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Brief Report

Status of Exudative Pleural Effusion in Adults of South Khorasan Province, Northeast Iran: Pleural Tuberculosis Tending toward Elderly

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Abstract

The causes and situation of exudative pleural effusion vary from one area to another. A cross-sectional study was conducted on 327 patients with exudative pleural effusion in South Khorasan province (Iran). The patients were older than 12 years and comprised 172 (52.6%) males and 155 (47.4%) females. The study commenced in 2007 with seven years duration. The Light's criteria were used to define exudative effusion. Procedures including pleural fluid analysis, microbiological study, pleural biopsy, and systemic investigations were conducted to determine the special cause of pleural effusion. The mean age of the patients was 63.4±18.4 years. Malignancies, tuberculosis, and parapneumonia pleural exudation were diagnosed in 125 (38.2%), 48 (14.7%), and 45 (13.8%) cases, respectively. Among malignant effusions, metastasis from lung cancer made 48 (38.4%) of the cases. The origin of metastasis was not determined in 44 (35.2%) patients. The mean age of patients was not significantly different between malignant (66.9±14.3 years) and tuberculosis (63.9±19.7 years) cases (P=0.16). The older age of tuberculosis patients could be a new discussion point on the overall impression created on the subject of tuberculosis pleural exudation (TB-PLE) occurring in young people.

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What's Known

- It is traditionally believed that tuberculosis pleural exudation (TB-PLE) is a presentation of primary TB seen mainly in adolescents and adults and that it less likely to be massive. Therefore, it will be less likely in the differential diagnosis with malignant pleural effusion.

What's New

- We found that TB-PLE tends toward the elderly and also be massive.
- One of our cases with a ruptured hydatid cyst was complicated with cholesterol pleurisy, which has not been reported so far.

Introduction

The causes and situation of exudative pleural effusion vary from one area to another. Tuberculosis is one of the most important causes of exudative effusion in many areas of the world.[1,2] It is traditionally believed that tuberculosis pleural exudation (TB-PLE) is a presentation of primary TB and seen mainly in adolescents and adults.[3] However, such understanding has been challenged in recent years. While reports from some areas have emphasized on the presentation of this condition at a young age,[4] others insist on an increase in the age of patients.[5] Malignant and parapneumonic pleural effusion are also common causes of exudative pleural effusion, especially in elderly. With increasing age of TB-PLE patients, they will be more likely included in the differential diagnosis with malignant pleural effusion. Studies about exudative pleural effusion have been carried out in different areas of the world, including Iran.[2,6-10] The aim of the current study was to determine the status of exudative pleural effusion (prevalence

and age distribution of most common etiologies) among the adults of our region.

Patients and Methods

A cross-sectional study was conducted on adult patients older than 12 years with the presence of more than 10 mm fluid thickness on lateral decubitus chest X-ray (CXR). These patients were among those admitted for diagnostic workup and treatment at Vali-e-Asre Hospital in South Khorasan (Iran) from 2007 for a period of 7 years. This hospital serves as the only tertiary referral center in South Khorasan. Informed consent was obtained from each participant for invasive diagnostic work-up. Thoracentesis was undertaken and 30 ml of fluid evacuated and transferred to a laboratory for analysis. Exudative nature of the fluid was defined using the Light's criteria. Color and odor of the fluid, glucose, protein lactate dehydrogenase, Gram staining, Ziehl-Neelsen staining, cytology and cytopathology of the fluids were mandatory investigations. Specific tests such as cholesterol, triglyceride, rheumatologic markers, Adenosine deaminase activity (ADA), and percutaneous pleural needle biopsy using Abrams pleural biopsy needle were performed in cases where it was necessary for definite diagnosis.

Fluid categorized into polymorph nuclear (PMN) dominant (PMN>50% of total white blood cell count) or mononuclear (MN) dominant (MN>50% of total white blood cell count) count group. Tuberculosis and malignancy were considered in differential diagnosis of all mononuclear dominant exudative fluids and confirmed by either pleural biopsy histopathology or cytopathology and Ziehl–Neelsen staining of fluid sediment. When the yields of studies on biopsy or fluids were not conclusive, extensive systemic investigations continued until a particular disease and pleural disease was identified and linked to it. In cases where signs and symptoms of patients were consistent with acute bacterial infections and more than 50% of white blood cell was extracted from pleural fluid sample was PMN, the diagnosis of parapneumonic effusion applied. Diagnosis of empyema was based on isolation of microorganism from Gram staining or culture of fluid. Lymphoma related pleural effusion was confirmed by bone marrow or lymph node biopsy and enzyme-linked immunosorbent assay (ELISA) of blood samples. Histopathological study of surgical samples was used for verification of ruptured hydatid cyst into pleural space. Pulmonary thromboembolism (PTE) was confirmed with computed tomography (CT) pulmonary angiography.

Diagnostic criteria for mesothelioma were (i) pleura CT scan findings highly suggestive for mesothelioma (diffuse and concentric pleural thickening), (ii) report of malignant mesothelioma on histopathological study, (iii) mesothelial hyperplasia on biopsy and (iv) immunohistochemical (IHC) staining. Patients who did not improve within 3 months and further reevaluations did not determine the etiology, were placed in the unknown category. Massive effusion was defined as the liquid volume occupying more than half of the hemithorax.

Using the SPSS-16 software, independent samples t-test was used for continuity variable and chi-square when comparing the frequency in different group. P values less than 0.05 were considered significant.

Results

During the study period, 327 cases comprising 172 (52.6%) males and 155 (47.4%) females were considered. The mean age of the patients was 63.4±18.4 years (men: 64.5±18.2, women: 62.1±18.6, P=0.25). The age range was from 12 to 91 years.

Malignancy and tuberculosis comprised more than 50% of the studied cases (table 1). The mean age of patients and frequency of massive effusion was not significantly different between the malignant and tuberculosis cases (P>0.05) (table 1).

From 48 cases with tuberculosis, pleural biopsy was performed in 37 (77%) and granuloma was reported in 33 (68.8%). Ziehl-Neelsen staining of the pleural fluid sediments was negative in all except one case. In 14 (29%) out of 48 tuberculosis cases, diagnosis of tuberculosis was confirmed according to staining of sputum and bronchial washing in patients who had concomitant chronic infiltration on CXR and MN dominant exudative pleural effusion.

Among 125 cases with malignant pleural effusion, both cytopathology and histopathology were not conclusive for 42 (33.6%) of metastatic pleural effusion (table 2).

In these cases, the effusion was linked to metastasis because of malignancy in any part of the body, evidence of lung metastasis, and excluding other cause of effusion. Malignant cell were significantly more frequently observed in massive malignant effusion (P=0.001). Metastasis from lung cancer made 48 (38.4%) of malignant cases. The origin of metastasis was not determined in 44 (35.2%) patients (table 3).

Among 5 cases with pleural effusions during pregnancy, 2 cases were with peripartum hemothorax treated with chest tube insertion. We

Table 1: Distribution of exudative effusion etiology in studied patients

Disease	Frequency (N, %)	Age (years±SD)	Sex (N, %)		Fluid volume (N, %)	
			Male	Female	Massive	Non-massive
Malignancy	125 (38.2)	66.9±14.2	59 (47.2)	66 (52.8)	73 (58.4)	52 (41.6)
Tuberculosis	48 (14.7)	63.9±19.6	22 (45.8)	26 (54.2)	20 (41.7)	28 (58.3)
Infections	45 (13.8)	56.8±21.5	28 (62.2)	17 (37.8)	15 (33.3)	30 (66.7)
Lymphoma	12 (3.7)	45.3±24.5	8 (66.7)	4 (33.3)	8 (66.7)	4 (33.3)
PTE	11 (3.4)	66.3±14.1	8 (72.7)	3 (27.3)	1 (9.0)	10 (91.0)
CABG	4 (1.2)	46.8±18.8	2 (50)	2 (50)	1 (25)	3 (75)
Pregnancy	5 (1.5)	28±5.3	0 (0)	5 (100)	2 (40)	3 (60)
CTD	10 (3.1)	58.9±13.8	7 (70.0)	3 (30)	5 (50)	5 (50)
Hydatid cyst	4 (1.2)	52.2±36.7	4 (100)	0 (0)	2 (50)	2 (50)
Mesothelioma	5 (1.5)	77±12.3	3 (60)	2 (40)	5 (100)	0 (0)
Unknown	23 (7)	67.7±14.8	11 (47.8)	12 (52.2)	9 (39.1)	14 (60.9)
Not follow up	29 (8.9)	72.7±13.7	16 (55.2)	13 (44.8)	5 (17.2)	24 (82.8)
Miscellaneous	6 (1.8)	50.7±21.7	4 (66.7)	2 (33.3)	4 (66.7)	2 (33.3)
Total	327 (100)	63.3±18.5	172 (52.6)	55 (47.4)	150 (45.9)	177 (54.1)

Infection: Parapneumonia and empyema; PTE: Pulmonarythromboembolism; CABG: Coronary artery bypass grafting; CTD: Connective tissue disease

Table 2: Description of diagnostic criteria in metastatic effusion

Type of malignancy	Cytopathology (N, %)		Biopsy (N, %)			Metastatic without pleural yield for malignancy (N, %)	Fluid volume (N, %)	
	Malignant	Non-malignant	Malignant	Non-malignant	Not taken		Massive	Non-massive
Lung	22 (45.8)	26 (54.2)	23 (47.9)	9 (18.8)	16 (33.3)	16 (33.3)	29 (60.4)	19 (39.6)
Breast	10 (58.8)	7 (41.2)	7 (41.2)	2 (11.8)	8 (47.1)	5 (29.4)	9 (52.9)	8 (47.1)
GI.M	22 (28.6)	5 (71.4)	2 (28.6)	3 (42.9)	2 (28.6)	5 (71.4)	2 (28.6)	5 (71.4)
GU.M	1 (16.7)	5 (83.3)	3 (50)	0 (0)	3 (5)	3 (50)	2 (33.3)	4 (66.7)
H&N	0 (0)	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.6)	1 (33.3)	2 (66.7)
Unknown	22 (50)	22 (50)	28 (63.6)	3 (6.8)	13 (29.5)	11 (25)	30 (68.2)	14 (31.8)
Total	57 (45.6)	68 (54.4)	64 (51.2)	18 (14.4)	43 (34.4)	42 (33.6)	73 (58.4)	52 (41.6)

GIM: Gastrointestinal malignancy; GUM: Genitourinary malignancy; H&N: Head and Neck malignancy; Unknowns: Metastasis with unknown origin

were unable to find specific causes of effusion in 2 cases with preeclampsia and one case in the third month of pregnancy.

There were 6 (1.8%) miscellaneous cases of pleural effusion among our patients (table 4).

In 9 (2.7%) out of the total number of patients, diagnosis of chylothorax was made. Lymphoma, metastasis from unknown origin, empyema, and post coronary artery bypass grafting (CABG) comprised of 3, 1, 1, and 4 cases of chylothorax, respectively. Pseudochylothorax was observed in 4 (1.2%) cases (two cases of rheumatoid arthritis, one case of TB-PLE, and one case of ruptured hydatid cyst into pleural space).

Among 12 patients who were diagnosed as lymphoma, histopathologic report was lymphocytic hyperplasia in 4 and non-specific lymphocytic inflammation in 8 cases. All cases of lymphoma had systemic involvement and the final diagnosis was confirmed by lymph node biopsy in 10 and bone marrow biopsy in 2 cases.

Among 10 cases with rheumatologic pleural effusion, chronic eosinophylic pleuritis was reported in one case. Because of prolonged asthma in association with peripheral eosinophylia, Churg-Strauss vasculitis was diagnosed in this special case.

Diffuse and concentric pleural thickening on CT scan, in association with mesothelial hyperplasia in biopsy, were constant finding in all except for one case of mesothelioma. IHC staining confirmed mesothelioma in an 82-year-old woman.

Serologic test (ELISA) was positive in three out of four cases with ruptured hydatid cyst. Ruptured hydatid cyst was confirmed on surgical samples of 2 cases.

Discussion

In our study, the most common cause of pleural effusion was malignant effusion. Tuberculosis was in the second place. These findings are consistent with those from Isfahan (central Iran),[6,10] however, they are in contrast

Table 3: The origin of pleural metastasis in the studied patients

Type of malignancy	Frequency (N, %)	Sex (N, %)		Age (years±SD)	Fluid volume (N, %)	
		Male	Female		Massive	Non-massive
Lung	48 (38.4)	29 (60.4)	19 (39.6)	68.9±12.8	29 (60.4)	19 (39.6)
Breast	17 (13.6)	0 (0)	17 (100)	54.5±11.9	9 (52.9)	8 (47.1)
GI.M	7 (5.6)	4 (57.1)	3 (42.9)	67.4±11.3	2 (28.6)	5 (71.4)
GU.M	6 (4.8)	4 (66.7)	2 (33.3)	62.5±20.8	2 (33.3)	4 (66.7)
H&N	3 (2.4)	3 (100)	0 (0)	53.3±25.5	1 (33.3)	2 (66.7)
Unknown	44 (35.2)	19 (43.2)	25 (56.8)	71.4±12.0	30 (68.2)	14 (31.8)
Total	125 (100)	59 (47.2)	65 (52.8)	66.8±14.2	73 (58.4)	52 (41.6)

GIM: Gastrointestinal malignancy; GUM: Genitourinary malignancy; H&N: Head and Neck malignancy; Unknowns: Metastasis with unknown origin

Table 4: Miscellaneous cause of pleural effusion

Disease	Frequency (N, %)	Sex (N, %)		Age (years±SD)	Fluid volume (N, %)	
		Male	Female		Massive	Non-massive
Myelofibrosis	1	1	0	62	1	0
Multiple myeloma	1	1	0	60	0	1
Lymph edema	1	0	1	51	1	0
Hypothyroidism	1	0	1	23	1	0
Onicolysis	1	1	0	51	0	1
Thymoma	1	1	0	28	1	0
Total	6	4	2	50.7	4	2

to studies from areas with high incidence of tuberculosis (Ethiopia, Nepal, India)[2,8] as well as a study conducted in Mashhad (north east of Iran).[9] The incidence of tuberculosis in Mashhad is near to our region. In contrast to our region, Mashhad is a great host of travellers. The prevalence of tuberculosis in Isfahan is lower than our region. Among 107 cases with exudative pleural effusion reported from Isfahan, TB-PLE was ranked in the third place after malignancy and parapneumonia, and most of the patients with TB-PLE (73%) were Afghan refugees.[10] Qatar is a country with low prevalence of tuberculosis, but tuberculosis was the most common cause of pleural effusion in a study conducted by Khan et al.[7] An interesting point in their study was a significant number of immigrants who came from countries with high prevalence of tuberculosis. Thus, higher frequency of TB in the studied populations can justify the predominance of TB-PLE. The incidence of tuberculosis in South Khorasan is reported as 25 per 100,000 in 2005.[11]

Parapneumonic and empyema combined, was the third common cause of pleural effusion in our study. The mean age of our patients in this group was approximately 56 years old. This condition is reported both in young and old ages by other researchers.[1,2,7] We had one patient with concomitant presence of chylothorax and empyema; a special condition that is extremely rare.

The mean age of tuberculosis patients in our study was much higher than those reported from areas with high incidence of tuberculosis,[2] as well as from areas such as USA[5] and Qatar[4] with the prevalence of tuberculosis lower than Iran. The mean age of our patients was found to be higher than those reported from Mashhad and Isfahan.[9,10] At present, it seems that TB-PLE more commonly arise from reactivation than primary infection in our region.

Regarding the insignificant difference in the age and frequency of massive pleural effusion between malignant-related pleural effusion and TB-PLE in our study, one should differentiate malignant from TB-PLE. Our results had more emphasis on massive pleural effusion and was not specific to malignancy.[12]

Granuloma was observed in 69% of TB-PLE in our study. More than 95% of pleural granulomas are due to tuberculosis.[13] The diagnostic yield of closed needle pleural biopsy concomitant with pleural fluid cytopathology was 66.4% for malignant pleural effusion. The sensitivity of closed needle pleural biopsy for malignant effusion is reported from 7% to 72% and combined cythopathology and biopsy increased the diagnostic rate.[6]

Lymphoma, PTE, mesothelioma, rheumatologic disorders, multiple myeloma, thymoma, myelofibrosis, and hypothyroidism are labeled as causes of pleural effusion in a limited number of our patients. Reports about these types of pleural involvement

are rare.[6,7,14-17] Hypothyroid related pleural effusions are usually transudative,[18] however, may have characteristic between transudative and exudative or occasionally exudative.[19] The presence of eosiniphylic, lymphocytic infiltration foci, or mesothelial hyperplasia on pleural biopsy study can be the key for further investigations on Churg-Strauss vasculitis, lymphoma and mesothelioma, respectively.

We had 52 (15.9%) cases of unexplained pleural effusion with the mean age of approximately 70. Thoracoscopic study of 59 patients with unexplained exudative pleural effusion revealed that metastatic adenocarcinoma ranked first and TB in fourth place.[20] A study conducted about the role of Epstein–Barr virus (EBV) in patients with undiagnosed pleural effusion claimed that 59% of such cases were EBV-polymerase chain reaction positive.[21]

Among pregnant women, 2 cases were presented with hemothorax shortly after vaginal delivery. The author believes that at the time of forced vaginal delivery, the congested pleural vessels may have ruptured; creating hemothorax.[22] We had 3 cases of undiagnosed pleural effusion during pregnancy. Some believe that the majority of pleural effusions during pregnancy are related to PTE.[23]

We encountered four cases of ruptured hydatid cyst into the pleural space. One was complicated with cholesterol pleurisy. There are reports about rupturing of liver or pulmonary hydatid cyst into pleural cavity.[24,25] Hydadic cyst complicated with cholesterol pleurisy is not reported till now.

We had certain restrictions in using advanced diagnostic tools, which may have reduced the accuracy of our results. However, this limitation could not change the essence of the outcome.

Conclusion

It is concluded that in our region, TB-PLE tends toward the elderly and the expression of malignant cells in the massive malignant effusion fluid is more likely.

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Conflict of Interest: None declared.

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