Malignant Mesothelioma of the Pleural Space

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Malignant pleural mesothelioma is an aggressive tumor associated with exposure to asbestos. Although this disease is rare, with an annual incidence in the United States of 2,000 to 3,000 cases, a steady rise in cases has

Introduction

Diffuse malignant pleural mesothelioma is an uncommon tumor characterized by local aggressiveness and historically poor patient prognosis. The relationship between asbestos and mesothelioma is a classic epidemiologic model of exposure leading to disease. At present, the evaluation of a patient with suspected mesothelioma can be challenging due to difficulties in securing a pathologic diagnosis and determining the appropriate management. Limited knowledge of the biology of this tumor and its poor response to conventional therapy has resulted in a variety of therapeutic approaches.

Clinical Presentation and Diagnostic Work-Up

The latency period between exposure to asbestos and the appearance of mesothelioma can be more than 15 years (median, 32 years).[1] The majority of patients seen are over 55 years of age at presentation.[2] The disease is more common in men (male-female ratio, 3:1).[3] Mesothelioma can occur in children but is thought to be unassociated with asbestos exposure.[4] The initial clinical presentation of mesothelioma may be variable. Most series report a 2- to 3-month median time from the appearance of symptoms to diagnosis.[5] Patients may present with nonspecific complaints, such as night sweats, weight loss, malaise, cough, and fever. Alternatively, 60% to 90% of patients may have specific complaints of dyspnea or chest pain.

Typically, dyspnea is first caused by a pleural effusion.[6] As the disease progresses, the effusion becomes loculated and the pleural space is replaced by tumor. In patients with progressive disease, dyspnea is caused by constriction over the underlying lung parenchyma. Usually, the chest pain is initially reported as poorly localized or dull; however, as the disease progresses, the pain becomes localized due to entrapment of the intercostal nerves. Historically, the right chest has been more commonly affected than the left (60% vs 40% of cases).[7] In advanced stages, chest and abdominal wall deformity, ascites, and cachexia are commonly observed due to uncontrollable tumor growth.[5] Metastases are infrequent; however, they have been observed in cases of advanced disease or in long-term survivors of multimodality therapy. The physical findings of mesothelioma vary according to the stage of the disease. Decreased breath sounds on the ipsilateral side secondary to pleural effusion may be the only early finding. Once the disease is advanced, a chest or abdominal mass may be palpable. The presence of an abdominal mass is an ominous sign indicating transdiaphragmatic involvement and an unresectable tumor. Symptoms of bowel obstruction indicate very advanced disease.

Although laboratory evaluation of the mesothelioma patient is typically unremarkable, nonspecific findings, such as anemia of chronic disease, eosinophilia, and hypergammaglobulinemia, may be present.[7] Occasionally, thrombocytosis (> 400 × 10^9/L) may be observed; it is thought to signal a worse prognosis.[8]

Radiologic Evaluation

The radiographic presentation of mesothelioma can be extremely variable, depending on the stage of the disease. Chest x-rays, as well as computed tomography (CT) and magnetic resonance imaging (MRI) of the chest, play a major role in the evaluation of this disease. Chest x-rays are helpful in showing pleural plaques, pleural thickening, pleural effusion, and parenchymal fibrosis—all of which are commonly present in mesothelioma patients. Scans of the chest improve visualization of these abnormalities and permit a better evaluation of tumor infiltration into fissures and mediastinal...
structures, as well as mediastinal adenopathy. Chest wall involvement, as evidenced by distortion of the intercostal spaces and infiltration of extrapleural soft tissue or encasement of the hemidiaphragm (suggesting diaphragmatic involvement), may be more difficult to determine with CT. MRI may be more useful in detecting these abnormalities because of its ability to define the disease extent by signal alteration in T1- and T2-weighted images. The use of both CT and MRI has been demonstrated to be effective in determining resectability. The radiologic signs of unresectability include the following: mediastinal organ invasion and full-thickness transdiaphragmatic involvement. Recently, fluorodeoxyglucose positron emission tomography (PET) has been shown to be a sensitive method for diagnosing and determining the invasiveness of diffuse malignant pleural mesothelioma. In addition to the aforementioned imaging modalities, two-dimensional echocardiography is utilized in the preoperative imaging work-up to rule out pericardial involvement and assess cardiac function.

**Thoracocentesis, Pleuroscopy, and Thoracoscopy**

Thoracocentesis is a valuable tool in the initial evaluation of a patient who presents with a pleural effusion. The fluid sample retrieved can be evaluated for macroscopic characteristics, as well as cytology and the chemistry profile. In mesothelioma, the fluid is typically clear yellow and rarely yields a diagnosis (30% to 35%) due to the difficulty in distinguishing between tumor cells and reactive mesothelial cells. Recently, however, with the development of histochemical and immunohisto-chemical staining techniques, as well as electron microscopic analysis, diagnostic accuracy has improved. Closed pleural needle biopsy has also been used to rule out diffuse malignant pleural mesothelioma. The results of this technique should be interpreted with caution due to its high false-negative rate; however, with the availability of more accurate histopathologic tests, diagnostic accuracy is improving.

With the evolution of minimally invasive technology, the evaluation of patients via pleuroscopy or thoracoscopy has been encouraged. These techniques allow for better visualization of the tumor, which, in turn, improves the adequacy of tissue sample biopsies. In cases that are not amenable to pleuroscopy, open biopsy is also encouraged. It is important to place biopsy sites or incisions strategically so that they can be resected should the patient be a candidate for surgical therapy. Mesothelioma is well known to be locally aggressive and recur at these sites. If the patient is not a candidate for surgery, pleuroscopy with biopsy is still the procedure of choice at Brigham and Women’s Hospital to confirm the diagnosis of mesothelioma.

**Pathology**

Microscopically, the cells of origin are pluripotential cells that can differentiate into mesenchymal or epithelial cells. Three different histologic types have been described: epithelial, sarcomatous, and mixed. The histologic classification also has prognostic significance. The sarcomatous and mixed types have been shown to correlate with a poorer patient prognosis than the epithelial type. The definitive diagnosis of diffuse malignant pleural mesothelioma may be elusive. It is particularly difficult to distinguish diffuse malignant pleural mesothelioma from adenocarcinoma. Table 1 displays useful parameters to differentiate between those two pathologies. In terms of gross pathology, the pleural surfaces of patients with mesothelioma are seeded by malignant cells. These cells grow into small nodularities that coalesce to create tumor masses. Over time, the pleural space is replaced by tumor, creating mechanical constriction of the normal lung parenchyma and pericardium. The uncontrollable tumor growth may invade the mediastinum, chest wall, or subdiaphragmatic structures. The patient usually succumbs to conditions secondary to local tumor invasion, as opposed to metastatic disease.

**Staging Systems**

Currently, no widely accepted staging system for diffuse malignant pleural mesothelioma exists. The first staging system, proposed by Butchart et al in 1976 and based on 29 patients, is widely used. This system has two main weaknesses: (1) nodes are classified as extrathoracic or intrathoracic based on their location, rather than on tumor burden; and (2) there is no correlation between stage and survival. In 1990, the International Union Against Cancer developed a system based on tumor, nodal
status, and metastases. This TNM system also had limitations and was revised in 1995 by the International Mesothelioma Interest Group (Table 2). It has to be validated in a prospective, multicenter, randomized trial.

Sugarbaker and colleagues proposed the Brigham Staging System based on tumor, resectability, and nodal status[24]; this system was revised in 1998 (Table 3) based on survival data from 183 patients (Figure 1).[25] For stage I disease, median patient survival was 25 months, as compared with median survival times of 20 and 16 months for patients with stage II and III disease, respectively.

**Single-Modality Therapy**

Traditional single therapeutic modalities have had little success in the treatment of diffuse malignant pleural mesothelioma.[26] When used alone, surgery (extrapleural pneumonectomy or pleurectomy)[27] or radiotherapy[28] have demonstrated unsatisfactory results, primarily due to the locally invasive behavior of this disease.

Chemotherapeutic agents, such as cyclophosphamide (Cytoxan, Neosar), doxorubicin, and cisplatin (Platinol), have demonstrated a degree of activity against mesothelioma (20% to 30% response rate); however, they have not shown any clear survival benefit when used alone or in combination.[29,30]

**Multimodality Therapy**

The poor survival rates and local control issues associated with single-modality therapy led to the development of a multimodality approach. This consists of a cytoreductive surgical procedure followed by chemotherapy and radiotherapy. The local control provided by cytoreductive surgery is maximized with adjuvant radiotherapy while simultaneously limiting such adverse effects as radiation pneumonitis. Similarly, adjuvant chemotherapy is thought to be more effective when the tumor burden has been reduced and the therapy is given in combination with other therapeutic modalities.

**Surgical Procedures**

Two surgical procedures have been used in the treatment of diffuse malignant pleural mesothelioma: pleurectomy/decortication and extrapleural pneumonectomy (Table 4).[19] These two cytoreductive procedures have not been compared in a randomized study.

**Pleurectomy/decortication** requires less cardiorespiratory reserve than does extrapleural pneumonectomy. A low morbidity (25%) and a low mortality (2%) have been reported in pleurectomy series.[31]

However, pleurectomy has four limitations: It may not be technically feasible if the pleural space is completely sealed by the tumor. It provides limited cytoreduction, particularly in cases of deep tumor invasion into the fissures, and results in a more rapid local recurrence, as compared with extrapleural pneumonectomy. Also, because of the potential for post-radiation pneumonitis, limited amounts of postoperative radiation therapy can be delivered to the ipsilateral hemithorax following pleurectomy.

**Extrapleural pneumonectomy** is a more extensive cytoreductive procedure. Historically, it has been characterized by increased mortality and morbidity.[21] Recently, extrapleural pneumonectomy has been performed as part of a multimodality approach with a 3.8% mortality.[25] Extrapleural pneumonectomy in a multimodality setting provides the best local control because it removes the complete pleural sac along with the lung parenchyma. This radical resection permits the delivery of a higher amount of radiotherapy without the concern for pneumonitis. The disadvantages of extrapleural pneumonectomy are related to the physiologic reserve required to undergo this procedure and its higher morbidity compared with pleurectomy.

**Preoperative Assessment**—Careful preoperative assessment of the patient is necessary prior to surgery, when surgery is part of a multimodality protocol. Although the eligibility criteria vary among institutions, the following approach has been used successfully at Brigham and Women’s Hospital in the multimodality setting.

First, premorbid conditions (eg, cardiac, renal, and hepatic) must be clearly documented and assessed because they may be aggravated by the multimodality regime. A Karnofsky performance score of ≥70 is recommended.[32]

Second, the patient must have sufficient physiologic reserve to tolerate the resection and subsequent chemotherapy and radiotherapy. Cardiopulmonary physiologic status can be determined using pulmonary function tests, arterial blood gases, and echocardiography. Patients with a forced
expiratory volume in 1 second (FEV$_1$) < 1 L, carbon dioxide partial pressure (PCO$_2$) > 45 mm Hg, oxygen partial pressure (PO$_2$) < 65 mm Hg, and an ejection fraction < 45% are excluded from surgery. If the patient has a preoperative FEV$_1$ < 2 L, quantitative ventilation perfusion scanning may be useful in more accurately predicting postoperative pulmonary function.

Third, the resectability of the tumor must be confirmed. Using the radiologic techniques previously discussed above, the patient is assessed to ensure that the disease is confined to one pleural space and that there is no transdiaphragmatic involvement or invasion of mediastinal structures (esophagus, vena cava, heart).

**Multimodality Approach Used at Brigham and Women’s Hospital**

At the Brigham and Women’s Hospital, a multimodality approach consisting of extrapleural pneumonectomy followed by adjuvant chemotherapy and external-beam radiotherapy has been used for nearly 20 years.

**Surgical Procedure**—In appropriate patients, we predominately perform extrapleural pneumonectomy[33] for diffuse malignant pleural mesothelioma (Table 4). After the incision is made, the parietal pleura is exposed and dissected from the chest wall, diaphragm, and mediastinum. The pulmonary vessels are then controlled, the bronchus is isolated and stapled, and a subcarinal node dissection is performed.

The lung, pleura, pericardium, and ipsilateral hemidiaphragm are removed en bloc. A pericardial fat pad is placed over the bronchial stump, and the pericardium and diaphragm are reconstructed with prosthetic patches. The pericardial patch is fenestrated to prevent tamponade. If gross disease is unresectable, radiopaque clips are used to outline it for postoperative radiotherapy.

**Postoperative care** is aggressive and similar to that used in patients who have undergone standard pneumonectomy; namely, pain control and scrutiny of intravascular volume changes. Management is carried out on a thoracic stepdown unit using arterial lines, central venous lines, continuous oximetry, respiratory monitors, and nursing on an 1:2 ratio.

Pain control is vigorously pursued to reduce atelectasis and resulting pulmonary dysfunction. We use regular chest physiotherapy and deep-vein thrombosis prophylaxis with subcutaneous heparin and pneumatic boots.

Postoperatively, we maintain continuous bedrest for the first 48 hours to allow the patient to achieve mediastinal stability. Following this, ambulation is begun and continued.

We maintain meticulous 24-hour fluid restriction during the first 3 to 5 days following surgery because patients tend to retain fluid and have episodes of capillary leak in the intact lung, which has the potential for producing desaturation. Desaturation is treated with diuresis and chest physiotherapy or, if this proves unsatisfactory, with bronchoscopy. Mediastinal shift is monitored with daily x-ray evaluation to anticipate tamponade or in-flow obstruction.

The nasogastric tube is removed on postoperative day 1 if clinical signs are acceptable. Because aspiration is a serious concern, oral intake is avoided until gastric function returns. We treat contralateral infiltrates aggressively.

**Chemotherapy and Radiation Therapy**—The current chemotherapeutic regimen, usually begun 4 to 6 weeks postoperatively, consists of two cycles of paclitaxel (Taxol; 200 mg/m$^2$ by continuous intravenous infusion [3 h]), plus carboplatin (Paraplatin; dosed to achieve an area under the curve [AUC] of 6). The two cycles are given 3 weeks apart.

Radiation is then given concurrently with weekly paclitaxel (60 mg/m$^2$). Following the completion of radiotherapy, an additional two cycles of carboplatin (AUC of 6) and paclitaxel (200 mg/m$^2$) are administered 3 weeks apart.

External-beam radiotherapy is delivered in 1.5-Gy fractions over 5.5 weeks, giving a total radiation dose to the hemithorax of 40.5 Gy. A boost dose (14.4 Gy) is administered to areas of gross residual disease, localized lymph nodes, or positive margins.

**Recent Analysis of Results**—Encouraged by the results of two previous series (52 patients in the first and 120 in the second), an analysis of 183 patients (43 women and 140 men; 1980 to 1997) was completed.[24,25,34] The mean age of the cohort was 57 years (range, 31 to 76 years), with 75% reporting exposure to asbestos and 65%, a history of smoking. Dyspnea was the most commonly reported symptom (73%), followed by chest pain (56%) and cough (36%). Notably, the duration of survival was not significantly associated with gender, age, history of smoking, or exposure to asbestos.

Major morbidity (classified as an untoward event leading to increased length of hospital stay) was noted in 24% of patients and minor morbidity in 41%. There were seven postoperative deaths (3.8%).

Overall median survival was 17 months, yielding overall 2- and 5-year survival rates of 36% and
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14%, respectively. A median survival of 19 months and 2- and 5-year survival rates of 38% and 15% were calculated for the 176 patients who survived surgery.[25] Two- and 5-year survival rates of 68% and 46%, respectively, were found for patients with the combination of epithelial tumor histology, negative resection margins following surgery, and negative nodal status. Based on this experience, we conclude that extrapleural pneumonectomy can be performed safely with acceptable morbidity and mortality and that a trimodality approach to selected patients with diffuse malignant pleural mesothelioma can result in long-term survivors. With the development of innovative staging techniques, such as PET, and minimally invasive surgery, it is hoped that the accuracy of preoperative staging will improve, leading to better patient selection for multimodality therapy.

Innovative Therapies

Gene Therapy, Immunotherapy, and Photodynamic Therapy
New and innovative therapeutic strategies are currently under study in an attempt to provide alternative therapies for diffuse malignant pleural mesothelioma. The location and localized nature of these tumors have spurred the development of intracavitary approaches, such as photodynamic therapy, immunotherapy, gene therapy, and vaccination therapy, to treat the primary tumor.[35]

Photodynamic therapy, alone or in conjunction with surgical debulking, has been reported to improve local control of mesothelioma.[36] To date, results have been variable. Recently, a phase III trial published by Pass and colleagues concluded that photodynamic therapy did not prolong survival or improve local control following surgical cytoreduction.[37] Enhancements in photosensitizing agents and the depth of penetration are needed to improve the effectiveness of this therapeutic modality.

Immunotherapy techniques using cytokines have been employed with some success. A study of 23 patients by Goey and colleagues using an intrapleural infusion of interleukin-2 (IL-2 [Proleukin]) for stage I and II pleural mesothelioma resulted in an overall survival of 16 months with acceptable drug toxicity.[38]

Boutin and colleagues reported on 89 patients with early-stage diffuse malignant pleural mesothelioma who were treated intrapleurally with recombinant interferon-gamma (Actimmune).[39] A partial response rate of 19% was noted; 61% of the partial responders were patients with stage IA disease. Clearly, further trials are needed to verify these results and to explore the role of these and other cytokines, such as tumor necrosis factor-alpha and interferon-alfa (Intron A, Roferon-A), in inhibiting the growth of mesothelial tumor cells.

Immunotherapeutic agents also have been combined with chemotherapy in an attempt to find an effective regimen that may also have synergistic effects. Cisplatin, interferon-alfa, and tamoxifen (Novaldex) have been used by Pass and colleagues at the National Cancer Institute. They demonstrated a partial response rate of 19% (> 50% reduction in tumor volume) and a median duration of response of 8.7 months (14.7 months in responders).[40] The main problem with this form of therapy is that the duration of response is short, suggesting a direct cytotoxic effect rather than an immune-mediated mechanism of activity.

Gene Therapy—The role of gene therapy in the treatment of diffuse malignant pleural mesothelioma has been limited by the inability of vectors to provide sufficient levels of gene product for a long enough period of time.[35]

Vaccination therapy also is under active investigation. The recent discovery of a simian virus 40 (SV40) gene–like sequence in 25% to 60% of mesothelioma tumor cells has led to the concept that SV40 may act as a carcinogen or co-carcinogen in this disease.[41] To date, no specific vaccine has been developed. However, work is continuing in this area to confirm the association between SV40 and mesothelioma.

Intracavitary (intrapleural) heated chemotherapy using cisplatin is presently being investigated as a means of delivering high concentrations of this drug locally with limited systemic toxicity. The rationale for a heated delivery system (43°C) is based on the documented toxicity of heat for neoplastic cells.[42] A phase I study is presently underway at Brigham and Women's Hospital to determine the safety and feasibility of this approach.

Conclusions

Preliminary results of innovative approaches to the treatment of diffuse malignant pleural mesothelioma are promising. These new strategies must actively be pursued, along with
multimodality therapy, in order to obtain long-term survival for patients with all stages of this disease.

References:


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