IBOM MEDICAL JOURNAL
Vol.13 No.3 Sept. - Dec., 2020. Pages 180 - 186
www.ibommedicaljournal.org

Management of Malignant Pleural Effusion (MPE) in a Tertiary Hospital in a low-income-country: Challenges and Prospects

Nwafor IA[1], Nnakenyi EF[2], Eze JC[1], Nwidenyi IO[3]

National Cardiothoracic Center of Excellence (NCTCE), University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu, Nigeria

Abstract

Background: In the West African sub-region, significant morbidity and mortality are known to affect patients with malignant pleural effusion (MPE) but are highly under reported unlike USA, Europe or South Africa.
Aim/Objective: To review cases of MPE in our tertiary hospital in the last 13 years with a view to determining the challenges and prospects.
Materials and Method: This is a retrospective study spanning over a decade from January, 2007 to December, 2019. Malignant pleural effusion from various neoplasms constitutes the commonest thoracic malignancy in our tertiary hospital. After 13 years of management of such patients, we reviewed the data from the hospital record's department. The data obtained were demography, aetiology, total number of pleural fluid specimens for cytology and pleural biopsies submitted for histology, pleurodesis and other treatment modalities.
Result: 211 patients with MPE were admitted and managed during the period under review. Of these numbers, 135(64.0%) were confirmed cytologically positive (MPE). 76(36.0%) tested falsely negative and were initially regarded as paramalignant, later confirmed MPE. The age affected was from 7 to 81 years with a mean of 44 years. Of 211 patients with MPE, 94 were males while 117 were females, with a male to female ratio of 4:5. Aetiologically, metastatic breast cancer was the highest followed by advance lung cancer.
Conclusion: Submission of insufficient samples resulted in false negative cytology. Review of recurrent pleural effusion and exophytic tumour at the sites of CTTD resulted in late diagnosis of MPE. Additionally, prolonged hospital stay awaiting CTTD and cytology results are among the challenges.

Keywords: Malignant, effusion, sclerosants, pleurodesis, cytology

Introduction

Pleural effusion is divided into 3 categories, namely malignant (MPE), nonmaligant and paramalignant. The effusion can accumulate freely in the pleural space or may be loculated. In either case, when massive, it leads to passive atelectasis of the underlying lung and eventual displacement of the mediastinum to the contralateral side, producing cardiorespiratory embarrassment.[1]

MPE is defined as pleural fluid containing malignant cells. Paramalignant effusion is defined as an effusion that is not a direct result of neoplastic involvement of the pleura, but rather indirectly related, including but not limited to post obstructive pneumonia, lymphatic obstruction secondary to mediastinal lymphadenopathy, or effusion secondary to pulmonary embolism in a patient with pulmonary malignancy. Nonmalignant effusion is the one occurring in patients without malignancy and itself contains no malignant cells. MPE is a

Corresponding Author: Dr Nwafor, IA

Department of Surgery/NCTCE, UNTH, Ituku-Ozalla, Enugu State, Nigeria.
E-mail: igbochinanya2@yahoo.com, ikechukwu.nwafor@unn.edu.ng, Phone: +2348037784860

complication of a number of cancers, most commonly lung, followed by breast, lymphoma, gyneacological malignancies, and mesothelioma.[2] Malignant pleural effusion (MPE) is a sign of advanced cancer and is associated with significant symptom burden and mortality. Given that patients with MPEs are heterogeneous with respect to their cancer type and response to systemic therapy, functional status, and pleural milieu, response to MPE therapy is also heterogeneous and difficult to predict.[3,4] It is estimated to affect 150,000 people each year in the US and over 100,000 people in Europe.[5,6] Management of MPE is predominantly palliative.[1]

Average survival following diagnosis ranges from 3 to 12 months and is dependent on the type of underlying malignancy, tumor characteristics, the extent of the disease, comorbidities and the composition of pleural effusion.[7-11] Prediction of survival has been found to be dependent on Karnofsky Performance Status (KPS) as it correlated with mortality.[8] Recently Eastern Cooperative Oncology Group (ECOG) score including pleural fluid characteristics like lactic acid dehydrogenase (LDH), neutrophil-lymphocyte ratio and the type of tumour has been found to be a better predictor of survival than KPS.[6] Indeed, diagnosis and management of MPE with the goals of palliation and improving quality of life poses a great challenge to multidisciplinary oncology team in low and middle income countries.[12]

Materials and Method:

This is a retrospective study spanning over a decade from January, 2007 to December, 2019. After 13 years of managing such patients, we reviewed the data from the hospital record's department. The data obtained were demography, aetiology, total number of pleural fluid and or pleural biopsy specimens submitted for cytology/histopathology, pleurodesis and other treatment modalities. Others included were success rate of pleurodesis and complications as well as the overall outcome of patients managed. Data were analyzed using SPSS version 20 (Chicago) and proportion was set as $P < 0.5$.

Results

Table 1: Age ranges with gender distribution of patients with malignant pleural effusion (MPE)

Age ranges	Male	Female	Total	Percentages(%)
0-10	5	2	7	6.0
11-20	4	3	7	6.0
21-30	4	6	10	8.6
31-40	6	12	18	15.5
41-50	7	14	21	18.1
51-60	5	8	13	11.2
61-70	7	13	20	17.2
71-80	3	8	11	9.5
81-90	3	6	9	7.8
	44	72	116	100

M:F = 0.6:1.0

Table 1: Here pleural fluid specimens were positive. They were 72 females and 44 males. Among the age range affected, 61-70 years were most affected followed by 31-40 years. Blind pleural biopsy was also confirmed positive and the specific neoplastic types were as described in table 3.

Table 2: Age ranges and gender distributions for initial diagnosed paramalignant Pleural effusion but later confirmed MPE

Age range	Male	Female	Total	Percentage (%)
0-10	3	0	3	3.9
11-20	5	6	11	0
21-30	4	5	9	11.8
31-40	7	11	18	23.7
41-50	8	7	15	19.7
51-60	7	11	18	23.7
61-70	4	6	10	7.9
71-80	3	6	9	6.6
81-90	1	1	2	2.6
	42	53	95	100

M:F = 0.8:1.0

This table shows the distribution of patients initially diagnosed as paramalignant plural effusion because pleural fluid cytology as well as blind pleural biopsy results were found negative. There was no facility for ultrasound or VATS guided pleural biopsy. CTTD was carried out on them. Within a month or two, most of the patients came back with recurrent effusion. The rest had variable sizes of exophytic

growth on the sites of the CTTD. The tumours were excised for histology and the results came out positive with the varied neoplastic growths as described in table 3. Pleural biopsy was subsequently repeated in those patients with recurrent effusion, this time under ultrasound guided in a peripheral referral center. The results also, all came out positive. In this table, females were 53 and males were 42 and the age ranges were mostly affected were 31-40 and 51-60.

Table 3: Aetiology of malignant pleural effusion (MPE)

Aetiology	Frequency	Percentage (%)
Metastatic breast cancer	38	18.0
Advanced lung cancer	24	11.4
Metastatic ovarian cancer	17	8.1
Metastatic esophageal cancer	16	7.6
Metastatic colorectal carcinoma	16	7.6
Lymphoma	14	6.6
Metastatic Cervical cancer	13	6.2
Metastatic thyroid cancer	13	6.2
Metastatic gastric cancer	13	6.2
Metastatic carcinoma of prostate	13	6.2
Metastatic mesothelioma	13	6.2
Metastatic endometrial carcinoma	12	5.7
Idiopathic (unknown primary)	11	5.2
TOTAL	211	100

Table 3 showed the distribution of all the types of neoplasms that resulted in MPE. Breast cancer was the highest followed by advanced lung cancer. The least was metastatic lung cancer from unknown primaries.

Table 4 shows the distribution of the types of pleurodesis done in this review. Chemosclerosis and surgical pleurodesis were employed. As a developing country, the availability of biological agent like corynebacterium parvum and other chemical agents like doxycycline, minocycline and bleomycin were not available. Cytotoxic drugs like doxorubicin, etoposide or cisplatin were not used in the patients encountered in this review. The failure rate of the types of pleurodesis used is as shown. The highest rate encountered is tetracycyline HCL, representing 62.5%. Intrapleural administration of the tetracyclines is usually in 30 to 50 mL of 0.9% saline, with an indwelling time of about 2 hours. Its mechanism of action has been attributed to growth-factor-like activity on fibroblasts from both direct mesothelial cell activation and indirect mesothelial cell activation through stimulated pleural macrophages.

Table 4: Chemical and Surgical Pleurodesis

Types	Total number	Recurrence (failure rate)	Percent (%)
Chemical agents			
Tetracycline hydrochloride	77	25	62.5
Talc slurry	31	2	4.6
Blood	21	6	13.6
Iodine	31	4	9.1
Silver nitrate	21	3	6.8
Surgery			
Pleurectomy	10	3	6.8
Abrasion	15	1	2.3
Total	211	44	100

Table 5: complications of pleurodesis

Agents/ Complications	Chest pain	Fever	Allergic reactions	Empyema thoracis
Tetracycline	30	10	10	0
Talc	30	10	30	0
Blood	0	40	30	
Iodine	40	10	30	0
Silver nitrate	40			30
Pleurectomy	40	0	0	30
Pleural Abrasions	40	0	0	30

Table 5 shows the complications of the types of pleurodesis and the degree of affectations of the individual method. Chronic empyema thoracis complicated open thoracotomy used for either pleurectomy or abrasions.

Table 6: Overall outcome of pleurodesis for MPE

Over all outcome of pleurodesis	Number	Percent (%)
Complete response (no recurrence effusion for > 1 year)	112	53.1
Partial response (recurrence between 6-12 months)	65	30.8
No response (recurrence 2weeks – 5 months.	34	16.1
	211	100

Table 6 shows the distribution of the overall outcome pleurodesis. In this review, most patients who did not have recurrence for more than 6 months after the initial pleurodesis were unlikely to have one because the constitutional effects from the particular neoplasms was overwhelming that added recurrence could have caused the demise of the patients. Partial response was described as those that had minimal recurrence or full recurrence between 6-12 months of the initial procedure while partial response within 2 weeks to 5 months.

Table 7: Current treatment modalities for MPE

Treatment modalities	Number	Percent (%)
Pleurodesis post CTTD alone	45	21.3
Pleurodesis post IPC alone	15	7.1
1 or 2 + chemotherapy	31	14.7
1 or 2 + radiotherapy	30	14.2
1 or 2 + chemoradio-therapy	90	42.7
	211	100

Keys: CTTD = Close Chest Tube Drainage,
IPC = indwelling pleural catheter

Table 7 showed that treatment modalities appeared variable. Systemic therapy like chemotherapy, radiotherapy or hormonal therapy was used in some patients evaluated in this review. This is the best long-term management option for drug- or radio-sensitive tumours like lymphomas, mesothelioma or small cell lung cancer.

Discussion:

Successful management of MPE represents an ongoing challenge in clinical practice. Recent scientific progress has shed light on the biological processes leading the mechanisms behind the pathobiology of MPE.[13] Development of novel, effective, biological treatment for patients is impaired by an incomplete understanding of basic aspects of cancer metastasis to the pleural space and effusion development.[14]

In a low-income-country, the multidisciplinary oncology team versed with management of MPE is comprised of thoracic surgeons, respiratory physicians, cytologists/histopathologists, radiologists, radio-oncologists, nurses, physiotherapists, pharmacists and psychologists as well as social health workers. In our center, patients are initially assessed by either thoracic surgeons or respiratory physicians, who evaluate them and carry out thoracocenteis and or pleural biopsy for pleural fluid cytology and biopsy. The cytologists/histopathologist carry out the cytological/histological study of submitted specimen(s). Radiological investigations like chest x-ray, computerized tomography scan (CT scan) and magnetic resonance imaging (MRI) as well as positron emission tomography (PET) scan are carried out by radiologists. Radio- oncologists carry out radiotherapy and chemotherapy when the cytology or pleural biopsy is adjudged positive, usually after multidisciplinary meetings.

Challenges:

Insufficient samples of pleural fluid specimens and cold ischemic time of samples of pleural fluid collected but submitted late for testing resulted in large numbers of false negative results. See table 2. Pleural biopsy carried out blindly or with aid of ultrasound in view of the prohibitive cost of computerized tomography also resulted in false negative outcome.

Prolonged stays of patients in hospitals while waiting for complete pleural fluid drainage prior pleurodesis and also delay in releasing cytology or histology results by cytologists/histopathologists affect the quality of life of patients and cause financial stress to family care givers. Multiloculated MPE as well as failed lung expansion due to entrapment lung syndrome led to prolonged CTTD and consequently prolonged hospital stay. The quality of life of patients was adversely affected. New modalities, such as pleuroscopy and long-term indwelling pleural catheters, offer cost-effective

outpatient or minimal hospital stay, less discomfort, and a chance to spend time with loved ones in the comfort of the home or hospicecare.[7]

In this study, we noticed that age range most affected in those primarily diagnosed with MPE was 41-50 (n= 21, 18.1%), followed by 61-70 (n= 20, 17.2%). There was slight female preponderance probably on account of breast cancer being the major aetiological factor. See tables 1 & 3. In those secondarily diagnosed as MPE, it was noticed the age range affected most was bimodal: 31-40 and 41-50 years with each (n= 18, 23.7%). Female gender was also dominant. Breast cancer as the commonest cause of MPE accounted for the female preponderance.

Aetiologically. metastatic breast cancer and lung cancer accounted for the majority of MPE in this study with absolute value of (n = 38, 18.0% and n = 24, 11.4%) respectively. The least in the causative factors was the one from unknown primaries with (n = 11. 5.2%). See table 3. This finding is in agreement with the works of other authors who stated that adenocarcinoma of lung and breast accounted for 50-60% of MPE.[15,16] They also stated that 7-11% of MPE were due to cancers from unknown primaries.[17,18]

Pleurodesis using various agents was carried out in the affected patients. In the course of guiding and supervising senior resident doctors in cardiothoracic surgery carry out dissertations for their exit examinations, the outlined agents or procedures were employed. The failure rate was also noted. See table 4. Tetracyline sclerosant appeared to be the most effective as it had low failure rate in the study. However, the number that used tetracycline was relatively higher. Multiple sclerosing agents have been studied, including doxycycline, tetracycline, bleomycin, and talc, with the preferred and most common agent used now being talc.[19,20] A Cochrane review and network meta-analysis published in 2016 reviewed 41 studies evaluating 16 pleurodesis methods and included 2,345 participants.[21] In the majority of cases, there was no evidence to support any difference among agents in terms of pleurodesis.

The sclerosing agents and open surgery procedure were associated with complications as outlined in table 5. Surgery was via open thoracotomy under general anaesthesia. There is significant associated morbidity (20%) and mortality (10%) according to other authors.[7,19] There was no availability of VATS for minimal access pleurectomy in our review.

Pleurodesis is therapeutic obliteration of the pleural space and is indicated in the management of malignant pleural effusion.[22,23] Pleurodesis can be achieved using surgical, mechanical, biologic or chemical method.[24] The overall outcome of pleurodesis in this review was divided into 3 groups, namely complete response, partial response and failed response. See table 6. Patients were regarded as having complete response if they had no recurrence after 6 months. On the other hand, those who had recurrence within 3 to 6 months were grouped as partial response while those who had recurrence in less than 3 months were regarded as failed response. Prior the use of IPC, failed pleurodesis was significant owing to the presence of trapped lung. Other authors carried out pleural fluid evacuation using CTTD and pleurodesis and followed the patients up for 3-12 months. Failure rate was noted in 3-30%.[25]

Prospects:

The treatment of MPE in our center initially was not multicentered which largely led to submission of insufficient samples of pleural fluid (<250 ml) with consequently many false negative results.[26] Currently its management rests squarely on the shoulders of multidisciplinary oncology team. MPE treatment is purely aimed at palliation, improvement in quality of life and reducing dyspnoea. To that extent, pleural fluid drainage (CTTD) followed by pleurodesis eliminated dyspnoea. Accordingly, the primary role of thoracocentesis or chest-tube thoracostomy is to evacuate the pleural space prior instillation of a sclerosant, with the goal of obliterating the visceral/parietal space and preventing recurrence.[27] Also the use of indwelling pleural drainage catheter(IPC) in cases of lung entrapment resulting in failure of lung expansion and consequent discharge of patients to family physicians resulted in reduced hospital stays, reduced financial and physical stress from family care givers and overall improvement in quality of life of patients. See table 7. IPCs alone have been found to cause spontaneous pleurodesis and in a randomized multicenter study with aggressive daily drainage, it was 54 days

compared to a less aggressive interval draining (90 days).[28-30] There is an inherent infectious risk and pleural tract metastasis with IPCs as well as the need for assistance with home drainage.[31-33]

Conclusion:

MPE is a continuous challenge to multidisciplinary oncology team. At present, the use of large or sufficient pleural fluid samples increases the diagnostic yield of pleural fluid cytology. The use of ultrasound guided pleural membrane biopsy has increased the yield of true positivity for malignancy. The use of indwelling pleural catheter drainage has equally improved the outlook of palliative care and quality of life of patients with MPE.

References:

1. Ekpe EE, Ikpe MC, Umanah IN. Palliative Treatment of Malignant Pleural Effusion. Diag Ther Stud 2013;2(1):8-20.
2. Sahn SA. Malignancy metastatic to the pleura. Clin Chest Med 1998; 19:351-361.
3. American Thoracic Society: Management of Malignant Pleural Effusion. Am J Respir Crit Care Med 2000; 162:1987-2001.
4. Benneth R, Maskell N, Management of Malignant Pleural Effusion. Curr Opin Pulm Med 2005; 11:296-300.
5. Davies HE, Mishra EK, Kahan BC. Effect of indwelling Pleural Catheter versus Chest tube and talc pleurodesis for relieving dyspnoea in patients with Malignant Pleural Effusion: the TIME2 randomized Controlled trial: JAMA 2012;10(8): 975-982.
6. Demmy TL, Gu L, Burkhalter JE. Optimal Management of Malignant Pleural Effusion. Thorac 2003;58 (Suppl 2): ii29-ii38.
7. Roberts ME, Neville E, Berrisford RG. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2: ii32-40. 10.1136/thx.2010.
8. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest 2000; 117:73-8. 10.1378/chest.117.1.73.
9. Bielsa S, Salud A, Martinez M. Prognostic significance of pleural fluid data in patients with malignant effusion. Eur J Intern Med 2008; 19:334-9. 10.1016/j.ejim.2007.09.014.
10. Pilling JE, Dusmet ME, Ladas G. Prognostic factors for survival after surgical palliation of malignant pleural effusion. J Thorac Oncol 2010;5:1544-50.
11. Clive AO, Kahan BC, Hooper CE. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax 2014;69:1098-104.
12. Desiar NR, Lee HJ. Dsiagnosis and Management of Malignant Pleural Effusion: state of the art in 2017. J Thorac Dis 2017;Sep.9(suppl. 10):S1111-S1122.
13. Psallidas I, Kalomenidis I, Porcel JM, Robinson BW, Stathopoulos GT. Malignant pleural effusion: from bench to bedside. Eur Respir Rev. 2016; 25:189–198.
14. Han HS, Eom DW, Kim JH. EGFR mutation status in primary lung adenocarcinomas and corresponding metastatic lesions: discordance in pleural metastases. Clin Lung Cancer. 2011;12:380–386.
15. Taghizadeh N, Fortin M, Tremblay A. USA hospitalizations for malignant pleural effusions: data from the 2012 National Inpatient Sample. Chest. Epub 2016 Nov 19.
16. Sahn SA. Pleural diseases related to metastatic malignancies. Eur Respir J. 1997;10:1907–1901.
17. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. Am J Med. 1977; 63:695–702.
18. Hsu C. Cytologic detection of malignancy in pleural effusion: a review of 5,255 samples from 3,811 patients. Diagn Cytopathol. 1987; 3:8–12.
19. Antunes G, Neville E, Duffy J, Ali N. BTS guidelines for the management of malignant pleural effusions. Thorax. 2003;58 (Suppl 2): ii29–ii38.
20. Apffelstaedt JP, Van Zyl JA, Muller AG. Breast cancer complicated by pleural effusion. J Surg Oncol. 1995; 58:173–175.
21. Clive AO, Jones HE, Bhatnagar R. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane

Database Syst Rev. 2016:CD010529.
22. Walker-Renard PB, Vaughan LM, Sahn SA. Chemical Pleurodesis for Malignant Pleural Effusions: Review. Ann Intern Med. 1994; 120: 56 – 6. 6.
23. Ruckdeschel JC, Moores D, Lee JY, Einhorn LH, Mandelbaum I, Koeller J, et al. Intrapleural therapy for malignant pleural effusions. Chest. 1991; 100: 152 8- 35.
24. 17. Hausheer FH, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. Cancer Metastasis Rev. 1985; 12: 54- 75.
25. Anthony VB, Loddkemper R, Astoul P, Boutin C, Goldstraw P, Holl J, et al Management of Pleural Effusion. European Resp J 2001; 18:402-419.
26. Management of Malignant Pleural Effusion. Am J Respir Crit Care Med 2000,16(5):1987-2000. WWW.atsjournals.org.
27. Patz EF, McAdams HP, Erasmus JJ. Sclerotherapy for malignant pleural effusions: a prospective randomized trial of bleomycin vs doxycycline with small-bore catheter drainage. Chest 1998; 113:1305–1311.
28. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65 (Suppl 2):ii32–ii40.
29. Wahidi MM, Reddy C, Yarmus L. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions: the ASAP trial. Am J Respir Crit Care Med. Epub 2016 Nov 29.
30. Sabur NF, Chee A, Stather DR. The impact of tunneled pleural catheters on the quality of life of patients with malignant pleural effusions. Respiration. 2013; 85:36–42.
31. Fysh ET, Tremblay A, Feller-Kopman D. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest. 2013; 144:1597–1602.
32. Thomas R, Budgeon CA, Kuok YJ. Catheter tract metastasis associated with indwelling pleural catheters. Chest. 2014; 146:557–562.
33. Clive AO, Taylor H, Dobson L. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. Lancet Oncol. 2016 17:1094–1104.