

Clinico- pathological profile and course of malignant pleural effusion in a tertiary care teaching hospital in western U.P. with special reference to lung cancer

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ABSTRACT

Background: Malignant pleural effusion is a major clinical problem associated with primary and metastatic pleural malignancies. Pleural effusions from an unknown primary are responsible for 7-15% of all malignant pleural effusions. Presence of malignant pleural effusion puts the patient in advanced stage and renders the prognosis as poor. **Aim:** In this study we intend to find out the incidence of malignant pleural effusion, its aetiology and clinical course in patients attending a tertiary care teaching hospital. **Results:** A total of 308 patients were included in this study. A majority of the patients were in age group 50- 70 years (median age = 58.8 years; range 32- 85 yrs). Male to female ratio was 2.5:1. The major primary cancers were lung cancer (135), lymphoma (40), breast cancer (36), female genital tract (30) gastrointestinal (21), and others (8). In 38 cases primary remained unknown. The yields of pleural fluid cytology, blind pleural biopsy, CT/USG guided pleural biopsy and thoracoscopy were 60%, 49%, 76% and 91% respectively. Chemical pleurodesis yielded complete response in 80%, incomplete response in another 13% patients. Only 136 (44%) cases could be followed up for minimum of 6 months. A majority of them (95, 69.85%) died. **Conclusion:** We conclude that malignant pleural effusion is a commonly misdiagnosed medical entity. Lung cancer is the commonest cause. Despite all efforts, in about 15% of the cases, primary remains undiagnosed. Thoracoscopy/pleuroscopy is a cost effective measure for diagnosis. Chemical pleurodesis provides expected results but mortality remains high.

KEY WORDS: Diagnosis, etiology, malignant pleural effusion

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INTRODUCTION

Many infectious, benign, and malignant diseases can cause pleural effusion.^[1] Approximately one-fourth of all pleural effusions and 30 – 70% of all exudative effusions in hospital settings are secondary to cancer.^[1] Lung cancer is the most common metastatic tumor to the pleura in men, while breast cancer is the most common tumor in women.^[2] Together, both cancers account for 50 – 65% of all malignant effusions. Lymphomas and tumors of the genitourinary and gastrointestinal (GI) tracts account for a further 25%.^[2,3]

The incidence of pleural effusion in Hodgkin's disease and non-Hodgkin's lymphoma is about 7 – 16%. Pleural effusions from an unknown primary are responsible for 7 – 15% of all malignant pleural effusions.^[3] In patients with cancer, only 50 to 60% of all effusions are positive on first thoracentesis.^[4,5] In approximately one-fourth of the patients with cancer and a recurrent pleural effusion, malignant cells may not be found on examination.^[5] Pleural biopsy, either blind or under ultrasonography (USG) or computed tomography (CT) guidance can help in a few patients. Medical thoracoscopy or pleuroscopy with pleural biopsy may yield higher results. The prognosis associated with malignant pleural effusion is generally poor. After the diagnosis of malignant pleural effusion, the mean survival is only 3 – 12 months.^[2,6]

MATERIALS AND METHODS

This prospective observational study included patients admitted, for pleural effusion, to the Department of

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Pulmonary Medicine and the referred patients of pleural effusion from other departments over a period of five years (July 2008 to June 2013). The presence of pleural effusion was confirmed with the help of a chest radiograph or ultrasonography. A few patients showed the presence of pleural effusion on a CT scan. The pleural fluid was aspirated and cytological evaluation was done along with other routine and special investigations, if needed. Three consecutive samples were sent for cytological examination. Blind pleural biopsy was done with a Cope's punch biopsy needle. On an average, three to four biopsy pieces were taken in each case. The USG or CT-guided biopsy of the pleura was done in still undiagnosed patients using a co-axial core biopsy needle. Thoracoscopy was performed with an Olympus pleurovideoscope on only 22 patients, as we acquired a medical thoracoscope in the final year of the study. Once suspected or confirmed for malignancy, the search for the primary was done with appropriate investigations. All the patients were further investigated for staging and metastasis.

Observations

A total of 1156 patients of pleural effusion were admitted to the Department of Pulmonology over the study period. Eight hundred and forty one (72.75%) samples were found to be exudative by the Lights' criteria. Three patients of lung cancer were suffering from transudative pleural effusion and another six patients had paramalignant effusion, they were excluded from the study. A total of 208 (18%) pleural effusion cases were found to be malignant. During the same period, 120 patients of different cancers with pleural effusion from different departments were also received. Eighteen patients were found to be suffering from paramalignant effusion and another two patients had transudative effusion, and were excluded from the study. Thus a total of 308 patients were included in the present study [Table 1].

A majority of the patients were in the age group of 50 – 70 years (mean age = 58.8 years; range 32 – 85 years). The male to female ratio was 2.5:1. A majority of the patients had symptoms of cough (91%), loss of appetite (87%), dyspnea (82%), weight loss (82%), and chest pain (57%), while a few also had hemoptysis (13%) and hoarseness of voice (12%) for a median duration of 4.5 months (range one to fourteen months). Out of 308 effusions, 172 were right sided, 115 left sided, and 21 were bilateral effusions. Pleural fluid cytology was positive for malignant cells in 185 (60%) cases and a definitive diagnosis could be achieved in 129 (42%) cases. Blind pleural biopsy was done in 108 and found positive in 53 (49%) cases. A CT/USG-guided pleural biopsy was performed in 93 cases and was positive in 71 (76%) patients. Thoracoscopy, which we acquired in the later part of the study, was performed on 22 patients and gave positive results in 20 (91%) patients.

The major primary cancers were lung cancer (135, 43.83%), lymphoma (40, 12.99%), breast cancer (36, 11.69%), cancer

of the female genital tract (30, 9.74%) and gastrointestinal tract (21, 6.81%), and others (8, 2.60%). Unknown primaries accounted for 38 (12.34%) cases. Among 135 lung cancer patients with pleural effusion, the most common cause was adenocarcinoma (62, 45.93%), followed by squamous cell carcinoma (19, 14.1%), small cell carcinoma (7, 5.18%), and poorly differentiated carcinoma (16, 11.85%). In 31 patients (22.96%), the type of lung cancer could not be confirmed. Out of 308, only 136 (44%) cases could be followed up for a minimum of six months. A majority of them (95, 69.85%) died. Only 41 (30.15%) patients were alive after six months [Table 1].

DISCUSSION

A total of 308 patients were included in this study. The major primary cancers were lung cancer (135, 43.83%), lymphoma (40, 12.99%), breast cancer (36, 11.69%), cancer of the female genital (30, 9.74%) and gastrointestinal (21, 6.81%) tracts, and others (8, 2.6%), which included three cases of mesothelioma, two cases of thyroid cancer, and one case each of soft tissue tumor of the chest wall, oral cavity cancer, and tongue cancer. Unknown primaries accounted for as many as 38 (12.34%) cases. Almost similar observations were made in various studies, where lung, breast, and hematological malignancies were the most common causes of malignant pleural effusion^[3,7-9] [Table 2].

Pleural effusion develops in a large number of patients with cancers. Pleural effusion results from obstruction of the pleural lymphatics through invasion, direct seeding of the pleura or obstruction of the hilar lymph nodes.^[8] The vascular endothelial growth factor (VEGF), a potent angiogenic mediator and promoter of endothelial permeability, is produced in large amounts by the diseased pleural tissue and is considered to play a role in the formation of malignant effusions and local tumor growth.^[5,8] Pleural effusion may initially present as a transudate, but it quickly develops into an exudate. The presence of a confirmed malignant effusion would upgrade the staging of a lung tumor of any size to stage T4 according to the tumor-node-metastasis (TNM) classification of the lung or M1 (metastasis to distant organs (beyond regional lymph nodes), suggestive of distant metastasis.^[10] The presence of an effusion should not be considered in the staging of rare cases, where the effusion remains a transudate and is consistently negative by cytological examination.^[11]

The most common symptom of malignant pleural effusion is dyspnea, resulting from the reduced compliance of the chest wall and diaphragm and reduced lung volume. In our study, a majority of the patients had symptoms of cough (91%), loss of appetite (87%), dyspnea (82%), weight loss (82%), and chest pain (57%), while a few also had hemoptysis (13%) and hoarseness of voice (12%) for a median duration of 4.5 months (range 1 – 14 months). A standard chest x-ray is the first radiological investigation and it can detect as little as 200 ml on the posterior–anterior

Table 1: Cases of malignant pleural effusion in different cancers and follow-up

Primary	Male	Female	Patients with PE or respiratory symptoms	Cancer patients who developed PE later on	Total (n=308)	No. of patients in follow-up	No. of patients alive after six months
Lung	123	12	126	9	135	65	10
Lymphoma	36	4	35	5	40	22	8
Unknown primary	32	6	34	4	38	17	7
Breast	0	36	3	33	36	11	8
Female genital tract	0	30	3	27	30	9	4
GI cancers	21	0	2	19	21	7	2
Other [#]	7	1	5	3	8	5	2
Total	219	89	208	100	308	136	41

[#]Mesothelioma (3 cases), thyroid cancer (2 cases), soft tissue tumor of chest wall, oral cavity cancer and tongue cancer (1 case each). GI: Gastrointestinal

Table 2: Etiologies of malignant pleural effusion in various studies

Tumor	Studies					
	Sprigs and Boddington (1968) ^[8]	Anderson et al. (1974) ^[8]	Johnston et al. (1984) ^[3]	Spanish study ^[7]	Combined nine series Sahn ^[9]	Present study (2009-2013)
Lung	275 (43%)	32 (24%)	168 (36%)	273 (37%)	641 (36%)	135 (44%)
Breast	157 (25%)	35 (26%)	70 (15%)	127 (17%)	449 (25%)	36 (12%)
Hematological	52 (8%)	34 (26%)	75 (16%)	74 (10%)	187 (10%)	40 (13%)
Female genital	33 (5%)	12 (9%)	38 (8%)	50 (7%)	88 (5%)	30 (10%)
GI cancer	41 (6%)	1 (1%)	28 (6%)	48 (7%)	42 (2%)	21 (7%)
Unknown	40 (6%)	8 (6%)	48 (10%)	72 (10%)	129 (7%)	38 (12%)
Others	36 (6%)	11 (8%)	45 (10%)	98 (13%)	247 (14%)	8 (3%)
Total	634	133	472	742	1783	308

GI: Gastrointestinal

view and 50 ml of pleural fluid on the lateral view. Most of our patients were diagnosed with the help of a standard PA view of the chest radiograph. A few patients (n = 12) with apparently no effusion on the chest radiograph, were diagnosed with the help of a CT scan of the thorax, when it was performed as a routine in suspected or confirmed lung cancer patients. Out of 308 effusions, 172 were right-sided, 115 left-sided effusion, and 21 were bilateral effusions. Computerized tomography can play a great role in distinguishing the malignant from the benign pleural disease, with high sensitivity and specificity. Nodular and parietal pleural thickening of more than 1 cm and mediastinal pleural involvement are highly suggestive of malignancy. In addition, malignant effusions tend to involve the entire pleural surface, while pleural calcifications suggest reactive pleurisy, (Leung's criteria).^[12] Magnetic resonance imaging (MRI) is useful in demonstrating tumor invasion into the chest wall and diaphragm. Positron emission tomography (PET) can identify malignant effusions, with 95% sensitivity and 80% specificity. A negative PET can be useful to rule out a malignant effusion.

A large number (n = 87, 28.24%) of patients of malignant pleural effusion (MPE) were prescribed with antitubercular treatment (ATT) (1 to 8 months). A recent study^[13] on wrong prescription of ATT in lung cancer patients found pleural effusion to be among the other factors in lung cancer patients who were likely to be prescribed ATT.

Thoracentesis and cytological examination of the pleural fluid is necessary to establish the diagnosis. In our study 122 (40%) samples were serous, 54 (17.5%)

were serosanguinous, 114 (37%) were hemorrhagic, and the remaining 18 (6%) samples were turbid to frank pus in appearance. The presence or absence of blood in the pleural effusions was not found to be useful in predicting cancer. On the contrary, in a study^[14] evaluating 390 patients who were diagnosed with cancer and underwent thoracentesis, 82.5% of the cytologically positive fluids were not bloody. Most malignant effusions have a high lymphocyte count and a considerable number have a high eosinophil count. A pH < 7.20 or glucose < 60 mg/dL suggests malignancy and renders a poor prognosis.^[6,8] Estimation of the ADA level of the pleural fluid is helpful in diagnosing and differentiating tubercular pleural effusions from malignant ones.^[15] In our study, the median ADA value in MPE was 24.12 ± 10.88 U/L, which was below the usual cut off of 40 U/L, for tubercular effusion.

In our study, pleural fluid cytology was positive for malignant cells in 185 (60%) cases. A maximum of three samples of pleural fluid were sent, 149 (80.5%) were positive on the first sample, while another 33 (17.8%) came positive on the second sample. The third sample helped in another three (1.6%). Definitive diagnosis could be achieved in 129 (42%) cases, and the rest showed a presence of malignant cells. Cytological evaluation has a wide range of reported diagnostic yield ranging from 62 to 90%. Percutaneous closed pleural biopsy was done in 108 and was positive in 53 (49%) cases. A closed needle biopsy of the pleura has been found to be very useful in cases of undiagnosed exudative pleural effusion,^[16] as it reaches a specific diagnosis in a majority of the cases, causes little morbidity or mortality, and can be performed

with little instrumental and manpower support. This is of importance in a developing country like India where the facilities of thoracoscopy and imaging-guided cutting needle biopsies are not easily available. CT/USG-guided pleural biopsy was performed in 93 patients and was positive in 71 (76%) patients. When cytology fails to establish a diagnosis, thoracoscopic pleural biopsy can be performed with video assistance as a method of choice to obtain a biopsy. Thoracoscopy, which we acquired in the later part of the study, was performed on 22 patients, and gave positive results in 20 (91%) patients. Thus, it played a significant role in the diagnosis of doubtful malignant pleural effusion. Pleuroscopy or video-thoracoscopy has a high sensitivity and specificity. It is a simple and safe method with a high diagnostic yield and with low complication rates.^[17] Bronchoscopy can also be performed in patients with hemoptysis or when a chest radiograph shows a mass lesion or collapse.

Lung cancer has caused the most cancer-related deaths in the world and makes up approximately one-third of the malignant pleural effusions among all causes.^[1-3] In our study 43.8% of the cases of MPE were found to be due to lung cancer. Approximately 15% of the lung cancer patients may have pleural effusion on initial presentation,^[18] but during the course of the disease, more than 50% of the patients develop pleural effusion. In the present study, a majority of the lung cancer patients with effusion had already consulted elsewhere before coming to us and there was a great lapse of time between the onset of symptoms and diagnosis of malignancy. In our study, a total of 135 lung cancer patients were found to be having pleural effusion, 89 were right-sided, 37 left-sided, and nine were bilateral effusions. Adenocarcinoma was the leading histological subtype associated with malignant pleural effusions of lung cancer.^[3,6] Less than 10% of small cell carcinoma patients developed pleural effusion. In the present study too, the most common cause was adenocarcinoma (n - 62, 46%) followed by squamous cell carcinoma (n - 19, 14%), small cell carcinoma (n - 7, 5%), and poorly differentiated carcinoma (n - 16, 12%). In 31 (23%) cases of lung carcinoma with malignant effusion, histological typing could not be confirmed owing to various causes. Seven patients were found to be suffering from paramalignant effusion and excluded from the study. The presence of anti-p53 antibodies was associated with development of pleural effusion in lung cancer patients.^[19] Irrespective of a positive cytology, the presence of pleural effusion in a lung cancer patient almost ruled out curative surgery.^[8,20,21] Irrespective of the size, site or type of lesion, the presence of malignant pleural effusion put a patient in the last stage and rendered poor prognosis.^[9,20] Recently, a serial DR-70 immunoassay was found, to identify the underlying malignancy in its early stages, especially lung cancer, as nonspecific pleuritis often turned into malignancy later on.^[22] Although it has no role in differentiating malignant from non-malignant pleural effusion.

The main goals of treatment for malignant pleural effusion are to decrease symptoms and improve the quality of life. The most common approaches are pleural effusion drainage and pleurodesis. For symptomatic and recurrent pleural effusion, drainage can be achieved by many different methods, including thoracentesis, small-bore catheter (SBC), tube thoracostomy, and video-assisted thoracoscopic surgery (VATS). Thoracentesis is the first management of choice, as it will also improve the breathlessness and indicate the rate of re-accumulation. We performed diagnostic and therapeutic thoracentesis of less than 1000 ml in 141 (46%) patients, as the fluid was mild to moderate in amount and the patients got relieved, while in another 107 (35%) patients, repeat thoracentesis was done. Repeat thoracentesis was not advised, as it could lead to complications such as adhesions^[8] and infections. For recurrent effusions, chemical pleurodesis was the method of choice, as it induced inflammation and fibrin deposition, and resultant adhesions between the layers of the pleura. Intercostal drainage was performed in 71 (23%) patients followed by chemical pleurodesis with tetracyclin, bleomycin or betadine in 55 of these patients, with satisfactory results, as 44 (80%) patients showed complete response, while another seven (12.73%) patients showed partial response. Only four (7.27%) patients failed, two of them were lost to follow-up, and two died. Even as Talc is the most common chemical used for pleurodesis, other agents, including bleomycin, tetracycline, betadine, and the like, have been used with comparable success. Pleurodesis is usually limited to patients with recurrent effusions resulting in respiratory distress, malignant effusions that are not responsive to chemotherapy, lung expansion to the chest wall after thoracentesis, and patients with a life expectancy longer than two to three months.^[23] A long-term indwelling pleural catheter is used when pleurodesis is not recommended.^[5,8] It provides immediate relief of dyspnea in over 90% of the patients, while allowing them to function independently at home. Complications include catheter dislodgment, infection, and loculation. An alternative approach, especially in patients with trapped lung or in adequate lung expansion, is a pleuroperitoneal shunt.^[8] This method can achieve effective palliation in most of the patients. However, complications such as shunt occlusion and infection are common. The prognosis associated with malignant pleural effusion is generally poor. After the diagnosis of malignant pleural effusion, a mean survival is only 3 – 12 months.^[6] In some series, the 30-day mortality was 29 – 50%. Survival depends upon the primary cancer and the patient's Karnofsky Performance Scale (KPS).^[8] The other bad prognostic factors are pleural fluid pH below 7.2, glucose level below 60 mg/dl, and high LDH. Out of 308, only 136 (44%) cases could be followed up for a minimum of six months. A majority of them (95, 69.85%) (Lung cancer - 55, lymphoma - 14, unknown primary - 10, breast cancer - 3, female genital tract cancer - 5, GI cancer - 5, others - 3) died. Only 41 (30.15%) patients (lung cancer - 10, lymphoma - 8, breast cancer - 8, unknown primary - 7, female genital

cancer - 4, and GI cancers - 2, and others - 2) were alive after six months.

CONCLUSION

Malignant pleural effusion commonly complicates an underlying malignancy, the most common being lung cancer in males and breast cancer in females. It should be suspected in appropriate clinical settings and searched for by every possible means of diagnosis, as the presence of malignant pleural effusion adversely affects the prognosis of the primary cancer. Despite an extensive search in a large number of patients, the primary remains undiagnosed. Thoracoscopy helps in the diagnosis of such patients. Intercostal drainage and chemical pleurodesis are the best palliative measures in the management of malignant pleural effusion.

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