Original Article

Epidemiology Of Pleural Effusion Syndrome In Malignant Neoplasms: Therapeutic Tactics

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Abstract

This article discusses the epidemiology of pleural effusion syndrome in malignant neoplasms: treatment and analyzes the worldwide data of scientists.

Keywords: epidemiology, pleural effusion syndrome, malignancies, medical management, scientists.

Introduction

The incidence of malignant pleural effusion (MPE) is 660 cases per million population according to the American and British Society of Thoracic Surgeons, affecting more than 1 million people worldwide and is a growing public health burden [51,9,10,13]. In the United States (USA) alone, more than 125,000 hospital admissions per year are due to MPE, with an in-hospital mortality rate of about 12% and associated costs of more than US$5 billion per year [43, 55].

Lung cancer is the most common cause of MPE, accounting for almost half of all cases, some studies have shown that up to 15% of lung cancer patients had MPE at the time of first presentation and up to 50% develop MPE during the course of the disease [14,21,7]. In lung cancer patients, secondary malignant pleural effusion is observed in 35% of cases. [46,8,9]. At the time of diagnosis, 15% of patients already have a pleural effusion, while over time this figure increases to 50%. Of the histological types, adenocarcinoma is the most common cause of MPE, while this condition is relatively less common in small cell lung cancer [9,11].

Breast cancer (BC) is the second most common cause of malignant pleural effusion and is the cause of complications in 23% of cases [47,14,37]. Banarjee et al. demonstrated that in patients with breast cancer, in 70% of cases, the effusion was observed on the side of the breast lesion, in 20% of cases on the opposite side, while bilateral effusion was observed in only 10% of cases [47].

Hematologic malignancies, especially lymphomas, are responsible for 10% of cases of MPE [37,36,14]. In Hodgkin's lymphomas, the cause is late in the disease, while in non-Hodgkin's lymphomas, pleural effusion may occur early in the disease. MPE is extremely rare in lesions of the female genital area, gastrointestinal tract, and genitourinary system [36,12,28,59,16].

There is also a significant geographical variation in the incidence of malignant pleural mesothelioma, which in 90% of cases is complicated by malignant pleural effusion [32,38,53,54].

The causes of MPE are direct germination of tumors (breast cancer, lung cancer, chest) into the pleural cavity, spread to the visceral pleura through embolization and invasion of the vessels of the pulmonary system, as well as spread to the parietal pleura through hematogenous spread and metastasis [37,27,41,10].

Malignant cells in the pleural cavity can block the lymphatic vessels, thereby disrupting the drainage of the pleural cavity. Also, due to invasion into the lymph nodes of the mediastinum, bronchial obstruction, chemoradiotherapy can cause a decrease in oncotic pressure and thereby cause a malignant pleural effusion. Another cause of MPE is angiogenesis, which causes the loss of the ability to form capillaries in the parietal pleura. [6,8,9,14].

The very occurrence of MPE is due to direct or hematogenous spread of malignant cells into the pleural cavity, as well as a secondary lesion of the parietal pleura [9,14,18,45]. Malignancy can also cause pleural effusion without direct involvement of the pleura. This condition, known as paraneoplastic effusion, can occur through various mechanisms such as obstructive pneumopathy, pulmonary embolism, mediastinal lymphatic obstruction, and superior vena cava syndrome. [10,12,16,18].

In 75% of cases of MPE, the volume of effusion varies between 500-2000 ml, while in only 10% of cases of PES, a massive effusion can be observed. [12,20,22,32]. Bilateral pleural effusion is observed in 50% of cases, without signs of cardiomegaly. An effusion of 200-300 ml can be diagnosed by x-ray, while a small effusion can be detected by computed tomography [13,15,22]. Ultrasound is an auxiliary research method for determining the small volume of fluid and navigation for thoracentesis. In 50% of cases, the amount of effusion is less than 500 ml. MRI (Magnetic resonance imaging) and PET/CT (computed tomography) are not used to diagnose MPE [56,30,42,].

An integral diagnostic step of MPE is the sampling of pleural fluid through thoracentesis, a cytological conclusion that gives a positive result in 40-80% [35,11,13]. However, its diagnostic accuracy is directly proportional to the number of thoracentesis performed. So, in the case of a single sampling of pleural fluid, the possibility of making a diagnosis through a cytological examination is 65%, a double sampling is 92%, and a 3-fold sampling 97% [7,17,23,33]. However, it should be noted that the amount of fluid withdrawn does not affect the response results.

An important characteristic of the pleural fluid is the glucose content and the indicator of acid-base balance in it. Usually the level of glucose in the pleural fluid is equal to that of plasma, however, due to the presence of a malignant tumor in the pleural cavity and its consumption of glucose, its level is often below 60 mg / dl (in milligrams per deciliter) [39,49]. This condition is a negative prognostic factor. In addition, low pH is also an unfavorable sign, as it is a predictor of treatment failure when using pleurodesis [49,53]. Also, one of the substances that can be found in the pleural fluid is amylase, which is often found in adenocarcinoma [56,11].

Immunohistochemical study is an important method for the differential diagnosis of adenocarcinoma and pleural mesothelioma. Often metastatic adenocarcinoma stains with Anti-CEA, Anti-Leu M1 and Musin, while mesothelial cells do not [26,47,]. In addition, IHC is useful in the diagnosis of pleural effusions caused by lymphomas. Percutaneous biopsy of the pleura, according to various authors, gives a positive result in 40-75% [24,55,18,19].

Dyspnea is the most common symptom in patients with pleural effusion and is one of the primary indications for intervention. The degree of dyspnea is often disproportionate to the size of the effusion, as underlying lung cancer can cause both lung collapse and pulmonary artery infiltration leading to reduced ventilation, which in turn leads to perfusion mismatch [19,57,14].

Chest pain is uncharacteristic; however, it can be observed in case of germination into the chest wall or malignant pleural effusion [1,27].

Interventions to control MPE are palliative as there is no procedure to date, noting that so far it has been shown to prolong life under these conditions. Unfortunately, there is no single approach to the treatment of MPE, and there is also a remarkably small number of scientific papers with high reliability of the study results, which is not surprising, a high degree of variability in the treatment of this condition [8,10,16].

The more therapeutic options we have, the greater the differences in practice, a trend that is especially noticeable when analyzing the treatment approaches of pulmonologists with representatives of other specialties. Pulmonologists are more likely to use talcum slurry pleurodesis or permanent pleural catheterization, even when video-assisted thoracoscopic surgery (VATS) is required, while nearly 70% of cardiothoracic surgeons opt for VATS pleurodesis as first-line therapy [2,3,11].

Another important limiting factor described in the literature is the fact that the main outcome measures were dynamic changes according to imaging modalities. Currently, one of the main indicators of treatment outcome and outcome measures are related to the patient, and include time spent in the hospital (or hospitalizations), symptom mitigation and improvement in quality of life [26,55,56].

The development of MPE is often associated with a poor prognosis, and indicates the incurability of the disease. The average life expectancy is about 3-12 months, but can vary significantly depending on the histological type, the general condition of the patient, the stage and sensitivity of the malignant neoplasm to chemoradiation [7,59]. Estimating expected survival in patients with MPE is of paramount importance as it helps in clinical decision making and influences the choice of intervention [35,12,13].

Patients with metastatic lung cancer and poor general condition have a significantly worse expected survival than patients with malignant pleural mesothelioma, who are in good condition and who have a number of favorable pleural fluid parameters (median survival 1.5 vs 10.5 months) [55,51].

Once the diagnosis of MPE is confirmed, palliative measures are assessed to improve quality of life (reduce dyspnea), limit pleural procedures, and eliminate the need for repeat hospital or doctor visits [48,53]. The choice of the type of procedure is influenced by many factors, such as prognosis, patient status, tumor size/recurrence rate, chemosensitivity of malignancy, experience of specialists and their personal preferences, as well as whether the lung will expand after fluid evacuation, whether therapeutic thoracentesis will bring relief of symptoms [43,55].

There are currently several areas of research that are open for discussion, further research, and are of great interest. As is known, tumor biomarkers can be divided into prognostic biomarkers (e.g., HER2, which predicts response to trastuzumab in breast cancer); predictive biomarkers and; diagnostic biomarkers (e.g., DNA testing of feces for colorectal cancer) [14,16,15,50]. A correct prognosis allows us to find adequate therapy and timely diagnosis, giving the patient a chance for a better outcome. Despite the large number of potential biomarkers, there are only a limited number of prognostic and diagnostic tumor biomarkers that have been confirmed (for example, mamma globulin, CK19 - BC diagnosis; BRCA1 and 2 gene mutations - OC diagnosis) [56,57,58]. Some examples of potential biomarkers related to MRI and major diseases: described by Porcel et al. He suggested that pleural fluid might represent an adequate sample for the analysis of molecular markers that would help patients with NSCLC choose appropriate targeted therapy [57,16].

Of particular interest are biomarkers in malignant neoplasms of the pleura. Numerous biomarkers have been reported including osteopontin, fibulin-3, soluble mesothelin proteins, high motility group 1 block, miRNA, etc [16,34,40,].

Of note are the promising results of the KEYNOTE-028 study (ClinicalTrials.gov ID: NCT02054806) using the single agent pembrolizumab, an antibody to programmed death protein 1 (PD-1), in patients with malignant pleural mesothelioma. This, in turn, has revived interest in the use of immunotherapy for mesothelioma and other advanced solid tumors [27]. However, to date there are no international guidelines recommending the use of anticancer treatment before standard palliative treatments for MPE [52,32,].

Moreover, there are several other areas of interest that are not fully understood. There is a lack of studies comparing palliative procedures for MPE with anticancer treatment [17]. Due to MPE being more commonly a complication of advanced malignancy, approaches currently remain largely focused on treating symptoms. It remains true that for the most effective treatment, clinicians must be able to identify the underlying disease early enough. Another area of interest with a low evidence base is the treatment of congestive lung in MPE. The authors believe that the use of the VO^2 max (maximal oxygen consumption) is effective; however, the use of other methods (eg, the use of intrapleural fibrinolytic therapy) may also be useful in certain cases. Moreover, there is still no consensus on the amount of pleural exudate to be removed. Traditionally, in therapeutic settings, fluid removal was stopped when the total amount of fluid removed reached 1000-1500 ml due to fear of re-expansion of the lung's edema and pneumothorax ex vacuo [55,51].

Ault et al. showed that general assumptions regarding the Safety Guidelines for the Treatment of Pleural Pathologies are usually inaccurate [43]. The authors believe that there is currently no absolute maximum volume of fluid that can be safely removed during therapeutic thoracentesis. The decision on how much fluid to remove should remain within the discretion of the physician [43,38,42].

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