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Malignant mesothelioma: A narrative review of the literature

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Abstract

Malignant mesothelioma, predominantly linked to asbestos exposure, is an aggressive cancer originating from mesothelial cells, which safeguard internal organs. Although rare, mesothelioma frequently affects the pleural layer surrounding the lungs. While asbestos, particularly amosite and crocidolite types, is the chief risk factor, the disease's infrequency means not every exposed individual contracts it. This malignancy, especially its pleural form, mainly arises from inhaled asbestos, causing cellular disruptions and eventual cancerous growths. Occupational exposure is common in professions like shipbuilding, mining, and insulation tasks, among others. The U.S. registers approximately 2,500 mesothelioma cases yearly, with the disease predominantly affecting older males following decades of asbestos exposure. Epidemiologically, areas with rampant asbestos use, such as China, report higher incidences, while regions like Hong Kong exhibit low rates despite high exposure. From a pathophysiological standpoint, mesothelioma exists in three primary forms: epithelioid, sarcomatoid, and mixed, with epithelioid variants having better prognoses. Clinical evaluations primarily involve chest CT scans and thoracoscopic biopsies. Distinguishing malignant pleural mesothelioma from other conditions is crucial. Prognostication is complicated, but several vital factors, such as disease stage and histological type, influence outcomes. Two main scoring systems, the Cancer and Leukemia Group B (CALGB) index and the European Organisation for the Research and Treatment of Cancer (EORTC) index, assist in patient stratification. Regarding treatment, standard therapeutic strategies, barring localized forms, seldom offer a cure. Procedures like pleurectomy offer symptom relief, while trimodality therapy combines chemotherapy, surgery, and radiation, often showing promising results when applied in specialized centers. Phase II studies indicate extended survival rates with post-surgery adjuvant radiation therapy.

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Introduction

Malignant mesothelioma is a relatively uncommon cancer that primarily arises from the mesothelial cells, which form the protective linings of the body's internal organs. The primary cause behind the development of this aggressive cancer is exposure to asbestos, a group of naturally occurring minerals used for decades in various industries because of their heat resistance, fiber strength, and insulating properties. Not all types of asbestos are equally dangerous; specifically, two subtypes, amosite and crocidolite asbestos, have been more directly linked to malignant mesothelioma (1).

Mesothelial cells play a vital role in covering and safeguarding the body's internal organs, such as the lungs, heart, and abdomen. Given their widespread presence, mesothelioma can manifest in different areas of the body. However, it most commonly develops in the pleural layer, the lining around the lungs, leading to the condition known as malignant pleural mesothelioma. Other mesothelial layers like the peritoneum, which surrounds the abdominal cavity, and the pericardium, which encases the heart, can also be affected, but these instances are less common (2).

The strong connection between asbestos exposure and mesothelioma has been substantiated by multiple studies and researches. The fibers of amosite and crocidolite asbestos, when inhaled or ingested, can lodge themselves into the mesothelial cells. Over time, this can lead to genetic mutations, ultimately giving rise to cancerous growths. It's worth noting that while asbestos is the main risk factor, mesothelioma's rarity means not everyone exposed develops the disease. Nonetheless, understanding the risks and the need for early detection can make a significant difference in outcomes for those affected (3,4).

The purpose of this review is to comprehensively analyze malignant mesothelioma's etiology, epidemiology, pathophysiology, clinical evaluation, diagnosis, treatment, and global implications.

Etiology

Malignant pleural mesothelioma is predominantly related to asbestos inhalation. Some studies propose that inhaling asbestos may cause ongoing pleural inflammation, disrupt normal cell division, activate cancer-causing genes, and generate harmful free radicals. While other factors like ionizing radiation from treatments for Hodgkin lymphoma or a hereditary mutation of BRCA 1 Associated Protein (BAP1) have also been linked, smoking hasn't been connected to mesothelioma. However, combining smoking with asbestos exposure notably elevates lung cancer risk (5,6). Certain occupations increase the likelihood of asbestos exposure (**Table 1**).

Table 1: Professions that pose risks

Occupations
Shipbuilding
Mining
Ceramics industry
Asbestos-inclusive cement production
Manufacturing auto components, particularly brake linings
Paper milling
Insulation tasks
Railroad maintenance

For statistical evaluation, the study utilized SPSS for Windows (version 25.0 by IBM Corp.). Continuous data points are expressed as mean ± standard deviation (SD), and categorical data is shown in terms of numbers and percentages (%). The independet t-test was used for the data with continue and normal distribution, and the Chi-square test was used for the categorical data. While the logistic regression test was used to determine the predictor, ROC analysis was used to evaluate the specificity and sensitivity of the achievement status.

Contrarily, no concrete evidence links alcohol, tobacco, or food consumption with malignant pleural mesothelioma (7). Genetic factors might enhance one's vulnerability to this disease. Studies have found that patients with this condition often lose a copy of chromosome 22. Additionally, other observed chromosomal irregularities involve deletions in chromosomal arms like 3p, 1p, 6q, and 9p (7).

Epidemiology

Each year, the U.S. sees roughly 2,500 new cases of malignant pleural mesothelioma. In contrast, lung cancer cases surpass 160,000 annually. A significant majority of mesothelioma cases in the U.S. can be traced back to asbestos exposure (8,9).

On average, patients survive about a year after diagnosis, with only a few experiencing long-term survival. This disease primarily affects men and typically arises in one's later years. The average age at diagnosis is 72, and it often follows 2 to 4 decades of asbestos exposure. While instances in children exist, they are not attributed to asbestos (7-9).

In countries like China, where asbestos use is rampant and poorly regulated, malignant pleural mesothelioma is more common. Conversely, places like Hong Kong have high asbestos exposure but surprisingly low mesothelioma rates. The reasons behind such disparities remain a mystery (8).

Pathophysiology

Mesothelioma has three main types: epithelioid, sarcomatoid, and mixed. Outcomes tend to be better for those with the epithelioid variety. Typically, these tumors are multifocal, presenting as numerous nodules that originate in the parietal pleura. From there, they spread locally to the visceral pleura and might later reach the chest wall, diaphragm, or mediastinum. Lymphatic spread initially affects the bronchopulmonary or hilar nodes, and then progresses to nodes such as the carinal, internal mammary, or peridiaphragmatic (9,10).

The metastatic spread to lymph nodes in malignant pleural mesothelioma differs from lung cancer. In the case of mesothelioma, lymph nodes experience a direct local invasion. However, it's worth noting that lymph node involvement in mesothelioma is relatively rare (11).

Clinical evaluation

The assessment involves a chest CT scan using intravenous contrast, a thoracoscopic examination of the pleura for biopsy, and, when pleural effusion is observed, thoracentesis followed by cytologic analysis. It's essential to differentiate malignant pleural mesothelioma from other conditions (12,13). This includes non-malignant pleural disorders and metastases from other tumors, such as lung adenocarcinoma or sarcomas of the chest wall. A chest CT might reveal specific regions of pleural thickness and, in advanced stages, an extensive invasive tumor. For checking metastatic disease, PET scans are beneficial, while MRI and laparoscopy can determine any diaphragmatic involvement. Megakaryocyte potentiating factor acts as a blood biomarker for malignant pleural mesothelioma. Before undergoing surgery, every patient must receive clearance from a cardiologist. They should undergo a stress test, and efforts should be made to improve lung functionality (13-15).

Diagnosis

Assessing the prognosis for malignant mesothelioma patients can be challenging due to the variability in diagnosis timing and disease progression speed (13-15). Comprehensive retrospective studies on pleural mesothelioma patients have highlighted several crucial prognostic factors (16,17) (**Table 2**).

Table 2: Prognostic factors

Factors
Disease stage.
Patient age.
Performance status (PS).
Histological type.

Two key prognostic scoring systems, specifically the Cancer and Leukemia Group B (CALGB) index and the European Organisation for the Research and Treatment of Cancer (EORTC) index, are utilized for stratifying patients in clinical trials for advanced, non-operable mesothelioma (18).

The CALGB index was formed from analyzing the clinical data of 337 patients over a decade who underwent chemotherapy for advanced mesothelioma. This index yielded six prognosis groups with median survival rates ranging from about 14 months to just over a month, based on a combination of factors like age, PS, hemoglobin levels, and white blood cell count (18). When tested on 105 patients in a separate phase II trial, the index's efficacy was evident, although there was some survival overlap in the intermediate groups (19).

On the other hand, the EORTC index was derived from data on 181 patients from five phase II chemotherapy trials over nine years. Several factors were pinpointed as associated with reduced survival (20) (**Table 3**).

Patients received a prognostic score based on these factors. They were then divided into two categories:

low-risk (score of 1.27 or below, indicating 0-2 risk factors) and high-risk (score above 1.27, with 3-5 risk factors). The mortality risk was almost three times higher for high-risk individuals than their low-risk counterparts, with stark differences in 1-year survival rates between the two groups (18-20).

Table 3: Survival predictors

Predictors
WBC count >8.3 × 109/L
ECOG PS ≥1
Unconfirmed histology on central review
Nonepithelioid histology
Male sex

Treatment

Typically, standard treatments for mesothelioma, except for the localized form, are not considered curative. While aggressive treatment approaches can result in extended survival for some, it remains debatable whether overall survival (OS) is significantly influenced by various treatments or their combinations (21-23).

Extrapleural pneumonectomy might enhance recurrence-free survival in select early-stage disease patients, but its effects on OS remain undetermined. Procedures such as pleurectomy and decortication can offer palliative relief from symptoms like effusions, discomfort from tumor size, and pain from tumor invasion (24). More details can be found under the topic of Cancer Pain. Trimodality therapy is a term for the combined use of chemotherapy, definitive surgery, and radiation therapy. Given mesothelioma's rarity and the intricate nature of selecting patients, surgical techniques, and treatment sequencing, outcomes are more favorable when administered in specialized centers with a track record in mesothelioma management. Mortality rates for pleurectomy with decortication are below 2%. In contrast, mortality rates for extrapleural pneumonectomy fluctuate between 6% and 30% (24,25).

A number of phase II studies have indicated extended survival durations (when contrasted with past benchmarks) for chosen patients who underwent adjuvant radiation therapy post-definitive surgery (26) The majority of pleural mesothelioma patients who undergo radiation therapy find relief from pain, although the relief tends to be temporary (24-26). Additional phase II studies examined neoadjuvant chemotherapy (primarily using platinum combined with pemetrexed or gemcitabine) which was then followed by definitive surgery and supplementary radiation therapy (24-26). Such studies revealed extended survival in contrast to previous benchmarks. Nonetheless, these benefits are still awaiting validation through a randomized study.

Conclusions

Malignant mesothelioma, closely tied to asbestos exposure, remains a rare yet aggressive cancer. Its diverse presentation and elusive etiology highlight the need for ongoing research. Despite various treatment options, outcomes are suboptimal. Established prognostic factors and scoring systems aid in patient stratification. Global efforts must prioritize regulating asbestos use. As treatment evolves, evidence mostly stems from phase II studies, necessitating randomized trial validation. Proactive research, prevention, and refined treatments are essential for improving patient outcomes.

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Data availability

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Contributions

Research concept and design: **LL**
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Collection and/or assembly of data: **LL**
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