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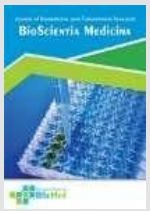

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Diagnosis and Management of Malignant Pleural Effusion: A Narrative Literature Review

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A B S T R A C T

Malignant pleural effusion (MPE) is defined as an effusion that occurs in association with malignancy, as evidenced by the finding of malignant cells on pleural fluid cytology or pleural biopsy. The pathophysiology of MPE is not yet clear, but several hypotheses have been developed to explain the mechanism of MPE. Accumulation of effusion in the pleural cavity occurs due to increased vascular permeability due to the inflammatory reaction caused by the infiltration of cancer cells in the parietal and/or visceral pleura. Other possible mechanisms are the direct invasion of the tumor adjacent to the pleura, obstruction of the lymph nodes, hematogenous spread, and primary pleural tumor. Pleural fluid from a malignant process is usually an exudate. To distinguish between exudate and transudate is to assess the protein and LDH levels of the pleural fluid. Hemorrhagic pleural fluid with a red blood cell count >100,000/mm3 suggests an MPE. Pleural fluid glucose levels at low < 60 mg/dl at about 15-20% MPE. The definitive diagnosis of MPE is by finding malignant cells in the pleural fluid (cytology) or pleural tissue (pathological histology). Management of malignant pleural effusions is principally palliative. Management that is often done in cases of MPE is therapeutic thoracentesis, pleurodesis, drainage with long-term indwelling catheter, manufacture of the pleuroperitoneal shunt, intrapleural therapy, and radiotherapy.

1. Introduction

Malignant pleural effusion (MPE is defined as an effusion that occurs in association with malignancy as evidenced by the finding of malignant cells on pleural fluid cytology or pleural biopsy. In the United Kingdom, there are 40000 cases of MPE per year. It is estimated that 50% of them are metastatic. The most common etiology of MPE, about 80%, is lung cancer, breast cancer, lymphoma, ovarian cancer, and gastric cancer. This malignant pleural effusion is also a very difficult complication of advanced malignancy, with more than 150,000 cases per year in the United States.[1,2]

Malignant pleural effusions may be spread from distant malignancies or maybe an early manifestation of an underlying intrathoracic or extrathoracic malignancy. Many experts classify the causes of MPE into primary malignancies in the lung, breast, ovary, mesothelioma, and other causes. Metastatic adenocarcinoma is the histopathological type of tumor that most often causes MPE.[2]

Malignant pleural effusion is a complex health problem for clinicians. The etiologic diagnosis is a major problem and difficult to determine given the many possible etiologies for the primary tumor of the MPE. The short median survival rate, the high recurrence rate of malignant pleural effusion, and very

rapid occurrence are other problems that further complicate the management of malignant pleural effusion.[3]

Pathogenesis of malignant pleural effusion

The pathophysiology of MPE is not fully understood, but several hypotheses have been developed to explain the mechanism of MPE. Accumulation of effusion in the pleural cavity occurs due to increased vascular permeability due to the inflammatory reaction caused by the infiltration of cancer cells in the parietal and/or visceral pleura. Other possible mechanisms are the direct invasion of the tumor adjacent to the pleura, obstruction of the lymph nodes, hematogenous spread, and primary pleural tumor (mesothelioma). Impaired absorption of fluid by lymph vessels in the parietal pleura due to deposits of cancer cells is the cause of fluid accumulation in the pleural cavity. Another theory states that there is an increase in permeability caused by impaired function of several cytokines, including tumor necrosing factor-α (TNF-α), tumor growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF). Other authors have associated MPE with metabolic disorders that cause hypoproteinemia and a decrease in osmotic pressure which facilitates the seepage of fluid into the pleural space. The mechanism of malignant pleural effusion can be seen in Figure 1.[4,5]

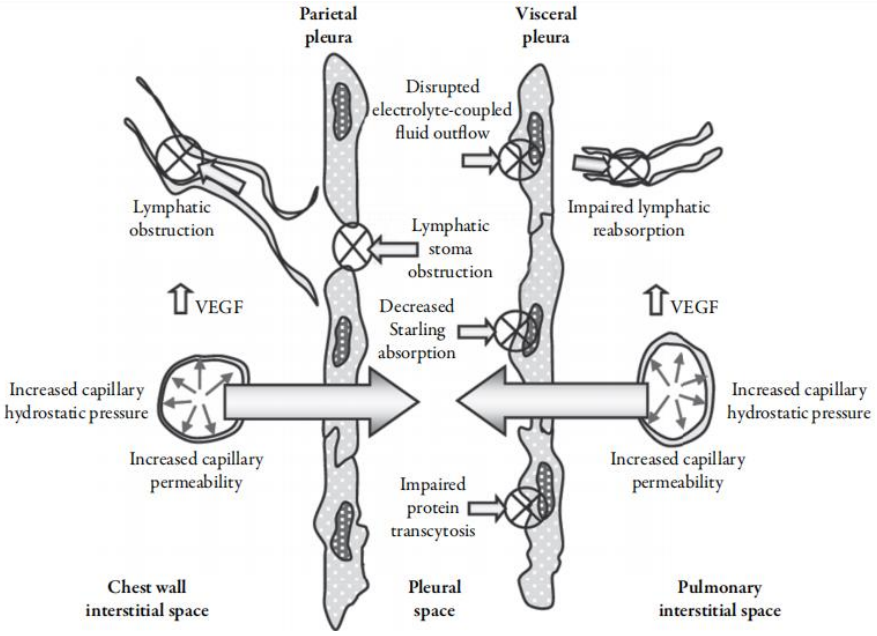

Figure 1. Pathogenesis of malignant pleural effusion.[5]

Malignant pleural effusion is confirmed by the presence of cancer cells in the pleural space. Metastatic malignant pleural effusion originates from the direct spread of malignant cells from surrounding sites (such as lung, breast, and chest wall malignancies), invasion of the pulmonary vasculature by embolization of tumor cells to the visceral pleura, or distant hematogenous metastases from the tumor to the pleura parietal. Tumor deposits spread along the parietal pleural membrane and obstruct the lymphatic stomata that drain the intrapleural fluid.[6]

Pleural tumors will also stimulate the release of chemokines that will increase vascular permeability and the pleural membrane, thus triggering a pleural effusion. Several chemokines, such as CCL22 and CCL17, are found in the MPE. Elevated chemokine

CCL22 in patients with EPG will directly induce T-cell infiltration into the pleural space. In MPE, there is an increase in chemoattractants such as monocyte chemoattractant protein-1 (MCP-1).[3]

Patients with cancer can also cause pleural effusion as an indirect effect of cancer, even without finding cancer cells in the pleural space. This type of effusion, known as a paraneoplastic or paramalignant effusion, can occur from tumor infiltration of mediastinal lymph nodes, pulmonary embolism, superior vena cava syndrome, or decreased oncotic pressure. Approximately 20% to 30% of patients with non-Hodgkin's lymphoma and Hodgkin's disease will develop pleural effusion. Most effusions in patients with Hodgkin's disease are paraneoplastic and result from thoracic duct obstruction. Whereas in most patients with effusion due to non-Hodgkin's lymphoma, there will be T-cell type lymphoma and direct pleural infiltration.[2,7]

Characteristics of malignant pleural effusion fluid

Pleural fluid originating from a malignant process is more often an exudate. To differentiate between exudate and transudate by assessing the protein and LDH levels of the pleural fluid. To determine the exudate, the protein content is > 3 g/dl, and the LDH level is > 200 U/L, in addition to the number of cells > 500/mm3. In addition, according to Light, the exudate found the ratio of pleural fluid protein to serum protein > 0.5; pleural fluid LDH to serum LDH ratio > 0.6; or the pleural fluid LDH level is greater than two-thirds of the upper limit of the normal serum LDH value.[7]

Malignant pleural fluid may be serous, serosanguinous, or hemorrhagic. Hemorrhagic pleural fluid with a red blood cell count >100,000/mm3 suggests an MPE. Hemorrhagic MPE fluids are about 55%. Hemorrhagic pleural effusion in MPE is caused by direct invasion of blood vessels, venous occlusion, induction of tumor angiogenesis, or increased capillary permeability caused by vasoactive agents.[1]

The number of nucleated cells is 1500-4000/µl consisting of lymphocytes, macrophages, and mesothelial cells. In the cell type count, ± 45% of lymphocytes were found, ± 40% of other mononuclear (MN) cells, and ± 15% of polymorphonuclear leukocytes (PMNs) were found. Nearly a third of the cell population is a lymphocyte (50-70% nucleated cells). Polymorphonuclear leukocytes (PMN) cells are usually seen in <25% of the cell population, but if there is active pleural inflammation, PMN leukocytes will appear more dominant.[1,7]

MPE is usually an exudate with a protein concentration of about 4 g/dl. Protein concentrations that have been reported ranged from 1.5-8 g/dl. MPE, which is a transudate, is only less than 5%. Pleural fluid-to-serum protein ratio <0.5 in nearly 20% of MPE; Among this 20%, the ratio of pleural fluid to serum lactate dehydrogenase (LDH) or absolute pleural fluid LDH almost always meets the criteria for exudate. MPE fulfills more of the exudate criteria based on their LDH levels, not because of their protein content.[1]

Nearly one-third of MPE have a pleural fluid pH below 7.3 (pH ranges from 6.95 to 7.29). This is associated with the production of acid produced by the combination of the pleural fluid and the pleural membrane and the inhibition of CO_2 secretion from the pleural cavity. High lactate concentration, high pCO_2, and low pO_2. Pleural fluid glucose levels at low MPE < 60 mg/dl at about 15-20% MPE. Pleural fluid to serum glucose ratio < 0.5. The low glucose level indicates the presence of a high tumor burden in the pleural cavity. Cytological examination and pleural biopsy are more often found to be positive in MPE patients with low glucose levels. With the presence of a high tumor burden so that glucose levels decrease, the patient faces a poor prognosis.[8,9]

Diagnosis of malignant pleural effusion

The diagnosis of malignant pleural effusion is made based on clinical findings, radiological investigations, and pleural fluid examination, both analysis and cytology. The main problem in establishing the diagnosis of MPE is to answer the question of determining the etiology and the primary tumor underlying this condition.[10]

In anamnesis, the history of the clinical course leading to malignancy of the thoracic cavity and other external thoracic organs must be well, systematic and precise. Most cases of MPE are symptomatic, although about 15% are present asymptomatically, especially in patients with fluid volumes of less than 500 ml. Shortness of breath is the most common symptom in cases of MPE, especially if the fluid volume is very large. Other symptoms are chest pain as a result of an inflammatory reaction in the parietal pleura, especially in mesothelioma, cough, coughing up blood (in bronchogenic carcinoma), anorexia, and weight loss.[6,7,11]

The physical examination can determine the location and estimated volume of fluid, in addition to finding other abnormalities in the patient's body, for example, tumors in the neck, supraclavicular, axillary, breast, chest wall, intra-abdominal, or enlarged prostate in men. The amount of pleural fluid less than 300 mL has not caused symptoms on physical examination. Pleural effusion < 300 mL is difficult to detect on physical examination. If the amount of fluid has reached 500 mL, symptoms may be found in the form of slowed or limited chest movement on inspiration on the side containing fluid accumulation. Tactile fremitus is also reduced at the posterior lung floor. Percussion sounds become dull, and breath sounds on auscultation sound weaker even though they are still vesicular. If fluid accumulation exceeds 1,000 mL, lower lung atelectasis is common.[7]

Radiological examination with standard chest radiographs can detect pleural effusions with a volume of at least 50 cc on lateral radiographs and 200 cc on PA radiographs. Massive and recurrent pleural effusions that cause mediastinal thrusting are usually malignant.[3,9]

Thoracic ultrasound is very helpful in confirming fluid and, at the same time, providing a site marker for thoracentesis and pleural biopsy. Thoracic ultrasound has 100% sensitivity in identifying pleural effusions. Findings suggestive of MPE include solid pleural density, hypoechoic pleural thickening with irregular or ill-defined borders, invasion of a pleural-based mass into surrounding tissue, and a circular pattern in the pleural fluid that suggests cellular debris.[5]

CT scan can differentiate malignant and non-malignant pleural effusion. In malignant pleural effusion can be found a picture of pleural thickening > 10 mm, irregular pleura, and nodules in the pleura. Sensitivity 36 - 51% with specificity 88 - 100%. In the MPE, a small volume of fluid not visible on the chest X-ray can be detected with a chest CT scan and, at the same time, can see abnormalities in the lung parenchyma and mediastinum and enlarged lymph nodes. Magnetic resonance imaging (MRI) is not necessary except for the evaluation of chest wall involvement or transdiaphragmatic extension in cases of mesothelioma and prediction for surgery.[6,9]

The definitive diagnosis of MPE is by analysis of the pleural fluid as well as cytologic examination and tissue biopsy. Several characteristics of the pleural fluid can provide clues to the diagnosis of MPE and are important in determining the type of further diagnostic workup. Exudative effusions have a higher likelihood of malignancy than transudates, but this finding is non-specific because of the many causes of inflammation from exudative pleural effusions. In addition, about 3% - 10% of MPE is said to be a transudate pleural effusion.

The amount of pleural fluid required to obtain malignant cells on the MPE is variable. Cytological positivity based on the volume of fluid examined (0.2-10 ml, 15-80 ml, 100-775 ml and 800-2800 ml) and sensitivity for each group were 53.9%, 52%, 46.9% and 63,3%. Positive results also affected the origin of the tumor. 51.6% of patients had primary intrathoracic tumors and 48% in cases of tumor metastasis. The accuracy of these cytology results can be improved by performing re-thoracentesis.[4,7]

Management of malignant pleural effusion

MPE management is palliative in principle. Until now, several treatments that are often performed in cases of MPE are therapeutic thoracentesis, pleurodesis, drainage with a long-term indwelling catheter, and the manufacture of a pleuroperitoneal

shunt.[12,13]

In patients with suspected malignant pleural effusion but asymptomatic, pleural intervention is not performed, whereas, in symptomatic patients with suspicious effusion and impaired lung expansion, large-volume thoracentesis is recommended. Patients with clinical manifestations of pleural effusion and obvious disturbances in lung expansion may receive an Indwelling Pleural Catheter or pleurodesis as the mainstay of treatment for MPE.[7,14]

Therapeutic thoracentesis

Initial management for symptomatic MPE is therapeutic thoracentesis. With this approach will be able to assess the response to shortness of breath, lung reexpansion, and recurrence rate. Although thoracentesis can reduce clinical symptoms, this usually does not last long. Complaints usually recur within 1 month, so repeated thoracentesis is needed. Thoracentesis maximum of 1.5 liters per procedure. Thoracentesis is a safe procedure. Complications have decreased significantly since the use of ultrasound before thoracentesis. The most common complication is pneumothorax. In a retrospective study of 445 patients with MPE who underwent thoracentesis, the incidence of pneumothorax was 0.97% in the pre-procedural ultrasound group, and 8.89% in the non-USG guided thoracentesis group.[9,12,15]

Pleurodesis

Pleurodesis is the permanent union of the parietal and visceral pleura to prevent the accumulation of pleural fluid in the pleural cavity. The exact mechanism that causes this fusion is unclear, but it is thought to be due to inflammation caused by the chemical agents used in pleurodesis. Chemical agents commonly used in pleurodesis are talc, bleomycin, tetracycline, corynebacterium parvum, and doxycyclin. Pleurodesis is the treatment of choice for MPE patients who improve after thoracentesis and good lung re-expansion on postoperative chest radiographs. Until now, the combination of drainage and pleurodesis with a sclerosing agent is an effective measure to treat MPE.[12]

Before performing pleurodesis in malignant pleural effusion, several things need to be considered, including whether the symptoms (especially shortness of breath) are directly related to pleural effusion. If shortness of breath is not caused by pleural effusion, then pleurodesis will not reduce the symptoms of shortness of breath. Some experts recommend performing pleurodesis before recurrence occurs. This is because the success rate of pleurodesis in advanced cancer is relatively lower than that performed in the early stages. Furthermore, what is assessed is impaired lung expansion, occlusion of the bronchi, or trapped lung due to a tumor mass in the pleura can cause. Then what must be considered is life expectancy because pleurodesis is an invasive procedure, so it is not recommended for patients with a short life expectancy. Clinical parameters such as the Karnofsky index can assist decision-making. In addition, examination of the pH and sugar levels in the pleural fluid can also help make decisions. A pH < 7.20 and a sugar level < 60 mg/dl have been associated with a shorter life expectancy (mean life expectancy is only 1.9 months). In such cases, repeated thoracentesis may be an alternative.[16]

Sclerosing agents are introduced into the pleural space for pleurodesis more and more and more. Of these agents, asbestos-free talc is said to be the best for pleurodesis. Many clinical studies support the superior effectiveness of talc over other sclerosing agents, and recently talc has been accepted as the sclerosing agent of choice for pleurodesis in cases of MPE.[17]

The use of talc as a sclerosing agent can be done through two techniques. Talc poudrage by using thoracoscopy to insert talc and talc slurry which inserts talc through a chest tube which is simpler and easier. Dresler et al. (2005), through a randomized trial study comparing the success of pleurodesis of talc poudrage and talc slurry, found results that were not much different, namely 78% and 71%. A meta-analysis study conducted by Xia et al. (2014) stated that talc poudrage was superior to talc slurry with a relative

ratio of 1.12 with a 95% confidence level.[17,18]

The pleurodesis procedure is performed by positioning the patient's half-lateral decubitus on the contralateral side (the side with the chest tube on top) and placing a towel between the patient and the bed. Pethidine 50 mg IM, 15-30 minutes before administration of pleurodesis agent. The chest tube was clamped with 2 clamps, then removed from the WSD adapter, the clamp was opened for a moment so that the lung was slightly collapsed in the pleural cavity, and 20 ml of 2% lidocaine was injected through the chest tube, then the clamp was re-installed. The position of the patient is changed so that the lidocaine is evenly distributed over the entire pleural surface. Using a sterile technique, the sclerosing agent is mixed with the saline solution in a sterile bowl. Aspirate the mixture with a syringe. The syringe is placed on the chest tube, both clamps are opened, and the solution is injected through the chest tube. Rinse with 0.9% NaCl. The patient was asked to breathe several times to draw the solution into the pleural space, the clamps were immediately reattached, and the chest tube was connected to the WSD adapter. Avoid negative suction for 2 hours after pleurodesis. The patient's body position was changed (supine, right-left lateral decubitus) for 2 hours. Then the clamp was removed. The pleural cavity is connected by suction with a pressure of -20 cm H_2O. Consider removing the chest tube if daily pleural drainage is < 100 ml or fluctuations in the WSD bottle are no longer visible.[16]

Indwelling pleural catheters (IPCs)

Long-term indwelling pleural catheters can provide intermittent drainage of up to 1000 ml of pleural fluid 2 to 3 times a week. Decreased complaints of shortness of breath are immediately felt in 94-100% of patients. Indwelling pleural catheters can be used on an outpatient basis, thereby reducing health care costs. This procedure is mainly used in MPE patients with trapped lungs and failed pleurodesis.[14]

Indwelling pleural catheters are performed by placing a silicone catheter in the pleural cavity with a one-way valve at the distal end. This allows the patient to drain the effusion fluid according to the complaints he feels. Drainage of pleural fluid can be done daily or every day. Indwelling pleural catheters can stimulate an inflammatory reaction that can lead to spontaneous pleurodesis. In a meta-analysis study conducted by Van meter et al. (2015), autopleurodesis occurred in 45.6% of 943 MPE cases that underwent IPCs procedures.[18,19]

In general, complications that occur are minimal (5 - 27%), and complications that arise include bleeding, pneumothorax, cellulitis, and empyema. In a multicenter study conducted by Fysh et al. (2013) on 1020 MPE patients undergoing IPCs, the incidence of infection associated with IPCs <5% and controlled with antibiotics (94%). Overall mortality from infections associated with these IPCs is only 0.29%.[20]

Pleuroperitoneal shunting (PPS)

Pleuroperitoeal shunting (PPS) is the treatment of choice in MPE patients with trapped lungs who cannot perform pleurodesis or fail to perform pleurodesis and patients with largely localized effusions. Installation of the tool is done with the help of thoracoscopy or mini-thoracotomy. Equipment for this technique is two unidirectional valves with pleural and peritoneal catheters that are perforated at both ends.[3]

Intrapleural therapy

Intrapleural therapy consists of intrapleural chemotherapy, intrapleural gene therapy, and intrapleural fibrinolysis. Several intrapleural chemotherapy agents used are 5-fluorouracil, cisplatin, etoposide, paclitaxel, carboplatin, cytarabine, and docetaxel are said to be safe in phase 1 and phase 2 studies. Cisplatin is widely used for intrapleural chemotherapy. Abedini et al. (2018), in their study of 18 patients who underwent intrapleural chemotherapy with cisplatin, 50% of them experienced a complete response, 22.2% experienced a partial response, and 2.8% had no response.[13,21]

Approximately 13.5% of MPE patients undergoing IPCs develop a localized pleural effusion. Intrapleural fibrinolysis can overcome this and can improve pleural

drainage. An observational study conducted by Thomas et al. (2015) in 66 patients with localized MPE who underwent intrapleural fibrinolytic (tissue plasminogen activator, urokinase, and streptokinase) had a 93% improvement in pleural drainage and clinical improvement in dyspnea in 83% of patients.[10,22]

Radiotherapy

Approximately 40% of mesothelioma patients suffer from needle tract metastases NTM after intervention in the pleura, especially after thoracostomy and thoracoscopy. This can be prevented by local radiation at the access site within 2 weeks. SMART Study in 2011 - 2014 on 213 mesothelioma patients concluded that patients who underwent prophylactic radiotherapy did not experience a decrease in the incidence of NTM and did not improve clinical and quality of life.[10,23]

2. Conclusion

Malignant pleural effusion is an effusion that occurs in association with malignancy, as evidenced by the discovery of malignant cells on pleural fluid cytology or pleural biopsy. Malignant pleural effusion is a complication of several cancers, the most common being lung cancer, breast cancer, lymphoma, gynecological malignancy, and mesothelioma. The definitive diagnosis of MPE is by finding malignant cells in the pleural fluid (cytology) or pleural tissue (pathological histology). Management of malignant pleural effusions is principally palliative. Management that is often done in cases of MPE is therapeutic thoracentesis, pleurodesis, drainage with long-term indwelling catheter, manufacture of the pleuroperitoneal shunt, intrapleural therapy, and radiotherapy.

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