REVIEW

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Malignant Pleural Effusion: Medical Approaches for Diagnosis and Management

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Malignant pleural effusions (MPEs) are the second leading cause of exudative pleural effusions after parapneumonic effusions. In the vast majority of cases, a MPE signifies incurable disease associated with high morbidity and mortality. Considerable advances have been made for the diagnosis of MPEs, through the development of improved methods in the specialized cytological and imaging studies. The cytological or histological confirmation of malignant cells is currently important in establishing a diagnosis. Furthermore, despite major advancements in cancer treatment for the past two decades, management of MPE remains palliative. This article presents a comprehensive review of the medical approaches for diagnosis and management of MPE.

Keywords: Diagnosis; Pleural Effusion, Malignant; Disease Management

Introduction

Malignant pleural effusions (MPEs), which are diagnosed by the identification of malignant cells in pleural fluid or on pleural biopsy, represent an advanced malignancy disease associated with high morbidity and mortality, precluding the possibility of a curative treatment approach. Although almost all types of cancers can cause an MPE, more than 75% of MPEs are due to metastases originating from tumors in the lung, breast and ovary, as well as from lymphomas. Metastatic adenocarcinoma is the most frequent histological finding. However, the primary tumor is not identified in approximately 10% of patients with MPEs[1-3].

Despite major advances in cancer treatment in the past two decades, the median survival time following a diagnosis of MPE depends on the origin of the primary tumor, histological type and stage, and usually ranges from 4 to 12 months. In particular, lung cancer patients with MPE have the shortest survival time[1,2,4,5]. For this reason, the recently revised staging system for non-small cell lung cancer (NSCLC) upstaged the presence of MPE from T4 to M1a[6]. A small amount of pleural effusion sometimes presents in cancer patients in whom cytological or histological diagnosis for the effusion using thoracentesis is not feasible. Our recent study demonstrated that the presence of only a small amount of pleural effusion could confer poor prognosis in NSCLC patients[7]. This article presents a comprehensive review of the medical approaches to the diagnosis and management of MPE and an attempt to derive a treatment algorithm for the management of MPE based on a review of the recent literature.

Diagnosis of MPEs

The most common symptom reported by patients with MPE is dyspnea, which occurs in more than 50% of patients, followed by cough, weight loss, and chest pain. However, an MPE can initially be found incidentally on imaging studies in

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an asymptomatic patient[8].

Recently, the diagnostic accuracy of MPEs has been improved by the development of new chest imaging modalities[3,9]. However, confirmation of malignant cells in the pleural fluid or in the pleural biopsy is required to establish a diagnosis of MPE.

1. Pleural fluid analysis

Diagnostic thoracentesis is usually the first diagnostic step in determining pleural effusion characteristics. Analysis of pleural fluid using thoracentesis may help establish the origin of MPE. Pleural fluid samples are routinely analyzed for total and differential cell counts, proteins, lactate dehydrogenase (LDH), glucose, and pH, as well as subjected to microbiological and cytological examinations. MPEs are almost always categorized as exudates using the Light's criteria[2], including LDH and protein values. However, very few MPEs with other systemic disorders can be categorized as transudates[10,11]. The general pleural fluid characteristics suggestive of the probability of MPE and differential diagnosis are summarized in Table 1.

2. Tumor markers in pleural fluid

Many articles have suggested the possibility of diagnosing MPE when increased levels of tumor markers are found in the pleural fluid. To improve the diagnosis of MPE, a number of tumor markers have been evaluated intensively. However, the search for a highly accurate tumor marker in pleural fluid that reliably confirms MPE has been fruitless thus far[12]. Meta-analysis conducted for conventional tumor markers, such as carcinoembryonic antigen (CEA), carbohydrate antigens (CA) 15-3, CA 19-9, CA 125, and cytokeratin 19 fragments (CYFRA 21-1), reported pooled results on the diagnostic accuracy of each tumor marker in MPE (Table 2)[12,13]. These results illustrate several factors for consideration for tumor marker measurements in pleural fluid. First, measurement of pleural CEA is likely to be a useful diagnostic tool for confirming MPE and is useful for the differential diagnosis between malignant pleural mesothelioma and metastatic lung cancer. A high level of pleural CEA seems to rule out malignant mesothelioma. Second, CA 15-3, CA 19-9, and CYFRA 21-1 are highly specific but insufficiently sensitive to diagnose MPE, and the combination of two or more tumor markers appears to increase the diagnostic sensitivity. Therefore, the results of tumor marker assays should be interpreted in parallel with clinical findings and with the results of conventional tests[12,13].

Recently, there has been growing interest in vascular endothelial growth factor (VEGF) as a diagnostic biomarker of MPE because of the high levels of VEGF present in MPE[14]. VEGF is thought to be the key mediator in the formation of MPE via increased vascular permeability and vascular leakage of fluid. A recent meta-analysis based on 1,025 patients in 10 studies concluded that VEGF might play a role in the diagnosis of MPE, while its diagnostic value is not satisfactory (Table 2)[15]. Mesothelin and fibulin-3 in pleural effusion have also been introduced as potential new biomarkers to detect pleural mesothelioma at an earlier stage[16,17].

However, the clinical applicability of measuring these tumor markers in pleural fluid is limited because, even at high concentrations, further confirmatory cytohistologic diagnosis is necessary[18].

Table 1. The differential diagnosis and characteristics of pleural fluid suggestive of malignant pleural effusion (MPE)[2,3]

Cell counts	
Lymphocytes	More than 50% of MPEs have lymphocyte predominant effusions. Lymphocyte counts >85% can suggest of tuberculous pleurisy, lymphoma, sarcoidosis, chronic rheumatoid pleurisy, yellow-nail syndrome, or chylothorax.
Erythrocytes	Grossly bloody effusions suggest of MPE but also may indicate benign asbestos pleurisy, postcardiac injury syndrome, trauma, and pulmonary infarction.
Eosinophils	12–24% of eosinophilic effusions (>10%) may be malignant in etiology.
Chemical analysis	
Proteins and LDH	Most MPEs are exudates according to Light's criteria; 3–10% are transudates. LDH>1,000 IU/L can suggest empyema, rheumatoid pleurisy, and pleural paragonimiasis.
Glucose	Levels <60 mg/dL in 15–20% of MPE cases, also found rheumatoid pleurisy, complicated parapneumonic effusion, tuberculous pleurisy, lupus pleuritis, or esophageal rupture. A low glucose level in MPE suggests of a high tumor burden in the pleural space and a worse prognosis.
pH	Levels <7.30 in 30% of MPE cases. Patients tend to have a low glucose level at low pH.
Amylase	Elevated amylase levels (>100 IU/L) in 10% of MPE cases; high levels in MPE are associated with shorter survival times. Generally, routine amylase measurement is not cost-effective unless pancreatic disease or a ruptured esophagus is strongly suspected before the test.

Adopted from Heffner and Klein[3], with permission from Elsevier.
LDH, lactate dehydrogenase.

Table 2. Pooled results of the diagnostic accuracies of each tumor marker in malignant pleural effusions based on meta-analysis[12,13,15]

	CEA	CA 125	CA 15-3	CA 19-9	CYFRA 21-1	VEGF
No. of studies	45	10	11	7	18	10
No. of patients with MPE/non-MPE	2,834/3,251	512/801	819/966	598/488	1,152/1,122	514/511
Sensitivity (95% CI)	0.54 (0.52–0.55)	0.48 (0.44–0.53)	0.51 (0.47–0.54)	0.25 (0.21–0.28)	0.55 (0.52–0.58)	0.75 (0.68–0.76)
Specificity (95% CI)	0.94 (0.93–0.95)	0.85 (0.83–0.88)	0.96 (0.95–0.97)	0.96 (0.94–0.98)	0.91 (0.90–0.93)	0.72 (0.68–0.76)
Positive likelihood ratio (95% CI)	9.52 (6.97–13.01)	5.96 (2.27–15.68)	11.69 (5.05–27.07)	10.42 (2.66–40.78)	6.55 (3.09–13.88)	2.94 (1.97–4.41)
Negative likelihood ratio (95% CI)	0.49 (0.44–0.54)	0.54 (0.38–0.78)	0.52 (0.43–0.62)	0.70 (0.55–0.88)	0.43 (0.34–0.54)	0.38 (0.27–0.51)
Diagnostic odds ratio (95% CI)	22.5 (15.6–32.5)	19.61 (6.25–61.52)	24.74 (10.50–58.28)	19.88 (4.19–94.24)	16.24 (9.60–27.49)	9.05 (4.60–17.80)
Area under curve	0.86	0.88	0.73	0.78	0.83	0.82

Adopted from Liang et al.[12], with permission from BMJ Publishing Group Ltd.
CEA: carcinoembryonic antigen; CA: carbohydrate antigens; VEGF: vascular endothelial growth factor; MPE: malignant pleural effusion; CI: confidence interval.

3. Cytology and biopsy

Pleural fluid cytology has traditionally been the analytical method of choice for the detection of tumor cells in pleural fluid. Many studies have shown a large variation in the diagnostic sensitivity of pleural fluid cytological analysis, ranging from 40–87%[2]. In particular, a cytomorphologic distinction between reactive mesothelial cells, mesothelioma, and metastatic adenocarcinoma, as well as between lymphomas and reactive lymphocytosis, can often be difficult because of significant overlapping cytologic features. Therefore, other procedures, such as immunohistochemistry (IHC) using monoclonal antibodies against tumor markers and chromosomal analysis, complement cytology in the diagnosis of MPEs. IHC staining can be performed on conventional cytology specimens and cell blocks. There have been many reports on the application of different IHC markers in pleural effusion samples to diagnosis MPE and to identify the primary site of origin. However, while there is no agreement on the ideal combination of IHC markers, a diagnostic sensitivity of ~80% is desirable for inclusion[18,19].

When cytology is negative and MPE is still suspected, a pleural biopsy might be indicated. There are benefits of undertaking pleural biopsy, which allows for histological analysis of the samples and also characterization of specific hormonal or mutation statuses. In an early prospective intrapatient comparison, the diagnostic yield of nonsurgical biopsy methods in MPEs was studied simultaneously in 208 patients[20]. The diagnostic yield was 62% using pleural fluid cytology, 44% using closed pleural biopsy, and 95% using medical thoracoscopy. Medical thoracoscopy exhibited significantly higher diagnostic sensitivity than did cytology combined with closed needle biopsies from effusions, which were positive in 74% of cases. The combined methods were diagnostic in 97% of the MPEs[20].

Recently, image-guided and thoracoscopic biopsy techniques have improved the diagnostic yield, as compared with traditional closed pleural biopsy using Abram's or Cope needles. In a randomized study of patients with cytologically negative suspected MPEs, a blind Abram's pleural biopsy had a sensitivity of 47% for correctly diagnosing malignancy, in contrast to 87% sensitivity for computed tomography (CT)-guided cutting needle pleural biopsy[21]. The diagnostic advantage of CT-guided biopsy may be <5-mm pleural thickening and fewer adverse events.

Another option for obtaining pleural biopsy samples is to perform a medical or surgical thoracoscopy, both of which allow for direct visualization of the pleura.

4. Novel diagnostic tool

Recent progress in molecular biology has provided a framework to develop novel diagnostic tools for MPEs. Molecular biology techniques, such as analyses of DNA copy number, gene

sequence, mRNA and miRNA expression, and DNA methylation status and protein expression studies on malignant and normal cells within pleural effusions, have identified novel molecular diagnostic biomarkers that demonstrate potential for complementing cytology in the diagnosis of MPEs. Several challenges need to be addressed prior to the incorporation of these molecular tests into routine clinical diagnosis, including validation of molecular diagnostic markers in well-designed prospective and comparative studies with analysis of cost-effectiveness[19].

Management of MPEs

The presence of an MPE generally indicates that the malignancy cannot be cured by surgery. Because the prognosis of patients with MPEs is so poor, treatment is focused on palliation of symptoms rather than a cure. Therefore, the management options for MPEs should consider several factors such as symptoms and performance status of the patient, the primary tumor type and its response to systemic therapy, and expected survival, as well as the social and financial status of the patient. Options for management include observation, repeated therapeutic thoracentesis, indwelling pleural catheter (IPC), chemical pleurodesis, and shunt[22]. The ideal management would offer immediate and long-term relief of symptoms and have minimal side effects. It would involve a procedure that requires the least amount of time spent in the hospital and clinic, avoids repeat uncomfortable procedures, and has the least cost[1]. Therefore, the British Thoracic Society (BTS) guidelines recommended that if the patient is asymptomatic and the tumor type is known to be responsive to systemic chemotherapy, observation is recommended[23].

1. Therapeutic thoracentesis

Thoracentesis is typically the first step in the management of newly diagnosed MPE. Although symptoms can improve after thoracentesis, almost all patients with MPE experience reaccumulation of fluid and recurrence of symptoms within 30 days. If the patient remains symptomatic despite large-volume thoracentesis, causes such as lymphangitic spread, pulmonary embolism, or malignant airway obstruction should be suspected and investigated appropriately[3,24]. The complications related to thoracentesis include vasovagal reactions, cough, chest pain, hemothorax or pneumothorax, and reexpansion pulmonary edema. In addition, repeated thoracentesis (RT) often leads to fluid loculation, which can make further thoracentesis or subsequent pleurodesis difficult. Therefore, repeated therapeutic thoracentesis should be performed in patients with slowly reaccumulating pleural effusion, low life expectancy (1–3 months), cancers that commonly respond to therapy with resolution of the associated effusions, and who cannot tolerate other more interventional procedures to control pleural fluid, such as pleurodesis[3,23]. To prevent reexpansion pulmonary edema, the amount of fluid removed by thoracentesis should be assessed by patient symptoms (cough, chest discomfort) and limited to 1.5 L on a single occasion[23].

2. Indwelling pleural catheter

IPC is also known as a tunneled or small gauge catheter. Insertion of an IPC is an alternative method for controlling recurrent and symptomatic MPEs, including trapped lung. Several catheters have been developed for this purpose, and published studies employing them have reported encouraging results[23]. Generally, the IPC system is composed of a silicone catheter, allowing ambulatory pleural drainage into plastic vacuum bottles, with fenestrations on the distal margin and a one-way valve on the proximal margin[25]. Placement is simple and is generally performed on an outpatient basis with local anesthesia.

A recent unblinded randomized control study comparing IPC and talc slurry pleurodesis via chest tube demonstrated that there was no significant difference in relieving patient-reported dyspnea between the two methods[26]. However, while the IPC-treated group spent reduced time in the hospital, it was associated with an excess number of adverse events. In light of the limited life span of patients with MPE, IPCs show promise in requiring fewer hospital days, improving dyspnea, and decreasing the need for additional procedures[25,26].

Long-term IPCs may lead to spontaneous pleurodesis in 40–58% of patients with IPC[2,3,23,25]. Therefore, sclerosants can be instilled through the catheter if spontaneous pleurodesis does not occur after several weeks of drainage. In addition, IPC placement and maintenance are safe and free of complications in the vast majority of patients. Complications include infections, clogging of the catheter, or other rare events, such as empyema or tumor spread along the catheter track[25].

3. Pleurodesis

Pleurodesis is defined as the process of mechanical or chemically induced pleural inflammation to obliterate the area between the visceral and parietal pleura and prevent the accumulation of either air or liquid in the pleural space. The pleural mesothelial cell is the primary target for the sclerosant and plays a pivotal role in the entire pleurodesis process. Many different sclerosing agents share similar mechanisms of inducing pleural mesothelial cell-mediated biological responses. These mechanisms include diffuse inflammation with pleural coagulation/fibrinolysis imbalance, recruitment and proliferation of fibroblasts leading to collagen production, and release of several mediators (such as interleukin 8, transforming growth factor β, and basic fibroblast growth factor) that contribute to the required fibrotic state[1,2,27].

Numerous sclerosing agents have been studied in regard to management of MPEs, including talc, tetracycline/doxycycline/minocycline, *Corynebacterium parvum* extract, chemotherapeutic agents, such as bleomycin, cisplatin, doxorubicin, etoposide, and mitomycin, and biologic agents, such as interleukin-2 and interferon[2,3,28-30]. Recent studies suggest that silver nitrate[31] and iodopovidone[32] should be considered as reasonable alternative to other commonly used pleurodesis agents. Another study showed that *Staphylococcus aureus* superantigen, which is a powerful T-cell stimulant, might be an attractive alternative to existing palliative modalities for NSCLC patients with MPE who are not candidates for systemic chemotherapy[33]. However, the results of many studies have demonstrated diverse success rates with pleurodesis and no survival benefit. In addition, due to extensive practice variation and lack of adequately large comparative trials of different agents, the ideal agent choice remains controversial. To date, talc has the best rate of success with pleurodesis and is the preferred agent according to the BTS guidelines[23], a recent review[28], and Cochrance systematic review[30].

The most common complications of chemical pleurodesis are fever and pain. Other rare complications include empyema and local site infection, arrhythmias, cardiac arrest, myocardial infarction, and hypotension. Acute respiratory distress syndrome (ARDS), acute pneumonitis, respiratory failure, and treatment-related mortality have also been reported after talc pleurodesis. ARDS occurs in up to 9% of talc pleurodesis cases[1-3,23,30]. In a recent multicenter, prospective study of 558 patients with MPE, none of the patients who received large-particle talc pleurodesis developed ARDS[34]. The development of ARDS is believed to be due to the small particle size of some talc preparations, which allows for systemic absorption and results in diffuse capillary leakage in the lung itself[1]. Therefore, experts now recommend the use of talc calibrated to a mean particle size of less than 20 μm with no particles less than 10 μm[3].

Generally, pleurodesis should be restricted to patients who have respiratory symptoms caused by effusion, life expectancy longer than 2–3 months, MPE that is nonresponsive to systemic chemotherapy, and lung expansion to the chest wall after therapeutic thoracentesis[2,3]. A pleural agent can be instilled at the bedside via an intrapleural chest catheter (thoracostomy) or using thoracoscopic techniques, including video-assisted thoracoscopic surgery.

The BTS guidelines recommended the following pleurodesis procedure[23]: 1) small-bore (10–14 F) intercostal cath-

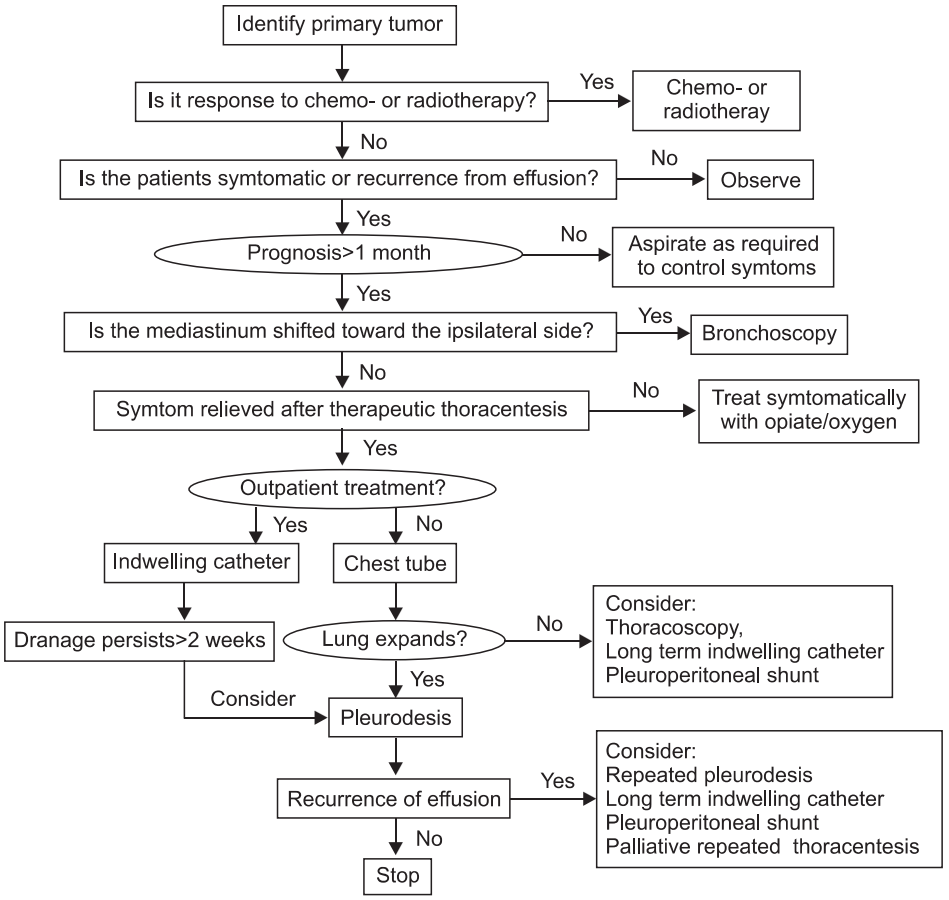

Figure 1. Algorithm for the management of malignant pleural effusion[36]. Adopted from Nam and Ryu[36], with permission from The Korean Association of Internal Medicine.

eters should be the initial choice for effusion drainage and pleurodesis, 2) lidocaine (3 mg/kg; maximum 250 mg) should be administered intrapleurally immediately prior to sclerosant administration, 3) premedication should be considered to alleviate anxiety and pain associated with pleurodesis, 4) patient rotation is not necessary after intrapleural instillation of the sclerosant, 5) the intercostal tube should be clamped for 1 hour after sclerosant administration, and 6) in the absence of excessive fluid drainage (> 250 mL/ day), the intercostal tube should be removed within 24–48 hours of sclerosant administration.

4. Cost considerations

A relative cost-effectiveness analysis of MPE treatment modalities was recently reported, comparing RT, tunneled pleural catheter (TPC), bedside pleurodesis (BP), and thoracoscopic pleurodesis[35]. The results of the analysis showed that TPC is the preferred treatment for patients with MPE and limited survival. BP is the most cost-effective treatment for patients with more prolonged expected survival.

5. New therapeutic approach

Numerous new therapeutic modalities, such as intrapleural chemotherapy and gene therapy, and the use of a subcutaneous implantable pleural port have been investigated in comparison to the present standard treatment[1].

Summary

MPEs usually present in disseminated and advanced stages of malignancy. Prompt diagnosis using a minimally invasive test is important, because the median survival after diagnosis is only 4–9 months. Considerable advances have been made in the diagnosis of MPEs through the development of improved methods for specialized cytologic and imaging studies. In the future, rapidly performed and minimally invasive diagnostic tests will enable clinicians to provide the most effective therapies for patients with MPEs in a timely fashion.

However, all management approaches remain palliative, and relief of dyspnea remains the primary objective. An algorithm based on various guidelines[1,2,23,24] for the management of MPEs is shown in Figure 1[36]. It is important to consider the patient's overall prognosis, symptoms, functional status, and social and financial situation when selecting the modality of choice. It is advisable to select the modality that is most cost-effective, least invasive, and most likely to lead to fewer hospitalization days.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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