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MASSIVE PLEURAL EFFUSIONS IN CANCER PATIENTS: AN EXPERIENCE FROM A TERTIARY CARE CENTRE IN INDIA

Oncology

Dr. Gayathri R Nair* Senior resident, Department of Medical Oncology, Madras Medical College, Chennai *Corresponding Author

Dr Senthil Kumar E Assistant Professor, Department of Medical Oncology, Madras Medical College, Chennai

Dr Sivasubramaniam K Assistant Professor, Department of Medical Oncology, Madras Medical College, Chennai

Dr S G D Gangadharan Professor, Department of Medical Oncology, Madras Medical College, Chennai.

ABSTRACT

Introduction
Massive pleural effusions are typically characterised by collection of 1000 ml or more fluid in the pleural cavity. It may be a malignant or a non-malignant effusion and is common in cancer patients.

Aims and objectives
1. To study the clinical profile of cancer patients who develop massive pleural effusions.
2. To analyse the management of massive pleural effusions in cancer patients.

Materials and methods
This is a retrospective study. Records of cancer patients diagnosed to have massive pleural effusions from the month of April 2022-November 2022, in our department were analysed in December 2022. Data regarding the clinical profile and management of pleural effusion of these patients was collected and analysed. **Results** During the study period,32 cancer patients were diagnosed to have a massive pleural effusion, out of which 24 had a malignant pleural effusion. The most common cause of malignant pleural effusion was lung cancer (38%), followed by breast cancer (29%). Therapeutic thoracocentesis alone was done for 14 patients. Therapeutic tapping was followed by Intercostal Chest Drain (ICD) insertion for 12 patients, whereas 6 patients had an upfront ICD inserted. Elderly age, ICD insertion and the development of hospital acquired pneumonia(HAP) were associated with significantly longer duration of hospital stay. ICD insertion was significantly associated with the development of HAP . No significant difference was observed in the recurrence rate between patients who underwent ICD insertion vs therapeutic thoracocentesis alone. **Conclusions** Upfront ICD insertion for management of massive pleural effusions in cancer patients is associated with increased rates of HAP, prolonged duration of hospital stay and no difference in the rate of recurrence of effusions, when compared to patients who underwent therapeutic thoracocentesis alone. Thus, we suggest that these patients undergo therapeutic needle thoracocentesis as the first line of management, with an attempt to avoid ICD insertion if possible.

KEYWORDS

massive pleural effusion, malignant pleural effusion, thoracocentesis, ICD

INTRODUCTION

Approximately 15 percent of all patients with cancer develop malignant pleural effusions (MPEs) [1], with lung cancer and breast cancer accounting for 50 to 65 percent of MPEs [2]. However, all pleural effusions in cancer patients need not be malignant. Pleural effusion may be classified into malignant vs non-malignant effusions, and massive vs non-massive effusions. Infiltration of cancer cells into the pleura leads to the formation of a malignant pleural effusion. Pleural invasion by neoplastic cells may be seen on pleural biopsy. This can be associated with successful demonstration of malignant cells in pleural fluid cytology. Non-malignant effusions are due to causes other than infiltration of pleura by cancer cells. Paramalignant effusion is a type of non-malignant effusion which occurs due to tumour effects that indirectly act on the pleural space such as by bronchial obstruction, mediastinal lymph node infiltration, thromboembolism, or superior vena cava syndrome. Like other non-malignant effusions, in paramalignant pleural effusions also, pleural fluid cytology and pleural biopsy are negative because cancer cells have not infiltrated the pleural membranes. Other causes of non-malignant effusions in cancer patients include congestive cardiac failure, cirrhosis, and renal failure.

Most of the studies done with respect to management of pleural effusions have been conducted in resource-abundant settings, which cannot be always extrapolated to resource limited countries like India. In this study, we have attempted to characterise the clinical profile and management of pleural effusions in cancer patients treated at a tertiary care hospital.

MATERIALS AND METHODS

This is a retrospective study. Records of patients diagnosed to have massive pleural effusions from the month of April 2022-November 2022, in the Department of Medical Oncology, Madras Medical College, Chennai, were analysed in December 2022. Only the patients who had a biopsy proven malignancy and were receiving systemic therapy for the same at Department of medical oncology, Madras Medical College were included. Massive pleural effusion was diagnosed if the Chest X Ray (CXR) showed complete or near-complete opacification of the ipsilateral thorax; that is, the opacification is at least two-thirds of the hemithorax. Patients whose records were incomplete, were excluded from the study. Patients who have received any intervention for management of pleural effusion previously were excluded. A total of 32 patients were included in this study. Data regarding age sex, comorbidities, laboratory parameters, type of neoplasm, stage of malignancy, Chest X Rays, Computed Tomography (CT) Thorax, pleural fluid cytology, and management of the pleural effusion were collected and analysed. As per Light's criteria, an effusion with any of the following characteristics is classified as an exudate: pleural fluid: serum protein ratio > 0.5, pleural fluid: serum Lactate Dehydrogenase (LDH) ratio > 0.6 or pleural fluid LDH > 2/3 of the upper limit of normal for the serum. An effusion with none of these characteristics is classified as a transudate.

Descriptive statistics, including frequency, percentage, mean, Standard Deviation(SD), median, and interquartile range, summarized data characteristics. We assessed relationships with Spearman's rho and Pearson correlation coefficients, selecting the appropriate method based on data properties. For group comparisons, independent sample t-tests and Mann-Whitney U tests were employed. To investigate associations in categorical data, Pearson chi-square tests were conducted. Significance was defined by P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 21.0 (IBM-SPSS Science Inc., Chicago, IL).

RESULTS

Between June 2022 and November 2022,32 patients were diagnosed to have a massive pleural effusion of which 17 were males, 15 were females (Table 1).

Table 1:Clinical profile of cancer patients with massive pleural effusions

Characteristic	Thoracocentesis (n=14)	Thoracocentesis Followed by ICD (n=12)	ICD upfront(n=6)
Age in years (mean, SD))	56(4.5)	51(3.8)	56(2.6)
Males (n)(%)	10(64%)	5(42%)	2(33%)
BMI(mean, kg/m2)(S.D)	20.4(2.25)	21.25(2.1)	22.3(2.3)
Comorbid (n)			
Diabetes Mellitus	3	4	2
Hypertension	1	0	0
Coronary artery disease	3	1	0
Chronic kidney disease	1	0	1
Chronic liver disease	2	1	0
Haemoglobin (mean g/dl)(S.D)	10.8(2.1)	9.2(1.9)	11.1(2.0)
Total White Blood Cell count(mean cells/microliter)(S.D)	8400	6200	7800
Albumin(mean, g/dl)(S.D)	3.6(0.5)	3.8(0.7)	3.7(0.3)
Stage (n)			
Stage 1	0	0	0
Stage 2	0	1	0
Stage 3	4	0	2
Stage 4	10	11	4
Malignant effusion	10	10	4
Cytology positive	8	10	3
Type of cancer			
NSCLC(adenocarcinoma)	4	3	0
NSCLC(squamous cell carcinoma)	2	1	0
Breast	3	3	2
Ovary	1	1	2
SCLC	1	1	1
DLBCL	1	1	0
HCC	1	1	0
Gastric cancer	1	1	0
Colon cancer			1

[Abbreviations used in Table 1: BMI=Body Mass Index, NSCLC= Non-Small Cell Lung Cancer, SCLC= Small Cell Lung Cancer, DLBCL=Diffuse Large B-Cell Lymphoma, HCC=Hepatocellular Carcinoma]

The mean age at diagnosis was 54.5 years(S.D=4.7 years). Most of the patients had stage IV disease at presentation (n=25, 78%). The most common symptoms attributable to the pleural effusion were dyspnoea (n=32,100%) and cough (n=27,84%) .The cause of pleural effusion in these patients have been summarised in Table 2.

Table 2:Etiologies of pleural effusions

Etiologies of non-malignant pleural effusions(n)	Etiologies of malignant pleural effusions(n)
Congestive cardiac failure (3)	NSCLC (9)
Superior Vena Cava (SVC) obstruction (3)	SCLC (2)
Cirrhosis of liver (2)	HCC (1)
	Carcinoma Breast (7)
	Carcinoma Ovary (4)
	DLBCL(1)
Total ,n=8	Total, n=24

[Abbreviations used in Table 2: NSCLC=Non-Small Cell Lung Cancer, SCLC= Small Cell Lung Cancer, DLBCL=Diffuse Large B-Cell Lymphoma, HCC=Hepatocellular Carcinoma]

24 patients had a malignant pleural effusion, all of them being predominantly unilateral. The most common cause of malignant pleural effusion was lung cancer (n=9, 38%), followed by breast cancer (n=7, 29%). Patients with malignant effusion were more likely to have stage IV disease compared to those with a non-malignant effusion (100% vs 12.5%,p=<0.0001).8 patients had non-malignant effusions, with the common causes being SVC obstruction (n=3,37.5%)and congestive cardiac failure (n=3,37.5%). 2 of these patients with non- malignant effusions had predominantly unilateral right sided effusion(one due to cirrhosis, and the other due to SVC obstruction).26 (81%) patients had an exudate. All 24 patients with malignant effusion had an exudate. In addition ,2 patients with non-malignant effusion due to SVC obstruction also had an exudative effusion. Malignant cytology was positive for 21 patients.

Therapeutic needle thoracocentesis alone was done for 14 patients. An average of 950 ml was removed in a single sitting (range 750-1250 ml). Multiple therapeutic needle thoracocentesis was not done for any patient. Therapeutic pleural tapping was followed by ICD insertion for 12 patients due to iatrogenic hydropneumothorax (1 patient), uncooperativeness during procedure (3 patients), rapid re-accumulation of the pleural effusion (4 patients), loculated effusion(4 patients).6 patients underwent upfront ICD insertion. 10 patients who had ICD inserted subsequently underwent pleurodesis with 60 Units of bleomycin.8 patients underwent pleurodesis with 500 mg of doxycycline.

Elderly patients had a significantly longer duration of stay in the hospital (p=0.002). The patients who had ICD inserted had a significantly prolonged average hospital stay, as compared to the patients who underwent needle thoracocentesis (average duration of stay, 16 days vs 5 days, p=<0.0001). HAP also prolonged inpatient hospital stay (median 18.5 days vs 6.5days, p=<0.0001). Older patients took a significantly longer time for ICD removal, (p =0.012). Hypoalbuminemia (Serum Albumin<3.5g/dl) also was significantly associated with time taken for ICD removal (median 11 days vs 8 days, p=0.008). 8 out of the 18 patients (44%) who underwent ICD insertion developed HAP, as compared to none who underwent therapeutic needle thoracocentesis (p=0.004).

50% (n=7) patients who underwent pleural tapping alone developed a recurrent ipsilateral pleural effusion during the study period, 5 of them being mild effusions, and 2 being moderate effusions. Among these patients, 5 were malignant effusions, and 2 were non-malignant effusions (one case of cirrhosis, another case of SVC obstruction). Only 2 patients (Both malignant effusions, both being cases of NSCLC-Adenocarcinoma, stage), required a repeat therapeutic thoracocentesis for moderate effusions. Out of the 18 patients who underwent ICD insertion followed by pleurodesis, only 4 patients (22%) developed a recurrent pleural effusion (2 being cases of Carcinoma breast, and 2 being cases of Carcinoma ovary), of which 3 were ipsilateral recurrences and one was contralateral.2 of these patients had previously undergone pleurodesis with bleomycin and 2 patients had undergone pleurodesis with doxycycline. There was no significant difference observed in rate of recurrences based on the agent used for pleurodesis (bleomycin vs doxycycline, p=0.064). All four of these pleural effusions were moderate and were managed with therapeutic pleural tapping. There was no difference in the rate of recurrence of pleural effusion between patients who underwent therapeutic thoracocentesis vs those who underwent ICD insertion(p=0.1).

DISCUSSION

Pleural effusions are common in cancer patients. The classification of pleural effusions into malignant vs non-malignant is of prime importance as it changes the staging of the cancer, thus influencing the treatment modalities, and ultimately, prognosis. They may be massive or non-massive. Massive pleural effusions have been defined differently in various studies. Some studies have defined the cut of at least 2/3rd of the hemithorax on chest x ray[3] and a volume of at least 1000 ml on a CT scan[4]. Some other studies have defined it as complete or near complete opacification of hemithorax[5]. Another study which was done in India took a cut off as opacification of more than ½ of hemithorax as a massive effusion[6]. In our study , we chose to take a cut off of opacification of more than 2/3rd of hemithorax on chest Xray. Besides CXR and CT scan, use of Ultrasonogram(USG) is also being

considered as a very sensitive method of quantifying pleural fluid [4]. However this remains subject to interobserver variability.

Most of the studies show that lung cancer is the most common cause of effusion in males, and breast cancer is the most common cause of malignant pleural effusion in females[7]. These findings could be validated in our study as well, as the most common cause of malignant pleural effusion was lung cancer in males (n=9 , 38%) and breast cancer in females (n=7,29%) .In addition to most of the studies which have focused on malignant pleural effusions alone, we could also find that 25% massive pleural effusions in cancer patients were non-malignant. Out of these, 37.5% (n=3) were paramalignant effusions, due to SVC obstruction. Malignant cytology was positive in only in 87.5% of the patients. As per the meta-analysis done by Kassirian et al, the overall diagnostic sensitivity of pleural fluid cytology for MPE was 58.2%[8]. The sensitivity was high in ovarian cancer (85.2%)and lung adenocarcinoma (83.6%), modest for breast cancer (65.3%), and lowest in lung squamous cell carcinoma (24.2%) and mesothelioma (28.9%)[8]. They have also reported a substantial heterogeneity among studies[8]. Thus, the overall higher percentage of patients in our study with a positive malignant cytology may be partially attributed to the fact that most of the patients were diagnosed to have lung adenocarcinoma, breast cancer or ovarian cancer , in which the above-mentioned study reported average sensitivities ranging from 65% to 85%.

All the patients with malignant pleural effusion in our study had stage IV cancer, which is consistent with other studies also, where they have found that presence of a malignant pleural effusion is commonly associated with advanced stage of cancer[9].

As per the ATS/STS/STR Clinical Practice guidelines and ERS/EACTS statement on the management of malignant pleural effusions, either upfront large volume thoracentesis or ICD insertion may be done to remove pleural fluid for a patient with symptomatic malignant pleural effusion[2,10]. We removed an average of 950 ml of pleural fluid for patients who underwent therapeutic thoracocentesis alone, with a range between 750 ml and 1250 ml. This is in accordance with current standard of care as most experts suggest removal of no more than 1.5 L of pleural fluid with therapeutic thoracocentesis, due to increase in the chances of complications such as rebound pulmonary oedema, associated with removal of higher volumes of fluid [11].

For all the patients who underwent ICD insertion, a large bore chest tube of size ranging from 32F to 36F was used. However, there are multiple studies that suggest that insertion of small-bore catheters is equally efficacious and also reduce patient discomfort [12-17].

Indwelling Pleural catheter (IPC), otherwise referred to as tunnelled pleural catheter is also an effective option for management of malignant pleural effusions as proven by several randomised controlled trials [18-22], as well as meta-analyses [23,24]. However, these studies also reported higher rates of adverse events such as cellulitis, catheter displacement, catheter blockage, and pain [18,19]. Also, these may not be readily available in resource limited settings like ours, where the first line management of a patient with massive pleural effusion is still a therapeutic thoracocentesis or ICD insertion.

Chemical or mechanical methods may be attempted to achieve pleurodesis. Chemical methods include use of agents like talc, bleomycin, tetracycline, iodopovidone and silver nitrate. Pleural abrasion is a mechanical method of achieving pleurodesis. Usually, the preferred method is chemical pleurodesis using talc [2]. However, at our hospital, we used bleomycin or doxycycline for pleurodesis, and no significant differences were observed in the rate of recurrences between the two agents.

In our study, elderly age, ICD insertion and the development of hospital acquired pneumonia significantly prolonged the duration of hospital stay.ICD insertion was associated with higher chances of developing hospital acquired pneumonia, and this may be the reason that ICD insertion was associated with a longer duration of hospital stay in our study population. There are not many prospective studies that have addressed the question of upfront ICD insertion vs therapeutic thoracocentesis in malignant pleural effusion. A randomised controlled trial done by Arnold et al, primarily in patients with non-malignant, infected pleural effusions showed that upfront thoracocentesis significantly reduced the duration of hospital stay[25].

The patients in our study received definitive treatment of the malignancy once the pleural effusion had settled significantly and they had obtained adequate symptom relief. For those patients who developed hospital acquired pneumonia, chemotherapy was initiated only once they had fully recovered from the infection.

Our study has also reported on the incidence and management of massive non-malignant pleural effusions in cancer patients.8 patients(25%) had non-malignant effusions ,out of which 6 patients(75%) had stage 3 disease, 1 patient had stage 2 disease and only 1 patient had stage 4 disease.25% cases of non-malignant effusions were exudative, highlighting the fact that an exudative effusion in a cancer patient should not lead to an erroneous misclassification as a malignant effusion. This signifies the importance of integrating data from history, physical examination, and imaging in addition to pleural fluid analysis, to be able to correctly categorise the type of effusion, which in turn plays a vital role in staging of the disease, thus determining the ultimate treatment strategy and prognosis of a patient.

Our study had its limitations in being a retrospective one with a limited sample size. However, it provides relevant real-world data regarding the clinical profile and management of massive pleural effusions in cancer patients in resource limited settings, and this is of crucial importance as management of every condition has to be adapted to the setting in which it is encountered.

CONCLUSION

Both malignant and non-malignant pleural effusions are common in cancer patients. ICD insertion was associated with longer durations of hospital stay and significantly high rates of hospital acquired pneumonia. With most of the western data moving towards placement of an Indwelling pleural catheter for management of Malignant pleural effusions, there is a dearth of data in India to guide on thoracocentesis vs ICD insertion and pleurodesis ,and our study shows that an initial approach with therapeutic thoracocentesis, with an attempt to avoid ICD insertion, may be a suitable option for management of malignant pleural effusions.

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Conflicts of Interest
The authors have no conflict of interest.

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