related lung cancer for every case of mesothelioma (50). Thus, it seems likely that the most frequent cause of exudative pleural effusions in Canada is lung cancer, followed by pleural mesothelioma, with tuberculosis being much less frequent.

CONCLUSIONS

The most frequent cause of exudative pleural effusions seen in the internal medicine service of our hospital is tuberculosis, followed by malignancy, particularly lung cancer. This etiological distribution may be typical of regions that, like North Lebanon, have a high incidence of tuberculosis.

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