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ORIGINAL ARTICLE

Histological Pattern of Neoplasm Resulting Malignant Pleural Effusion among the Patients Admitted in NIDCH, Bangladesh

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Abstract:

Background: *Malignant pleural effusion is a common findings in chest hospital like NIDCH. It may be due to pleural malignancy but mostly due to metastasis. Metastasis mostly occur from bronchial carcinoma but it may occur from any other organs. Sometimes primary site of malignancy is not known. Findings of specific type of malignant cells in pleural effusion or pleural biopsy examination may give information regarding histological type of malignancy. There is no available statistics regarding etiologies and histological type resulting malignant pleural effusion in NIDCH as well as Bangladesh.* ***Aim:*** *To detect the most common type of histological pattern of neoplasm resulting malignant pleural effusion. Which may be an important information for diagnosis and management of malignant pleural effusion.* ***Methods:*** *This was a crass sectional retrospective study, was carried out in the department of respiratory medicine of National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka, during the period of July 2010 to June 2011. Total 69 patients were enrolled consecutively. The information's regarding malignant pleural effusion was collected from each patient in whom the diagnosis was confirmed by pleural biopsy (done by Abram's punch biopsy needle) and presence of malignant cells in pleural fluid.* ***Results:*** *Figure II shows that among 69 patients 51(73.91%) patients diagnosed as Adeno-carcinoma and 7(10.15%) patients diagnosed as Squmous cell carcinoma. Lymphoma 4(5.8%) and small cell carcinoma 4 (5.8 %). So malignant pleural effusion is mostly due to adenocarcinoma.* ***Conclusions:*** *So, most common cause of Malignat Pleural effusion is adeno-carcinoma, it may be due to metastasis from bronchial carcinoma or any other part of the body.*

Key words: *Malignant pleural effusion, Adeno-carcinoma.*

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Introduction:

Malignant pleural effusions (MPEs) are a troublesome and debilitating complication of advanced malignancies. MPEs are one of the commonest causes of pleural effusion in our neighbouring country like Myanmar. According to the hospital statistics, approximately 500 patients with various causes of exudative pleural effusion were admitted to Chest Medical Ward, Yangon General Hospital in every year. The commonest causes are tuberculosis and malignant pleural effusions. Malignant pleural effusions are most commonly associated with cancer of the breast, lung, gastrointestinal tract, ovary, and with lymphomas. Malignant effusions also occur with pleural metastases, direct extension of lung cancer

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to the pleura, impaired lymphatic drainage from mediastinal tumors without direct pleural invasion (particularly in lymphoma). The mechanisms that cause the effusions include increased capillary permeability that allows fluid leakage into the pleural space, decreased oncotic pressure that normally holds fluid in the intravascular space due to hypoalbuminemia, increased negative pressure in the pleural space as a result of atelectasis [1]. A pleural effusion is a condition where abnormal fluid builds up in the pleural space. The accumulation of pleural fluid can usually be explained by increased pleural fluid formation or decreased pleural fluid absorption, or both. Increased pleural fluid formation can result from elevation of hydrostatic pressure, decreased colloid osmotic, increased capillary permeability, passage of fluid through openings in the diaphragm, or reduction of pleural space pressures. Decreased pleural fluid absorption can result from lymphatic obstruction or from elevation of systemic venous pressures resulting in impaired lymphatic drainage (e.g., superior vena cava obstruction syndrome). In patients with MPE, metastasis to pleural spaces may causes significant shifts or fluid imbalance from derangements in the Sterling forces that regulate the reabsorption of pleural fluid [2] . That derangement may cause MPE. MPE is caused by cancer that grows in the pleural space. It can be a complication of virtually any malignancy. The pleura is involved in neoplastic disease more commonly through metastasis than through primary tumours. Lung and breast cancers are the leading causes of metastatic disease to the pleura. Other less common causes are hematologic (e.g., lymphoma, leukemia), ovarian, mesothelioma and gastrointestinal tumours. Cytological examination of the pleural fluid is positive in more than 50% of cases with pleural involvement. Primary and metastatic pleural neoplasms, and non-neoplastic pleural diseases, can have similar clinical, radiographic and gross features. However, treatments and prognoses of these diverse pleural conditions vary greatly. Accurate diagnosis of pleural disease is therefore extremely important, and histological interpretation of pleural biopsies is vital to rendering an accurate diagnosis. Smaller biopsies contribute to the difficulties in accurately characterizing pleural lesions, and immunostains are frequently employed in their assessment[3].

Malignant pleural effusion is a common and debilitating complication of advanced malignant diseases. This problem seems to affect particularly those with lung and breast cancer, contributing to the poor quality of life. Approximately half of all patients with metastatic cancer develop a malignant pleural effusion at some point, which is likely to cause significant symptoms such as dyspnea and cough. Evacuation of the pleural fluid and prevention of its reaccumulation are the main goals of management[4]. Tumor markers (e.g., carcinoembryonic antigen) are not specific enough to be recommended routinely in establishing the diagnosis. Immunocytometry has been used to establish the diagnosis of lymphoma and has been helpful in cases of idiopathic effusions when conventional techniques were non-diagnostic[5]. Quality of life with MPE is often compromised due to debilitating symptoms like shortness of breath, dry cough, pain, feeling of chest heaviness, inability to exercise and malaise (feeling unwell). The diagnosis of malignant pleural effusion as well as finding of the exact location of the pleural effusion, or plan treatment will be based on physical examination, chest x-ray, Computed tomography scan, ultrasound and thoracentesis. The presence of fluid in the normally negative-pressure environment of the pleural space has a number of consequences for respiratory physiology. Pleural effusions produce a restrictive ventilatory defect and also decrease the total lung capacity, functional residual capacity, and forced vital capacity [6]. They can cause ventilation-perfusion mismatches and, when large enough, compromise cardiac output. Evaluation of exudative pleural effusion usually includes thorough history taking, complete clinical examination, appropriate blood tests, radiographs, studies of pleural fluid and needle biopsy of pleura using Abram's pleural biopsy needle. However following these procedures some patients still have undiagnosed condition and the clinical management of these cases is controversial. The initial step of the investigation is the distinction between transudates and exudates, as this gives an indication of the pathophysiologic mechanisms, the differential diagnosis and the need for further investigations. Various tests can be done on pleural fluid to determine the cause of a pleural effusion. If a malignant effusion is suspected, the fluid will be sent for cytology analysis. About 50% to 60% of

cytology tests on pleural fluid are positive for malignancy in patients already known to have cancer. At least 250 mL of pleural fluid is needed for a proper cytologic examination. Other tests done on pleural fluid include protein, LDH, glucose, pH, and cell counts. If a patient has cancer, but the pleural cytology is negative and there is no other obvious cause of the effusion (as will occur in about 25% of cases), thoracoscopy can be performed to confirm the diagnosis through a pleural biopsy of abnormal areas of the pleurae under direct visualization. Thoracoscopy is diagnostic in at least 90% of patients with malignant pleural effusion.[1] In a randomized controlled trial, Abrams' biopsy correctly diagnosed malignancy in eight of [7] patients (sensitivity 47%, specificity 100%, negative predictive value 44%, positive predictive value 100%).[8] Because of their high sensitivity in identifying exudates, the criteria proposed by Light et al8 have become the standard method for making the distinction. The classic work of Light and colleagues demonstrated that 99% of pleural effusions could be classified into two general categories: transudative or exudative .A basic difference is that transudates, in general, reflect a systemic perturbation, whereas exudates usually signify underlying local (pleuropulmonary) disease. The 'Light' criteria include a pleural fluid to serum protein ratio greater than 0.5, a pleural fluid to serum LDH ratio greater than 0.6 and a pleural LDH concentration more than two thirds normal upper limit for serum. If any one of these critical values is exceeded, the effusion is exudates. The original study of Light and colleagues had a diagnostic sensitivity of 99% and specificity of 98% for an exudates. In a study by Alemán C et al, 1014 consecutive pleural effusion patients were treated over a 12- year period, of whom 346 were diagnosed as having an idiopathic or malignant aetiology. Eighty-three patients with idiopathic effusions and 263 with malignant effusions were included. Idiopathic pleural effusion resolved in 47 patients, improved in 20 and persisted in 16. Biochemical pleural fluid analysis did not predict these outcomes. A history of neoplasm, chest X-ray and CT features, as well as additional examinations according to clinical findings, established a diagnosis or suspicion of malignancy in 256 (97.7%) of the 263 patients who received a diagnosis of malignant effusion. Diagnostic thoracoscopy was helpful in seven patients in whom malignant disease was strongly suspected, despite the absence of other pathological findings.[9] In this study they report their experience with 73 patients with confirmed diagnosis of MPE and discuss the clinical features, radiological findings, biochemical, cytological and microbiological analysis of pleural fluid, hematological and biochemical profiles of serum and positivity rates of blind pleural biopsy in these patients. We also analyzed the likelihood ratios of some of the important presenting features in this study. The objective of the study was to review the natural history of patients with a malignant pleural effusion but without obvious evidence of a primary lesion and to assess the value of investigations to confirm the diagnosis of malignant pleural effusion. They also like to report other findings such as age, gender, clinical features, nature and microscopic examination of pleural fluid, positivity rate of blind pleural biopsy results in patients diagnosed with bronchogenic carcinoma in the Chest Medical Department in Yangon General Hospital, Myanmar.

Material and Method:

This was a crass sectional retrospective study, was carried out in the department of respiratory medicine of National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka, during the period of July 2010 to June 2011. Total 69 patients were enrolled consecutively who was confirmed as a case of malignant pleural effusion. The information regarding malignant pleural effusion was collected from each patient in whom the diagnosis was confirmed by pleural biopsy (done by Abram's punch biopsy needle) and presence of malignant cells in pleural fluid. Exclusion criteria were 1) Multiple pathology of pleural effusion.2) Patients with more than one etiology of pleural effusion were excluded. 3) Patient's refusal Written informed consent was obtained from patient. Before requesting consent, the individual was explained in an understandable language about the aims of the study, the methods of conduct, expected duration of subject participation, benefits, foreseeable rights or discomfort, the extent of confidentiality, extent of investigators responsibility, provision of medical services, the right to refuse to participate and withdraw from

the study without affecting further medical care. Detailed history, thorough physical examination, radiological findings, haematological and biochemical findings were recorded in the proforma. Pleural aspiration and biopsy was performed on all patients after obtaining the written consent. Macroscopic examination, cytological, microbiological and biochemical analysis of pleural fluid were performed in all patients.

Results:

Among 69 patients 51(73.91%) patients were diagnosed as Adeno-carcinoma and 7(10.15%) patients were diagnosed as Squmous cell carcinoma. Cases of Lymphoma were 4(5.8%) and small cell carcinoma 4 (5.8 %). So malignant pleural effusion is mostly due to adenocarcinoma. Pleural effusion due to lymphoma were within the younger age group.

Table-I

Age group (years)	n=69	%
11 years to 25 years	3	4.35
26 years to 40 years	4	4.71
> 40 years	62	89.86
Total	69	100.0

Table-I: Age of the respondents in malignant pleural effusion. Most of the cases of malignant pleural effusion in more than 40 (forty) age group of patients as most of the malignancy including bronchial carcinoma occurs in this age group. All three cases of malignant pleural effusion in 11 years to 25 years were due to lymphoma. In the same way most of the malignant pleural effusion due to small cell carcinoma in earlier age group (26 years to 40 years age group). Malignant pleural effusion due to metastasis from extra pulmonary sites

Fig.-1: Sex distribution among the respondents suffering from malignant pleural effusion. Malignant pleural effusion was more common in male than female as bronchial carcinoma was more common in male respondent.

Fig.-2: Type of malignancy among the respondents suffering from malignant pleural effusion (n = 69). Malignant pleural effusion due to metastatic adenocarcinoma was significantly higher than any

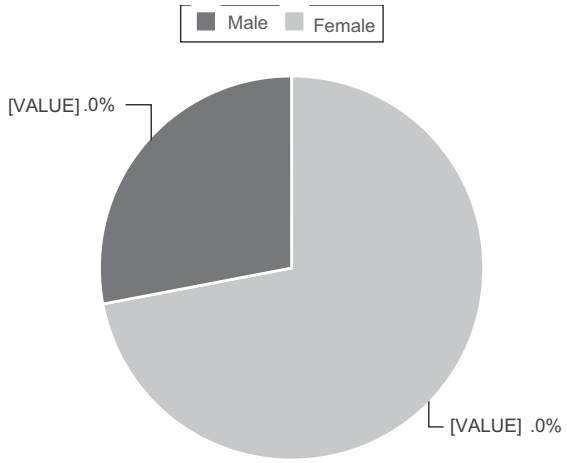

Fig.-1:

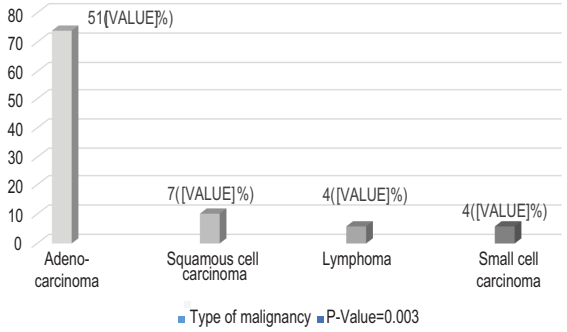

Fig.-2:

other histological type. As p-value less than 0.05 (typically ≤0.05) is statistically significant. Among the histological type of bronchial carcinoma, adeno-carcinoma are peripherally situated and they have tendency to metastasis in distant sites including pleura.

Table-II

Primary site	Total number	%	P value
Bronchial carcinoma	42	82.35	
GIT	2	3.92	
Breast	3	5.88	0.003
Primary site, not known	4	7.84	

Table-II: Primary sites of metastatic adenocarcinoma. Most common primary sites are bronchial carcinoma. As p-value less than 0.05 (typically ≤ 0.05) is statistically significant. Among the adenocarcinoma few have metastasis from extra-pulmonary sites like GIT, breast etc.

Discussion:

MPEs were more common in male than female. It may be related to chronic smoking history in male patient. It is obvious that incidence of MPEs is significantly higher in patients with age above 40 and those with history of heavy smoking. 82.2% of malignant pleural effusions are heavy smokers or ex heavy smokers. Heavy smoking is the primary cause of the high prevalence of this disease. Dyspnea and cough were significant symptoms in one study, which is consistent with our finding. In our study, breathlessness, cough, chest pain, weight loss, loss of appetite, and sputum production are common symptoms of malignant pleural effusion. Less than 50% of patient developed fever. Haemoptysis is an uncommon symptom of MPE (20.5%). According to the likelihood ratio calculation, chest pain and pulmonary consolidation are the important features for haemoptysis. These signs should guide in clinical teaching. Other features are not positively associated to each other in likelihood ratio calculation. MPEs were more common on left side and the reason of side predilection is unknown. Half of the pleural aspirates of MPEs were blood stained in their morphologic appearances. Mean ADA activity (SD) in malignant pleural effusion was general low. In our previous report, mean ADA activity of TB pleural effusion was significantly higher than malignant group (73.91 Vs 23.83)[10,11]. There was a linear correlation among biochemical parameters of pleural fluid such as protein and LDH. This can be concluded that production of all biochemical parameters in abnormal pleural fluid are related to single aetiology probably by inflammatory process. It is also suggested that pleural fluid levels of protein and LDH are partially depends on their plasma values and need measuring the plasma levels at the same time to get more accurate result. M Keshmir stated that pleural fluid cholesterol can be used to differentiate tuberculous from malignant pleural effusion[11]. There was no association between MPEs and any WBC subsets of peripheral blood. Although a number of tests have been proposed to differentiate pleural fluid transudates from exudates, the tests first proposed by Light et al have become the criterion standards [8] . The fluid is considered exudates if any of the following apply: Ratio of pleural fluid to serum protein greater than 0.5 and ratio of pleural fluid to serum lactate dehydrogenase (LDH) greater than 0.6 or pleural fluid LDH greater than two thirds of the upper limits of normal serum value. In our study, the nature of MPE was that of an exudates which is easily demonstrable by applying the Light criteria. Light RW et al also found that pleural fluid glucose level below 60 mg/dl (3.3 mmol/l) suggests MPE, TPE or lupus pleuritis. In our study mean pleural fluid glucose concentration was 4.8 mmol/l which is not consistent with the finding of Light et al. Most of the patients with MPE were anaemic (Mean haemoglobin concentration was 10.8 ± 1.65 g/dl) which are considered as multiple aetiology such as anaemia of chronic disease, depression, lack of nutrition and dietary deficiency. No leukocytosis is noted. Mean ESR was high at 62.23 which reflects inflammatory state in general. It has no diagnostic value for any specific disease. International Journal of Collaborative Research on Internal Medicine & Public Health Vol. 4 No. 5 (2012) 769 Diagnostic pleural aspiration and pleural biopsy could be performed by a single session of procedure. Since it is a blind procedure and in patients with non-informative pleural fluid and pleural biopsy examinations, the procedure needed to be repeated. Cagle PT, Allen TC pointed out that smaller biopsies contribute to the difficulties in accurately characterizing pleural lesions, and immunostains are frequently employed in their assessment. But in our study, we could not perform special staining procedures of the histology slides because of limited facilities. The positivity rate of first session of pleural biopsy was 65.7 % of MPE in this study. The second and third biopsy sessions were needed for the rest of patients. Repeat performance of pleural biopsy is obviously an inconvenience to the patients and also consumes a certain amount of medical resources. Closed pleural biopsy is a fairly blind procedure rendering it into a diagnostic procedure with less than desired positivity rate. Pleuroscopy resolves the diagnostic problem but the procedure requires more material resources and expertise . 8 patients (11.1%) were diagnosed only by identification of malignant cells in the pleural fluid cytology because subsequent biopsies revealed chronic nonspecific pleuritis. They were diagnosed by pleural fluid cytology and exact histological type of malignancy may not be

identified in the cytology report. However, 64.4% of overall MPEs revealed positive pleural fluid cytology for malignant cells which is a substantial number to diagnosed MPEs even though exact histology cell type is difficult to identify. This finding supports that statement about 50% to 60% of cytology tests on pleural fluid are positive for malignancy in patients already known to have cancer[1] . In a randomized controlled trial, Abrams' biopsy correctly diagnosed malignancy in eight of 17 patients (sensitivity 47%, specificity 100%, negative predictive value 44%, positive predictive value 100%).[7] In our study, 88.9% of patients were correctly diagnosed malignancy but needed to be repeated in 23.2%. In our study, metastatic adenocarcinoma carcinoma was the commonest histologically identified cell type. The origin is considered mainly from bronchogenic carcinoma.

Conclusion:

Pleural fluid analysis have an important contribution for investigation of patients with pleural effusion. Repeated pleural biopsy procedures will be necessary if first session failed to fetch the definitive tissue diagnosis. Pleuroscopy is recommended procedure for tissue diagnosis in MPEs. Most common cause of malignant pleural effusion is due to metastatic adeno-carcinoma. Most of the metastatic adenocarcinoma are due to bronchial carcinoma. Male are commonly affected by malignant pleural effusion. In few cases of adenocarcinoma primary sites might not be known, in those cases PET/CT could be done for further evaluation.

References:

1. Malignant Pleural effusion:Atrium Clinical Update Web site. Available at www. atriummed.com. Accessed December 2002.
2. Joe B. Putnam Jr. Malignant pleural effusion. Surg Clin N Am. 2002:82, 867-883.
3. Cagle PT, Allen TC. Pathology of the pleura: what the pulmonologists need to know. Respirology. 2011 Apr;16(3):430-8. doi: 10.1111/j.1440-1843.2011.01957.x.
4. Neragi-Miandoab S. Malignant pleural effusion, current and evolving approaches for its diagnosis and management. Lung Cancer. 2007 Feb;55(2):253-4.
5. Raed A Dweik. Immunocytometry and gene rearrangement analysis in the diagnosis of lymphoma in an idiopathic pleural effusion. Am Rev Respir Dis.1992: 145: 209-211.
6. Chalhoub M, Cruz AA, Marcilio C, Netto MB, Effects of pneumothorax or pleural effusion on pulmonary function. Thorax. 1985:40: pp 60-65. International Journal of Collaborative Research on Internal Medicine & Public Health V1985;4 (5):770.
7. Maskell NA, Gleeson FV, Davies RJ . Standard pleural biopsy versus CT-guided cuttingneedle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. Lancet. 2003 Apr 19;361(9366):1326-30.
8. Light RW, MacGregor MI, Luchsinger PC (1972). Pleural effusions: The diagnostic separation of transudates and exudates. Ann Interm Med ,1972;77:507.
9. Alemán C, Sanchez L, Alegre JQJM et al. Differentiating between malignant and idiopathic pleural effusions: the value of diagnostic procedures. QJM. 2007;100(6): 351-9.
10. Zay Soe, Wana Hla Shwe, Soe Moe. Value of pleural fluid Adenosine deaminase in Tuberculosis, International Journal Publication-International Journal of Collaborative Research on Internal Medicine and Public health(IJCRIMPH) 2010;2(3):32-48.
11. M Keshmir, Use of cholesterol to differentiate tuberculous from malignant pleural effusion. Med J Iran Hosp, 2006:Vol 3 No1 Pages 34-37 2. Muhammad Abdul Hadi, et al. Knowledge And Perception Of Breast Cancer Among Women Of Various Ethnic Groups In The State Of Penang, Malaysia: A Cross Sectional Survey. Med Princ Pract. 2010;19(1):61-7.